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Photo by: St Andrew's Mission Hospital and Singapore Anglican Community Services

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COMMENTARY

LETTER TO THE EDITOR

IMAGES IN MEDICINE

Editorial

The Facts, Fallacies and Uncertainties about Coronavirus Disease 2019 (COVID-19)

Tow Keang Lim, [1]*MBBS, FRCP*

It is now widely recognised that the coronavirus disease 2019 (COVID-19) outbreak has become the most significant pandemic of the century, and that we are only experiencing its initial stages.[1] After weathering the first wave of COVID-19 from around the world, it is appropriate to pause at this juncture to take stock and make some sense of this new respiratory infection to better anticipate its trajectory and the prospects for effective interventions.

The unprecedented speed at which the global scientific and public health communities have collaborated, collated and published their findings—a large proportion of which had been expedited in pre-print versions—has enabled us to begin to view a clearer picture, at least of some important aspects, of this pandemic. Unfortunately, it has also resulted in publications that were of poor quality and had errors by even some of the most prestigious medical journals.[2]

Most reports of COVID-19, especially in the media, had described it as a deadly respiratory tract infection with the assumption of a high case fatality rate (CFR). This is a fallacy which might lead, in certain situations, to inappropriate reactions, decisions and actions. The CFR of any new infectious disease can only be definitively known after epidemiological investigations are completed.[3] This is not yet the case for COVID-19. However, the salient clinical and epidemiological features in confirmed COVID-19 patients had been well described and a specific diagnostic test had been widely deployed globally. Based on this case definition, most experts now estimate that the CFR of COVID-19—as it is currently defined—is about 1%.[4] This is higher than seasonal flu, which is 0.1%, but is a lot less lethal than many other infectious diseases.

An important and—for a respiratory tract infection—a rather unusual feature of COVID-19 is the very high proportion of infections that are very mild or even asymptomatic. Consequently, the true CFR of this disease can only be determined after extensive population-based serological investigations are completed.[5] Preliminary results from a few limited serological surveys in selected populations suggested that the number of infected people may be much higher than those detected using current methods. One may conclude that the CFR of COVID-19 infection itself may be well below 1%. This makes it much lower—and less deadly—than severe acute respiratory syndrome that had a CFR of 14% in Singapore or the Middle East respiratory syndrome which had a CFR of 39% based on a meta-analysis.[6]

The likelihood of dying from COVID-19 may also be appreciated by comparing the mortality rates of patients hospitalised with COVID-19 against those with community-acquired pneumonia (CAP). A nation-wide analysis of outcomes of hospitalised patients with COVID-19 from 575 hospitals in Mainland China had reported an overall mortality rate of 3.2%; the rate was 7.3% in Hubei Province, the epicentre of the pandemic, against 0.3% outside the epicentre.[7]

In Singapore, the hospital mortality rate for COVID-19 is <1% and was influenced by case severity and hospital admission thresholds. This finding contrasts sharply with that of a recent large study from the island state that found a hospital mortality rate of 13.4% for CAP,[8] which was comparable to findings on expected mortality from CAP in the literature. Thus, one may say with some degree of certainty that, in Singapore, it is much less risky to be hospitalised with COVID-19 than CAP. Indeed, there is about a 10-fold difference in the risk of dying from these 2 diseases in local hospitals. Important factors that should be taken into account for the high hospital mortality rates reported in Hubei Province, Europe, the United Kingdom and the United States included extreme

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case overload on acute care services, particularly the availability of ventilators, inadequate protective equipment and COVID-19 infections and deaths among medical staff.[9]

Additionally, there is a great deal of interest and concern about COVID-19 as a potent killer of older adults.[10] Consequently, there was a spate of public health recommendations and advisories on ways to avoid infection by the older population. Although old age is a pivotal risk factor for mortality in respiratory infections, it is not unique to COVID-19 and is true of pneumonia that is caused by all types of pathogens. Age is incorporated into the most widely used clinical severity score in CAP, the "CURB-65" (Confusion, Urea, Respiratory rate, Blood pressure and ≥65 years old).[8] The recommendation that influenza and pneumococcal vaccines should be administered to the older healthy population is also motivated by such expectations.

It is still not certain whether COVID-19 poses any special risk to the elderly compared to other chest infections; careful examination of age-specific mortality rates in COVID-19 against that of CAP did not suggest that COVID-19 is more deadly than CAP in older patients. It should, however, be noted that most bacterial CAP infections are not transmissible; thus, they may not have the wider impact of COVID-19. Still, it is prudent to advise caution in the elderly against all types of respiratory tract infections, but keeping them "safe" through strict isolation in an extended lockdown while the rest of society returns to normal life could be viewed as another version of ageism that needs to be guarded against.

With daily reports in the media on the death toll and images of rows of newly dug graves in Qom, churches packed with coffins in Lombardy and body bags inside container trucks in New York, COVID-19 has been viewed as a deadly disease. However, one not only fails to consider the total number of infected individuals in those communities, but also fails to appreciate the real denominators of so many deaths for an accurate assessment of how truly lethal COVID-19 is. Uncontrolled epidemics can grow exponentially; when they reach the steep upstroke of the exponential curve in a naïve population, the number of cases and deaths will increase and spiral.

In COVID-19, the fatalities form just the tip of an iceberg that comprises a huge number of mild cases below the surface of detection. In communities that did not roll out robust detection and testing programmes, this translates into a sudden, unexpected surge in the number of critically ill and dying patients that threaten to overwhelm an unprepared health system. This was especially true of COVID-19; recent studies of the initial outbreak in Mainland China that used more precise information based on integration of high-resolution domestic travel data and early infection data reported in provinces other than Hubei Province to infer outbreak dynamics in Wuhan City had calculated the basic reproductive number (R0) at 5.7.[11] This was much higher than previous R0 estimates of 2–3 and suggested that COVID-19 was more contagious and spread faster and wider than previously thought. This high infectivity—combined with a large asymptomatic base—accounted for the apparent paradox of a high death toll despite a relatively low CFR.

When the outbreak is at the steep upstroke phase of the exponential curve, the sheer number of individuals in the community who become very ill at the same time is likely to overwhelm any health system since there will be a sudden surge in the number of critically ill patients.[9,12–14] Consequently, the ongoing efforts in Singapore to slow down the spread of COVID-19 among her migrant workers are critical; by mounting huge infrastructural and manpower resources to provide appropriate care for infected workers, it has helped to protect the functional integrity of her acute health services.

An important reason for the high contagiousness and transmission rate of COVID-19 is the potential for spread by asymptomatic and thus, undetected cases. By using a networked, dynamic metapopulation model and Bayesian inference to model the early spread of COVID-19 in Mainland China, analysis of data from Tencent—one of the largest social media and technology companies in the world—concluded that 79% of COVID-19 cases were attributed to undocumented infections before travel restrictions were implemented in the country on 23 January 2020.[15] These novel clinical and epidemiological features of the COVID-19 outbreak pose a much greater challenge to interventional strategies than had been previously anticipated based on models that were developed from respiratory pandemics of the past. To be effective against COVID-19, these interventions must be implemented as early and as stringently as possible.

Additionally, since the epidemic is driven predominantly by asymptomatic and thus undiagnosed cases, conventional symptom-based contact tracing is

relatively ineffective. This may also account for the success in South Korea and Taiwan to control their COVID-19 outbreaks through contact tracing using social media and mobile phone technology without the need to lock down a whole community.[16,17]

To be effective in eliminating COVID-19, there is an urgent need to learn more about the critical unknowns of this new disease, particularly its molecular biology, immunology and pathophysiological mechanisms and pathways to disease, complications and death.[18,19] Meanwhile, a high degree of control and containment can still be achieved when deliberate efforts are made to apply—with insight—the valuable and costly lessons that have been learned in the first few months of this spectacular global pandemic.

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Original Article

High Resolution Computed Tomography (HRCT) Imaging Findings of Oval Window Atresia with Surgical Correlation

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Abstract

Introduction: Isolated oval window atresia (OWA) is a rare cause of congenital conductive middle ear deafness and may be overlooked owing to the normal appearance of the external ear. This anomaly has been previously described, although the published numbers with both imaging and surgical findings are few. Our aim is to correlate the imaging features of OWA with intraoperative findings. Materials and Methods: This is a single-centre retrospective evaluation of patients who were diagnosed with OWA and who received surgery from January 1999 to July 2006. No new case was diagnosed after 2006 to the time of preparation of this manuscript. High resolution computed tomography (HRCT) imaging of the temporal bones of the patients were retrospectively evaluated by 2 head and neck radiologists. Images were evaluated for the absence of the oval window, ossicular chain abnormalities, position of the facial nerve canal, and other malformations. Imaging findings were then correlated with surgical findings. Results: A total of 9 ears in 7 patients (two of whom with bilateral lesions) had surgery for OWA. All patients had concomitant findings of absent stapes footplate with normal, deformed or absent stapes superstructure and an inferiorly displaced facial nerve canal. HRCT was sensitive in identifying OWA and associated ossicular chain and facial nerve abnormalities, which were documented surgically. Conclusion: OWA is a rare entity that can be diagnosed with certainty on HRCT, best visualised on coronal plane. Imaging findings of associated middle ear abnormalities, position of the facial nerve canal, which is invariably mal-positioned, and associated deformity of the incus are important for presurgical planning and consent.

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Key words: Absent oval window, Conductive hearing loss, Temporal bone

Introduction

The oval window niche contains the stapes footplate, allowing the transmission of sound from the ossicles to the cochlea. Oval window atresia is a rare cause of congenital hearing loss owing to abnormal embryological development. It is commonly associated with middle ear abnormalities as well as an aberrant course of the facial nerve. In our institution, high resolution computed tomography (HRCT) is routinely performed in patients with hearing loss, to provide a detailed assessment of the middle and inner ear, including evaluation of the ossicles and facial nerve.[1,2] This offers a non-invasive alternative to an exploratory tympanotomy.

There have been predominantly small case reports and case series published in surgical literature regarding the external and middle ear anomalies associated with oval window atresia and the outcomes of surgical treatment.[3–7] In some surgical papers, HRCT was deemed useful to exclude inner ear abnormalities but insensitive for evaluating ossicular chain abnormalities or malposition of the facial nerve.[8,9] However, Zeifer et al. reported that HRCT enables preoperative

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diagnosis of anomalous course of the facial nerve as well as absence of the oval window.[10] This is likely due to advancements in CT imaging, allowing high spatial resolution and image quality. There are a few radiological publications[10,11] and, recently, some papers with both radiological and surgical correlation.[12–14]

Our aim is to review the imaging findings in patients with isolated oval window atresia, from preoperative HRCT of the temporal bones, and to correlate these findings with those documented during surgery.

Methods

Study approval was obtained from our local institutional review board. Using a computerised database, we identified 9 patients who were diagnosed with oval window atresia on HRCT between 1 January 1999 and 31 July 2006 in our institution. A review of the institution Radiological Information System (RIS) revealed that no new case of oval window atresia was diagnosed since 2006. All patients had been seen in our otolaryngology department and referred for HRCT of the temporal bones to evaluate the cause for congenital deafness. Two patients who declined surgery were excluded. Both clinical and operative notes were available for the remaining 7 patients.

In the HRCT protocol, multi-slice axial sections were obtained using 4 and 16 row detector helical CT scanners (Aquilion, Toshiba Medical, Tochigi, Japan; and Sensation, Siemens Medical Systems, Erlangen, Germany). The slice thicknesses were 0.5 mm and 0.65 mm, respectively. Images were reconstructed with a bone algorithm in the coronal plane using 1.0 mm sections.

The HRCT images of all 7 patients were retrospectively reviewed by 2 head and neck radiologists in consensus, who were blinded to the clinical and surgical findings. Oval window atresia was identified as a contiguous bony plate covering the expected site of the oval window niche, best seen on coronal view, with a dysplastic stapes. As the stapes footplate shares the same embryological origin as the otic capsule,[2,10] an absent oval window is invariably associated with the absence of stapes footplate. Abnormalities in the middle ear (including the stapes superstructures, incus, malleus and facial nerve canals), and of the inner ear structures, were documented. The ossicles were evaluated on both coronal and axial images, with the stapes crura best seen on axial images. Displacement of the facial nerve canal was best evaluated on coronal images.

Results

All patients gave a history of hearing loss since childhood, with no antecedent inflammatory middle ear disease, trauma or known progression of hearing loss. One patient (Patient E) (see list of patients in Table 1) had Turner's syndrome. Pre-surgical audiometry showed conductive hearing loss with a large air-bone gap of 50 to 60dB in all affected ears. On routine clinical examination, the external ear canals and tympanic membranes were normal. All patients were referred for HRCT of the temporal bones, prior to surgery.

Of the 7 patients, 5 were male while 2 were female, with an age range of 10 to 22 years at presentation. Two had bilateral and five had unilateral oval window atresia on HRCT. Exploratory tympanotomy was done for all patients, giving a total of 9 ears. The intraoperative findings were compared with the HRCT findings (Table 2).

Of the 2 patients with bilateral oval window atresia, 1 received corrective vestibulotomy in both ears. In the 5 patients with unilateral oval window atresia, 4 had vestibulotomy and one surgical attempt was abandoned due to a dehiscent facial nerve overlying the oval window area (Patient C).

The presence of a bony plate at the expected position of the oval window is invariably associated with absence of the stapes footplate with a normal, deformed or absent stapes superstructure. These findings were identified on HRCT for all patients, with an accurate diagnosis of oval window atresia confirmed intraoperatively. Apart from a tortuous external ear canal but normal tympanic membrane in one patient, there was no external ear atresia or microtia. The inner ear structures were also normal in all the patients.

In 3 ears, the stapes superstructure was found to be completely absent on both imaging and surgery (Figs. 1 and 2). In 5 ears, the stapes showed free-floating stapes superstructure. One patient had a thickened, shapeless bone representing a rudimentary stapes. Absence of the stapedius tendon was found during surgery in 1 patient; this was not identifiable on imaging.

The malleus was present and was normal in all the patients. A dysplastic incus was seen in 2 patients on imaging; this was confirmed during surgery. One patient (Patient G) had a malformed incus with the lenticular process pointing antero-superiorly. As such, vestibulotomy was not advisable owing to the unfavourable position of the incus long process for insertion of prosthesis. Another patient (Patient B) had

Table 1. Detailed Summary of Imaging Findings with Intra-operative Correlation

PATIENT	IMAGING FINDINGS			INTRAOPERATIVE FINDINGS				PROCEDURE
	STAPES	INCUS	FACIAL NERVE POSITION	STAPES	INCUS	FACIAL NERVE POSITION	REMARKS	
A	N	Normal	Cochlear promontory	N	Normal	Cochlear promontory; bifid	Absent stapedial tendon	Vestibulotomy
B	A	Normal	Oval window niche	A	No lenticular process	Round window.		Vestibulotomy
C	D	Normal	Oval window niche	D	Normal	Oval window; dehiscent inferior portion of horizontal segment	Stapes - single posterior crus	Exploratory tympanotomy only
D	N	Normal	Just below oval window niche	N	Normal	Just below oval window niche		Vestibulotomy
E	N	Normal	Cochlear promontory	N	Normal	Cochlear promontory		Vestibulotomy
F1	N	Displaced posteriorly	Cochlear promontory	N	Normal	Cochlear promontory		Vestibulotomy
F2	N	Normal	Cochlear promontory	N	Normal	Dehiscent below oval window		Vestibulotomy
G1	A	Shortened long process with absent lenticular process	Cochlear promontory	A	Broad incus; lenticular process facing anterosuperiorly	Cochlear promontory; dehiscent		Exploratory tympanotomy only
G2	A	Absent long process and lenticular process	Cochlear promontory	A	Deformed incus; long process thick and short	Cochlear promontory		Unsuccessful

A – Absent
D – Deformed superstructure
N – Normal superstructure

Table 2. HRCT and Surgical Imaging Findings

	HRCT	SURGERY
Number of ears	9	9
Absent oval window	9	9
Normal stapes	0	0
Abnormal stapes	9	9
• Normal superstructure	5	5
• Deformed superstructure	1	1
• Absent superstructure	3	3
Normal incus	6	6
Malformed incus	3	3
Normal malleus	9	9
Inferiorly displaced facial nerve	9	9
• Oval window niche	3*	2*
• At Cochlear promontory	6	6
• Round window		1

*1 located just below the oval window niche

both an absent stapes superstructure and a shortened incus; the latter abnormality was not identified on HRCT. Stapedotomy was successfully performed in this patient despite the shortened long process.

Discussion

Isolated oval window atresia is a rare entity that is present at birth. Patients present with conductive hearing loss without an antecedent history of suppurative ear disease or progression of hearing loss. At audiometry, a large air-bone gap is found. Oval window atresia and ossicular chain anomalies may occur in combination with external ear atresia, owing to the common association of abnormal development of the first and second branchial arches.[15] There have been familial cases reported, which suggest a genetic predisposition, or association with Turner's or CHARGE syndromes [coloboma, heart defect, atresia of the choanae, retarded growth, genital abnormality and ear abnormality].[16–18]

However, when the external ear canal and tympanic membrane are normal on clinical examination, the cause of conductive hearing loss is not immediately apparent. Diagnosis is made by exploratory tympanotomy, which is the gold standard. Some surgical publications have reported inaccurate assessment of the middle ear cavity using preoperative radiological assessment, owing to poor resolution of the ossicular chain,[8] whilst others suggest that CT remains helpful in excluding inner ear malformations and providing some assessment of the facial nerve, ossicular chain and oval window.[5] In our experience, preoperative HRCT evaluation was able to accurately assess oval window atresia with its associated absence of the stapes footplate, abnormality of stapes superstructure, if present, as well as the inferiorly displaced facial nerve. These findings correlated well during surgery in all cases. There are increasing reports that illustrate the value of high-resolution CT in the diagnosis of oval window atresia,[10–14] in part owing to the technical advances in CT with improvement of spatial resolution and image quality. With the higher spatial resolution of cone beam computed tomography (CBCT), assessment of the temporal bone and the middle ear structures may be performed reliably at a significantly reduced radiation dose.[19] Given the recent advances in multi-slice helical CT (MSCT) with increased spatial resolution and dose reduction protocols, we believe that the gap between these 2 modalities may be narrowing.

Oval window atresia is nearly always associated with ossicular chain abnormalities. An absent or malformed stapes is the most common associated anomaly, followed by an abnormal incus and, rarely, malleus deformities. Our results also showed that most of the incus abnormalities were accurately assessed preoperatively, although 2 cases were incorrectly reviewed. Patient G was deemed to have a normal incus on pre-operative imaging, but was found to have absence of the lenticular process of the incus during surgery. Patient F1 was assessed to have a posteriorly displaced incus on imaging, which, however, was noted to be normal during surgery. An aberrant course of the tympanic segment of the facial nerve canal is also commonly found; the facial nerve may be inferiorly displaced or overlie the expected position of the oval window. The ossicles (in particular the stapes), oval window and facial nerve development are intricately related. Anson and Cauldwell were among the first to describe the dual origin theory of stapes development.[20] The stapes superstructure and the tympanic segment of the footplate develop from the second branchial arch (Reichert's cartilage) in the 5th week of gestation, whilst the vestibular portion of the footplate arises from the otic capsule. Between the 7th and 9th weeks, a depression forms in the otic capsule at the site of the future oval window, deep to the stapedial footplate which is held in place by the annular ligament.

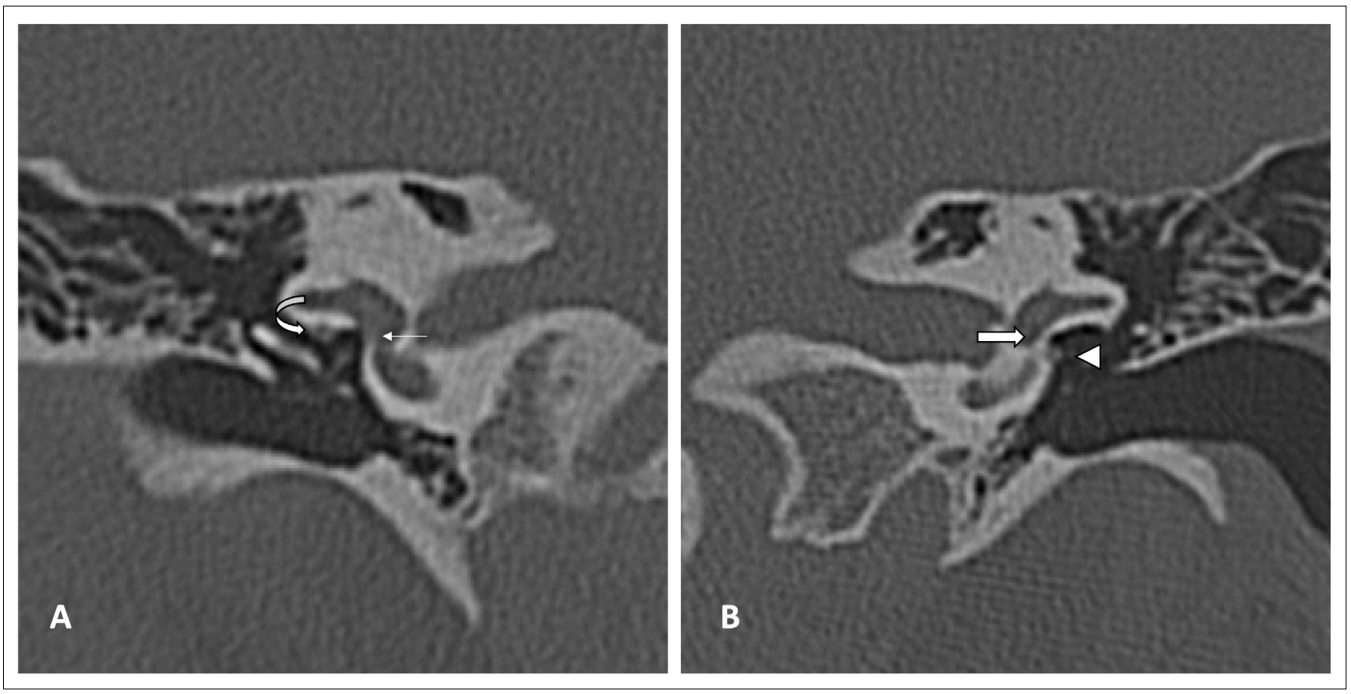

Figure 1. HRCT coronal images of Patient D with left oval window atresia, inferiorly displaced facial nerve and dysplastic stapes. (A) Right ear: normal oval window (thin arrow) with normal position of the facial nerve canal (curved arrow). (B) Left ear: absence of the normal oval window at its expected location (arrow). The facial nerve is displaced inferiorly, located just below the oval window niche (arrowhead).

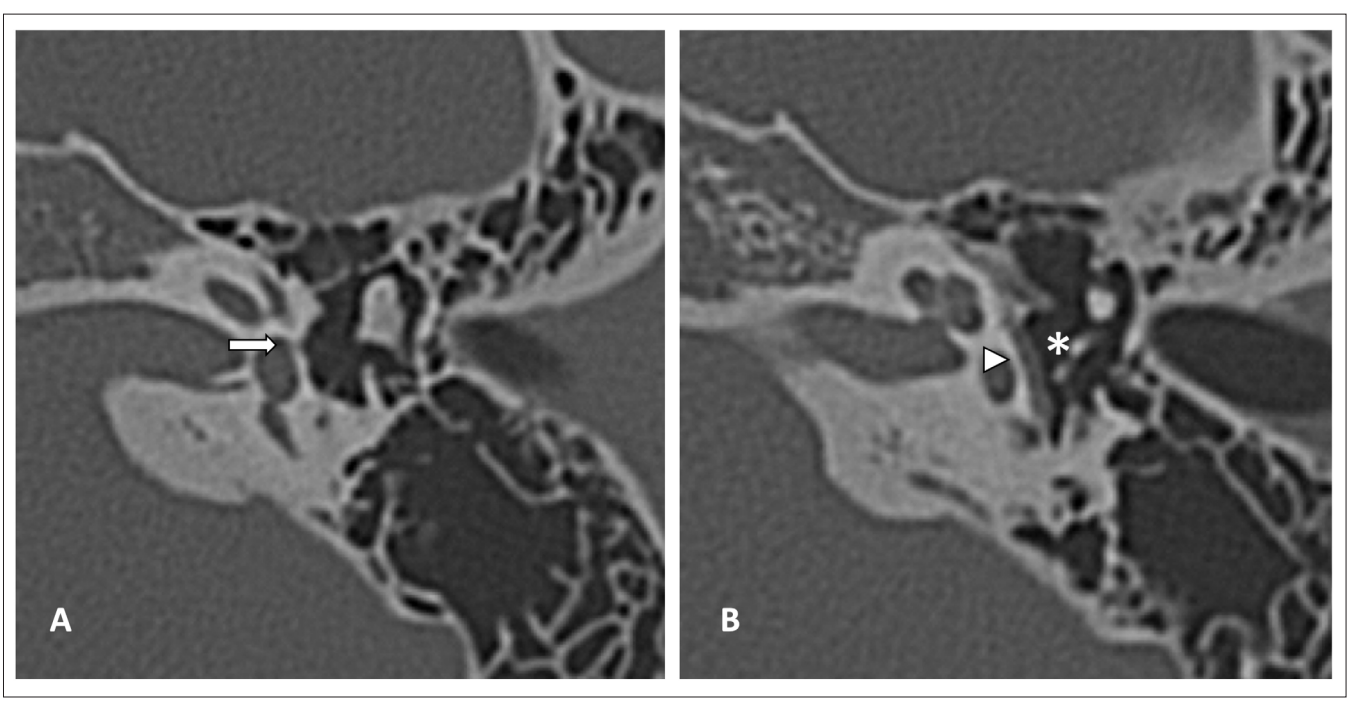

Figure 2. HRCT axial images of Patient D with left oval window atresia, inferiorly displaced facial nerve and dysplastic stapes. (A) Left ear: absence of the normal oval window at its expected location (arrow). (B) Left ear: inferiorly displaced facial nerve imaged on the axial section (arrowhead). Note the dysplastic stapes with floating superstructure (asterisk).

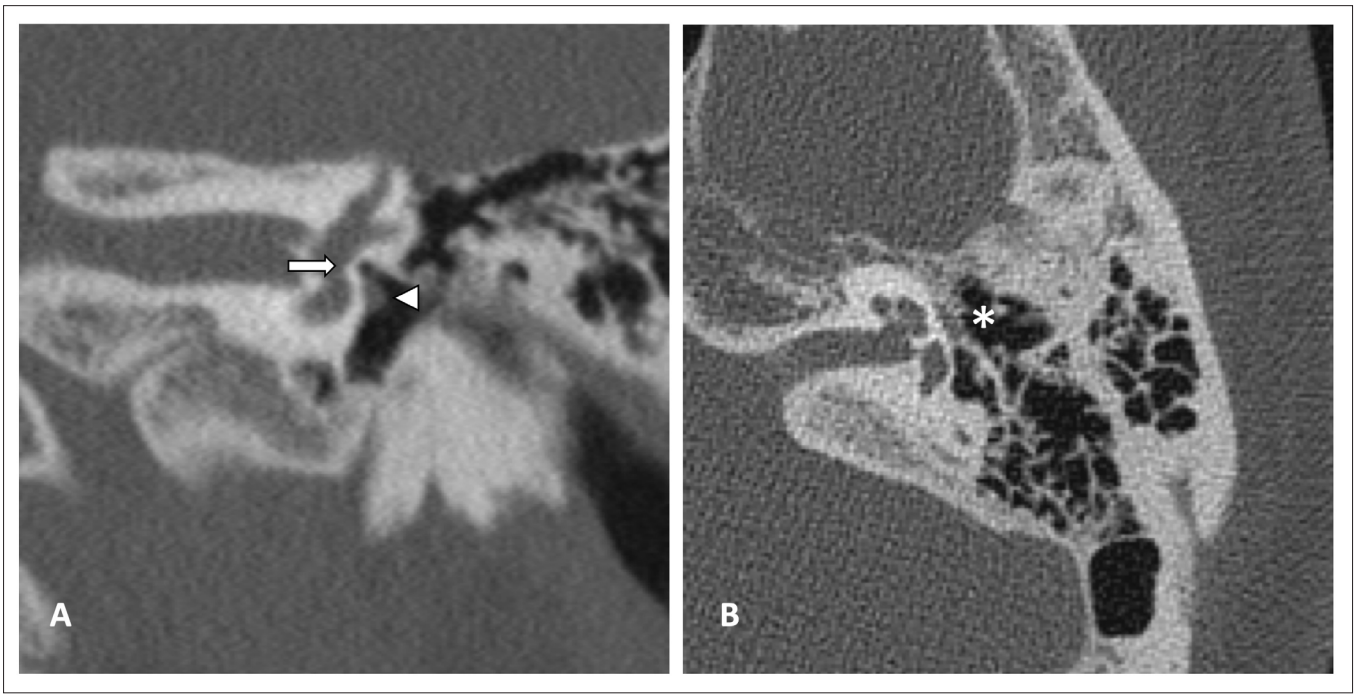

Figure 3. HRCT of Patient G1 with left oval window atresia, inferiorly displaced facial nerve and absent stapes. (A) Coronal section of the left ear: absence of the normal oval window at its expected location (arrow). The facial nerve is displaced inferiorly, located at the level of the cochlear promontory (arrowhead). (B) Axial section of the left ear: the stapes is absent (asterisk).

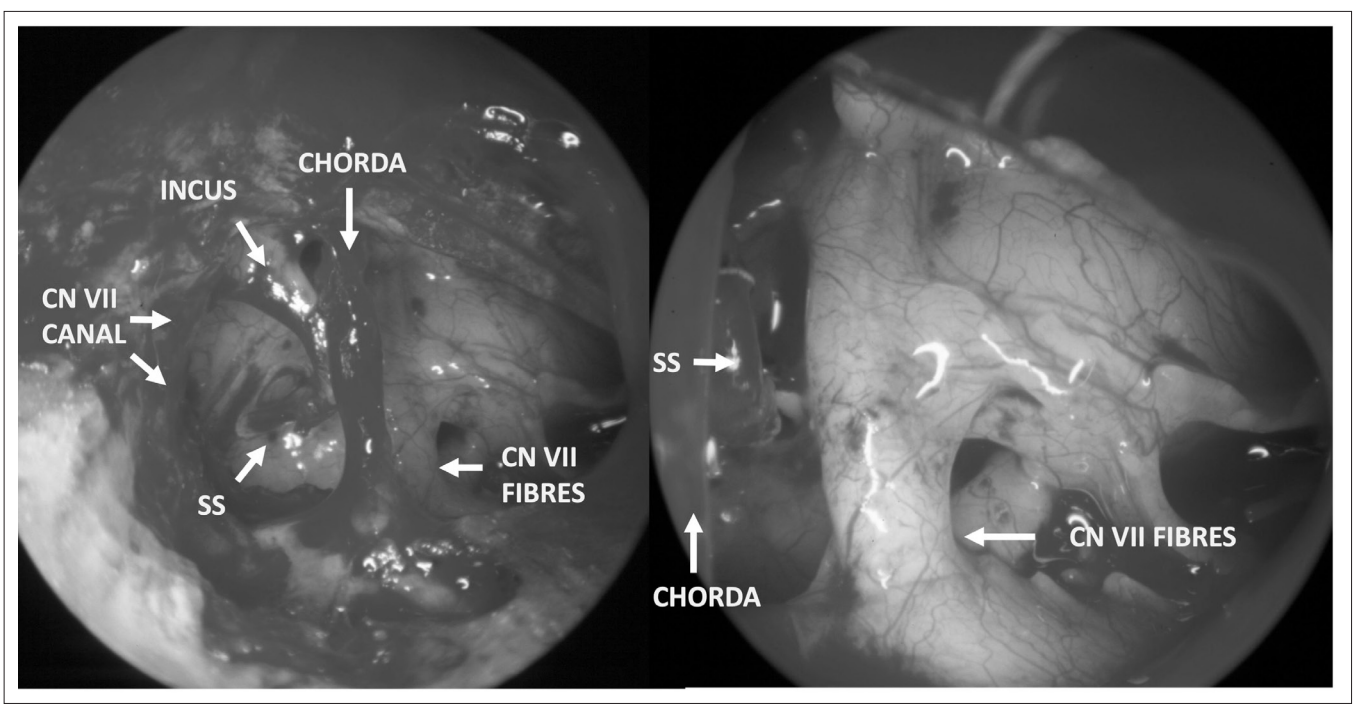

Figure 4. Intra-operative image of the right ear of Patient E with Turner's syndrome. There were free-floating stapes with incudostapedial joints, inferiorly displaced facial nerve and absent oval window. CN VII – Facial nerve, SS – stapes superstructure.

More recently, the use of transgenic mice showed that the presence of an oval window appears dependent on induction by signals from the stapes.[21] In the absence of the main body of the stapes, the mesodermal or vestibular part of the stapedial footplate does not form, and the oval window remains rudimentary. Thus, it appears that while the development of the stapes and otic capsule occur independently and at the same time, the process is highly regulated to coordinate accurate growth and integration.

Our data, in addition to the case reports and series reviewed, demonstrate that oval window atresia and abnormal stapes occur simultaneously, thus offering support to the dual origin theory. However, the innate cause of abnormal stapes and oval window development remains uncertain. Inferior displacement of the facial nerve may prevent the developing stapes from making contact with the otic capsule, resulting in the absence of the oval window and stapes malformation. This was first hypothesised by Gerhardt and Otto 1981, followed by Jahrsdoerfer 1988 and Lambert 1990.[5,22,23] This appears plausible, especially given that there are reports of the stapes crura being embedded in the displaced facial nerve. Our results showed aberrant facial nerves in all patients with oval window atresia, lending support to this theory. However other published studies showed displacement of the facial nerve ranging from only 59% to 90% of cases.[4,5,9–11,23] Another theory suggests that under-development of the first branchial arch causes a compensatory shift of the second branchial arch and the facial nerve.[22] However, this appears doubtful given the lack of external ear abnormalities in our study, and likewise in previously published literature.[11] Thus, the aetiology of oval window atresia remains uncertain, although we believe facial nerve displacement plays an important role.

There is a very low prevalence of inner ear malformations associated with congenital absence of the oval window.[10] We also did not detect inner ear malformations in our series.

Bone conduction hearing aid rehabilitation and surgical correction are treatment options for oval window atresia, although variable results are reported with the latter. Sterkers and Sterkers (1988) described drilling a fenestrum above the expected location of the oval window followed by placement of a piston, and that this achieved long-term correction in 6 of 8 cases.[7] In order for the fenestration into the vestibule to be performed, surgical access is vital. An inferiorly displaced facial nerve at the level of the oval window niche, such as in the case of Patient C, or presence of an anomalous structure, would result in poor surgical access. In addition, the placement of a prosthesis requires a suitable incus with an appropriate distance from the incus and new vestibule opening. Therefore, preoperative assessment with HRCT may be crucial for planning and patient counselling. Using HRCT, the position of the facial nerve, the integrity of the ossicular chain and abnormal development of other structures can be evaluated. However, evaluation of the temporal bone using HRCT involves a steep learning curve and requires an experienced reader for an accurate assessment of these structures. While the results in our study appear promising, we believe that HRCT plays a key role as an adjunct, rather than a replacement for tympanotomy, which is currently the gold standard. Exploratory tympanotomy is important to confirm radiological findings on HRCT and to ascertain if stapedotomy is appropriate.

Lambert (1990) reported initial improvement in hearing in 4 of 6 patients who underwent vestibulotomies and placement of prostheses, although the majority of the initial hearing gain was lost.[3] De Alarcon (2008) reported hearing improvement in all 13 patients one month following oval window drill-out procedure.[4] However, there was reduction of hearing gain in several of the patients over time. Revision surgery of these patients revealed regenerated bone around the previously drilled oval window in 2 patients, erosion of the long process of incus in 1 patient, while another patient had displaced prosthesis.[4] More recent publications show variable results. Hasegawa (2012) and Sennaroglu (2014) reported all patients achieved long term hearing improvement following vestibulotomy (3 patients in each series).[12, 24] A larger series by Su (2014) reported that 29 of 56 ears (51.8%) showed hearing improvement in 6 months, although 10 ears (17.9%) showed decline over the long term.[9] This could possibly be related to slow regeneration of bone at the site of the newly-created oval window, as suggested by De Alarcon et al.[4] Variable results post-surgery and long-term decline of hearing improvement, in addition to operative risks, should be clearly communicated to the patients and/or guardians during preoperative counselling. Other options such as conventional hearing amplification and osseo-integrated auditory implant may also been considered for patients who decline surgery.[4] Overall, we believe counselling of the patients and/or guardians

regarding all treatment options, potential benefits, risks and complications of surgery versus conventional hearing aid, is key in treating these patients.

Limitation

This is a single-centre retrospective study with limited cases diagnosed since 1999. To our best knowledge, no new cases were identified since 31 July 2006. This is attributed to the fact that oval window atresia is a rare cause of congenital hearing loss. Secondly, we do not deal with paediatric cases in our centre; there is a possibility that there may be a higher prevalence seen in a paediatric practice. In addition, long term follow-up on hearing changes of the patients was not included in this study owing to incomplete data.

Conclusion

Oval window atresia is a rare cause of congenital hearing loss, which may be initially missed by the otologist owing to the normal appearance of the external ear and tympanic membrane. Based on our findings, oval window atresia is consistently associated with the absence of stapes footplate with normal, deformed or absent stapes superstructure and anomalous position of the facial nerve. An unfavourable position of the facial nerve obscuring the surgical access seen on preoperative imaging may obviate unnecessary surgery. In addition, other associated abnormalities of the ossicles, particularly that of the incus, is important for surgical planning. The diagnosis of oval window atresia and associated findings can be achieved using HRCT. This vital information must be highlighted to the surgeon as it is important for the consideration of treatment options, including presurgical planning and consent taking.

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Original Article

Effects of Cast Immobilisation on Skin Barrier Function

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Abstract

Introduction: Cast immobilisation remains the mainstay of treatment for various fractures in paediatric patients, yet patients commonly complain of skin irritation and discomfort. This study aimed to perform a qualitative and quantitative evaluation of the effects of cast immobilisation on the skin of children and adolescents. Materials and Methods: Patients aged 6–17 years of age with a fracture treated in a fiberglass short-arm or short-leg cast were recruited. Transepidermal water loss (TEWL), stratum corneum (SC) hydration, hair density and presence of any skin signs were assessed before and after cast. Patients were required to complete a weekly questionnaire to rate itch, malodour, warmth, and dampness of the skin under the cast. Results: A total of 60 subjects completed the study. Thirty-six patients received a short-arm cast; 24 received a short-leg cast. Upon cast removal, TEWL was significantly increased on the volar surface of the arms and legs (P <0.05), and the dorsal surface of the arm (P <0.05). Likewise, SC hydration was significantly increased at most sites (P <0.05), except the volar surface of the leg (P = 0.513). There was no change in hair density. Throughout the duration of casting, there was an increase in itch and malodour scores. Conclusions: Moderate but significant changes in TEWL, SC hydration and subjective symptoms were observed during the duration of cast immobilisation, demonstrating that cast immobilisation for up to 4 weeks exerts moderate adverse impact on patients' skin. Further studies to explore the use of better materials for cast immobilisation to improve skin barrier function and overall patient satisfaction are warranted.

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Key words: Cast immobilisation, Transepidermal water loss, Stratum corneum hydration

INTRODUCTION

Fractures account for up to 25% of all paediatric injuries.[1] Cast immobilisation remains the mainstay of treatment in many paediatric acute fractures, with the period of casting ranging from 2 to 8 weeks depending on the type of injury. Skin irritation, itch, discomfort and malodour are commonly encountered during and after casting, especially in hot and humid environments.[2,3] Complications from casting, such as hypertrichosis, xerosis, skin atrophy and ulcerations have been reported in adults and children.[4-8] However, none of the existing studies objectively evaluates the effect of cast immobilisation on the skin. Our study aimed to evaluate the effects of cast immobilisation on the skin of children and adolescents both qualitatively and quantitatively by measuring transepidermal water loss (TEWL), stratum corneum (SC) hydration, hair density, as well as clinical assessment of the skin and patients' self-assessment of discomfort associated with cast immobilisation.

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Materials and Methods

Study Design

We performed a prospective qualitative and quantitative evaluation of the effects of cast immobilisation on the skin. The study was approved by the SingHealth Centralised Institutional Review Board (CIRB) and supported by a grant from the KK Women's and Children's Hospital (KKH) Health Endowment Fund. Patients were recruited from an outpatient Orthopaedic Surgery clinic at KKH, a tertiary paediatric hospital in Singapore, between January and June 2015. Informed consent was obtained from parents or legal guardians. Inclusion criteria were children and adolescents between 6 and 17 years of age with a fracture amenable to treatment in either a short-arm or short-leg cast, using standard materials of fiberglass cast over a layer of cotton stockinet liner with cotton undercast padding. Exclusion criteria were fractures that required surgical fixation, treatment in a long-limb or other cast configurations (e.g. hip spica), or the use of a non-standard cast material (e.g. waterproof Hybrid Mesh cast). Paediatric patients with a fracture would usually be attended to by the hospital's Children's Emergency Department or primary care clinic. Fractures that do not require surgical fixation will be treated by the emergency department or primary care clinic with a backslab cast in the acute period. A new fiberglass cast would then be applied at our Orthopaedic Surgery outpatient clinic 3–7 days later. At this clinic visit, patients were invited to enrol in this study.

One study investigator would take three independent measurements of TEWL, SC hydration, hair density, and observe the condition of the skin on both volar and dorsal surfaces of the injured arm or leg. To ensure that the same skin area was measured before cast application and after cast removal, a measuring guide consisting of three sets of 3 x 3 cm grids were overlaid approximately 5cm below the elbow crease and kneecap. All measurements were taken within the designated grids.

TEWL was measured using the Delfin Vapometer™ and registered in g/h/m^2; SC hydration was measured using the Delfin Moisture Meter SC™ and registered in units. At the follow-up clinic review, after the cast was removed, repeat assessments of the same parameters were performed. Similarly, photographs of the injured limbs within the designated boxes were taken using a digital SLR camera with a macro lens and ring light flash before cast application and after cast removal. Total number of visible hair follicles per unit area of hair in all photographs were counted independently. A localised skin examination was performed by the same investigator, noting any rash, abnormal pigmentation, ulceration or abrasion before application and after removal of the cast. These findings were documented as present or absent. If present, further description of the skin findings and severity were documented. Lastly, patients were required to complete a weekly questionnaire (Table 1) to rate levels of itch, malodour, warmth, and dampness of the skin under the cast during the duration of casting, with 1 being the worst rating and 5 being the best rating for each category.

Table 1. Patient Experience Questionnaire

1. Circle the option that best applies during the casting period:

	Itch		Odour		Heat and dampness
5	Not itchy at all	5	Not smelly at all	5	I don't feel it more than usual
4	It rarely itches (1 time a week)	4	It rarely smells	4	I only feel it on a warmer day
3	It sometimes itches (2-3 times a week)	3	It sometimes smells, usually after a long day or on a warmer day	3	I feel it sometimes but I can relieve it by staying in an air-conditioned room
2	It itches daily but tolerable	2	It smells daily but only when I sniff closely	2	I feel it daily but tolerable
1	Very itchy and I want my cast removed	1	Very smelly and noticeable by others	1	Very warm and damp and I want my cast removed

2. Did you do anything to relieve the above discomfort?

❑ Nothing
❑ Blow cold air from a hairdryer
❑ Apply talcum powder into the cast
❑ Spray perfume or air freshener over the cast
❑ Stay in air-conditioned room

Statistical Methods

Statistical analyses were performed using the SPSS software version 19.0. Paired samples t-test was used to compare TEWL, SC hydration, and hair density before cast application and after cast removal. A *P*-value of less than 0.05 was considered significant.

Results

Demographics

A total of 67 patients were recruited into the study. Of these, 7 patients did not complete the study or were lost to follow-up. Sixty patients completed the study and were included in final data analysis. Four patients had incomplete questionnaire responses and this data was excluded from analysis of the quantitative questionnaire. Of the 60 patients, there were 39 boys (65%) and 21 girls (35%), with a mean age of 11.8 years (range = 6–17 years). Thirty-three patients sustained injuries to their right side, while 27 had injuries to their left. A total of 36 short-arm and 24 short-leg casts were applied, with distribution of type of injury shown in Table 2. Their cast duration ranged from 7 to 29 days (median = 21 days) (Table 2).

Objective Assessments

As shown in Table 3, upon cast removal, TEWL increased significantly from baseline by 4.20 g/h/m^2 (95% CI: 2.60 – 5.79; P <0.001) and 1.26 g/h/m^2 (95% CI: 0.15 – 2.38; P = 0.028) on the volar surface of arm and leg, respectively. However, this change was relatively more modest on the dorsal surface, with TEWL on the arm increased by 1.03 g/h/m^2 (95% CI: 0.12 – 1.93; P = 0.028) and 0.55 g/h/m^2 on the leg (95% CI: -0.37 – 1.48; P = 0.226). SC hydration increased by 16.87 units (95% CI: 9.51 – 24.23; P <0.001) and 1.51 (95% CI: -3.18 – 6.19; P = 0.513) on the volar surface of arm and leg, respectively. On the dorsal surface, SC hydration was significantly increased by 5.45 units (95% CI: 1.56 – 9.34; P = 0.007) on the arm and 6.64 units (95% CI: 1.52 – 11.75; P = 0.013) on the leg. There was no significant difference in hair density before cast application and after cast removal on the arm (14.63 ± 6.04 versus 15.39 ± 5.50; P = 0.302) or leg (12.09 ± 6.32 versus 12.54 ± 5.68; P = 0.364). Overall, there was no dyspigmentation or ulcerations detected after cast removal. However, one patient developed abrasions secondary to a pen cap being lodged between the

Table 2. Patient Demographics and Characteristics

	N = 60
Age, Mean ± SD	11.8 ± 2.5 years
Race, n (%)	
Chinese	30 (50)
Malay	18 (30)
Indian	11 (18)
Others	1 (2)
Gender, n (%)	
Male	39 (65)
Female	21 (35)
Side of casted limb, n (%)	
Right	33 (55)
Left	27 (45)
Fracture diagnosis, n (%)	
Distal radius buckle fracture	19 (31.7)
Distal radius greenstick fracture	6 (10)
Distal radius SH1 fracture	6 (10)
Distal radius SH2 fracture	3 (5)
Wrist contusion	2 (3.3)
Distal fibula SH1 fracture	15 (25)
Distal fibula SH2 fracture	1 (1.7)
Ankle sprain	4 (6.7)
Metatarsal fracture	3 (5)
Lisfranc fracture	1 (1.7)
Fraction location, n (%)	
Upper limb	36 (62)
Lower limb	24 (38)
Type of cast, n (%)	
Below elbow	36 (62)
Below knee	24 (38)
Cast duration, n (%)	
0 – 7 days	0 (0)
7.1 – 14 days	17 (28.3)
14.1 – 21 days	34 (56.7)
21.1 – 29 days	9 (15)

SD = Standard deviation; SH = Salter-Harris

Table 3. Transepidermal Water Loss (TEWL), SC hydration, and Hair Density before Cast Application and After Cast Removal

Variable	Before Cast (mean ± SD)	After Cast (mean ± SD)	Differences of means (95% CI)	*P* value
Upper Limb (n = 36)				
TEWL, g/h/m²				
Volar	7.67 ± 2.39	11.86 ± 4.85	4.20 (2.60, 5.79)	**<0.001**
Dorsal	6.68 ± 2.33	7.70 ± 2.63	1.03 (0.12, 1.93)	**0.028**
SC hydration, units				
Volar	22.14 ± 8.14	39.01 ± 23.04	16.87 (9.51, 24.23)	**<0.001**
Dorsal	19.72 ± 6.40	25.17 ± 12.67	5.45 (1.56, 9.34)	**0.007**
Hair Density (hairs/cm²)	14.63 ± 6.04	15.39 ± 5.50	0.76 (-0.72, 2.25)	0.302
Lower Limb (n = 24)				
TEWL, g/h/m²				
Volar	6.76 ± 1.60	8.03 ± 2.25	1.26 (0.15, 2.38)	**0.028**
Dorsal	6.73 ± 1.58	7.28 ± 2.31	0.55 (-0.37, 1.48)	0.226
SC hydration, units				
Volar	20.76 ± 10.18	22.26 ± 10.89	1.51 (-3.18, 6.19)	0.513
Dorsal	21.40 ± 8.47	28.04 ± 14.90	6.64 (1.52, 11.75)	**0.013**
Hair Density (hairs/cm²)	12.09 ± 6.32	12.54 ± 5.68	0.45 (-0.55, 1.44)	0.364

SD = Standard deviation; TEWL = Transepidermal water loss; SC = Stratum corneum

cast and skin (Fig. 1), and another patient developed erythema with some follicular accentuation deemed secondary to skin irritation (Fig. 2A and 2B).

Subjective Assessments

There was an increase in itch and malodour over the duration of casting, worsening with increasing duration. However, the majority of patients did not feel their skin under the cast was overly warm or moist.

Discussion

This study measured the skin barrier function and hair density of paediatric patients aged between 6 and 17 years, following immobilisation in a short-arm or short-leg cast. We demonstrated that cast immobilisation increased TEWL and SC hydration on dorsal and volar surfaces of the forearm and lower leg, in varying degrees. In addition, there was an increase in itch and malodour perceived by patients over the duration of casting, but most of them did not report that their skin under the cast was overly warm or moist.

There has been only a handful of studies investigating the effects of cast immobilisation on the skin, with most studies reporting only subjective evaluation of cutaneous symptoms and signs. In a retrospective review of 297 children, DiFazio et al reported skin complications in 28% of patients who underwent cast immobilisation.[2] A subsequent prospective study reported a skin complication rate of 13.6 per 1000 casts applied in patients under 18 years of age,

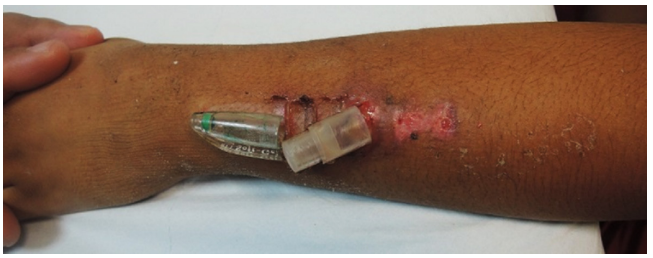

Fig. 1. A patient developed abrasion secondary to a pen cap being lodged between the cast and skin.

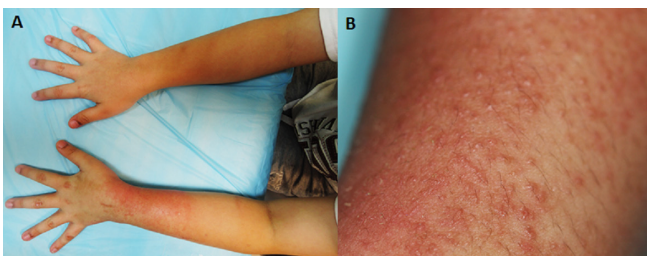

Fig. 2. A patient developed erythema with follicular accentuation.

including erythema, excoriation, wound dehiscence, maceration, and pressure ulcers.[3] In a prospective study by DiPaola et al, 3% of paediatric patients had to undergo unplanned cast changes due to skin irritation, while 3% of patients developed superficial infections requiring treatment with systemic antibiotics.[4] To the best of our knowledge, our study is the first to objectively examine epidermal barrier function after fiberglass cast immobilisation in a paediatric population.

TEWL is the loss of water across the stratum corneum, the outermost layer of the skin, which functions as the major barrier to diffusion. When the skin barrier is compromised by physical or chemical agents, TEWL would increase.[10] Our study showed that casting increased TEWL on both volar and dorsal sides of the limbs, albeit to a much lesser extent on the dorsal surface. This may be due to differences in skin structure between the two areas, including differences in thickness of the cornified layer, vascularity, and number and size of sweat glands.[11] Increased TEWL is known to be associated with skin barrier disruption[12] and if prolonged and severe, can lead to the development of dermatitis, especially in more susceptible patients.

Our results showed that casting increased the moisture content of stratum corneum on both dorsal and volar surfaces of the casted limbs, except the volar leg. We postulate that due to the low permeability of the casting material, there was increased moisture trapping between the skin and the cast, resulting in an increase in SC hydration. Although decreased SC hydration has been reported in dermatoses associated with dry skin, for example asteatotic eczema,[13] prolonged, excessive skin hydration can conversely lead to increased maceration and break down.

Hypertrichosis refers to excessive hair growth on any part of the body beyond the norm for a patient's age and gender. It has been widely reported following prolonged pressure, for example after cast immobilisation, but is benign and transient.[6-9] In our study, we did not detect a significant increase in hair density after cast immobilisation. We hypothesise that this may be due to the short casting period ($\leq$ 4 weeks) for our patients.

Overall, the rate of skin complications after casting was found to be 6.7% in our study, with erythema the most common complication. Itch and malodour associated with casting gradually increased throughout the study period. However, warmth and dampness did not seem to be a concern to most participants. Besides objective measures, subjective symptoms are important to consider when developing new materials for cast immobilisation. If these are too common or excessive, it can lead to adverse outcomes for patients, for example self-removal of casts before fractures are adequately healed or as in one of our cases, insertion of foreign bodies under the cast to relieve itch.

One of the limitations of our study was the relatively small sample size, leading to non-significance of some study parameters. In addition, before the initial set of readings was obtained, all patients had a half cast applied at the Children's Emergency Department or other clinics, albeit only for a few days. This may have underestimated the TEWL level and overestimated stratum corneum hydration value. Lastly, the study questionnaire designed by our investigators had not been validated. However, it was designed to specifically address paediatric patients' perceptions on itch, odour, warmth and dampness caused by casting. The closed-questions were phrased in a way that prevented misunderstandings or ambiguities and only allowed responders to choose one answer from the multiple-choice questions and 5-point rating scales. The flow of the questions was also optimised to enable smooth transition from one question to the next.

In conclusion, the present study suggests that cast immobilisation for up to 4 weeks exerts moderate

adverse impact on patients' skin, in particular changes in TEWL and SC hydration. Further studies to explore the use of better materials for cast immobilisation to improve skin barrier function and overall patient satisfaction are warranted.

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Original Article

Mid-term Outcomes of Patients with Central Venous Occlusive Disease Undergoing Surveillance Venography and Intervention

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Abstract

Introduction: To evaluate the mid-term outcomes of regular surveillance venography with or without percutaneous transluminal angioplasty in haemodialysis patients presenting with central venous occlusive disease. Materials and Methods: A single-centre retrospective analysis of haemodialysis patients who presented with central vein occlusion (CVO) and central vein stenosis (CVS) between January 2008 and December 2011 was performed. CVO and significant CVS were defined as 100% and >50% luminal narrowing respectively. Upon successful angioplasty on first presentation, patients were followed up with regular surveillance venography within 3–6 months of the intervention and were re-treated when a significant stenosis or occlusion was demonstrated. Data on patient's demographics, comorbidities, presenting symptoms, type of upper limb dialysis access, lesion characteristics and complications were collected. Technical success, primary patency and primary assisted patency were analysed. Results: Thirty-five patients with CVO and 77 patients with CVS were enrolled. The technical success of initial PTA was 77% and 73% for the CVO and CVS groups, respectively. The primary patency at 3 months was 65% and 55% for the CVO group and CVS group, respectively ($P = 0.32$). The primary assisted patency at 1 year was 88% and 99% for the CVO group and CVS group, respectively ($P = 0.009$). At 2 years, the primary assisted patency were 77% and 90%, respectively ($P = 0.07$). There was significant difference in the overall primary assisted patency ($P = 0.048$) between the CVO and CVS groups. Conclusion: CVOs are more difficult to treat than CVS. High primary assisted patency rates can be achieved with surveillance venography, albeit at the expense of increased number of interventions. Further cost effectiveness studies need to be performed to study the true benefit of our surveillance programme.

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Key words: Dialysis circuit, End stage renal failure, Renal replacement therapy

Introduction

Central venous occlusive disease (CVD) is a common problem seen in end-stage renal failure (ESRF) patients on haemodialysis, occurring in 29%–40% of patients.[1] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommends percutaneous transluminal angioplasty (PTA) as the first line treatment for CVD. For recurrent stenoses (within 3 months) or stenoses refractory to PTA, the recommended treatment is stenting.[2]

The treatment of central vein occlusion (CVO) is technically more challenging than that of central vein stenosis (CVS). At our institution, a strategy of 3–6 monthly surveillance venography was instituted for haemodialysis patients with CVD. Significant stenoses (>50% luminal loss) were initially treated with PTA. If these lesions were found to be again significant on follow-up surveillance venography, regardless of symptoms, they were re-treated to prevent subsequent progression to CVO.

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This single arm study evaluates the mid-term outcomes of patients with CVO and CVS who underwent regular surveillance venography after successful PTA on initial presentation.

Material and Methods

This is a retrospective single-centre study analysing consecutive cases of central vein PTA performed at our institution between January 2008 and December 2011. Approval was obtained from our Institutional Review Board for access to these patients' medical records. Patients' demographics, comorbidities, presenting symptoms, indications for central vein venogram, details of each PTA or venogram, location of haemodialysis access, the use of tunnelled central venous catheter (CVC), the use of antiplatelet or anticoagulant medication and procedural-related complications were recorded. The venograms were reviewed by 2 radiologists together in consensus. If the patient had presented with more than one central vein lesion, only the more severe lesion was studied.

Patients

ESRF patients on arteriovenous (AV) haemodialysis who newly presented with CVO and CVS (ipsilateral central veins or superior vena cava) between January 2008 and December 2011 were recruited into the study. Inclusion criteria were patients with ipsilateral functioning AV haemodialysis access on the upper extremities and who had not undergone PTA of central veins prior to 2008. These patients were included if the lesion could be crossed and angioplastied on the first procedure. These patients were then placed on regular surveillance venography (within 3–6 months of the initial PTA) and they were followed up for a period of 2 years. Exclusion criteria were patients with only contralateral CVS or CVO, lesions which could not be treated percutaneously at presentation, patients who had undergone stenting on their first intervention or those who had no follow-up after the first PTA.

Definitions

Central veins are defined as the subclavian vein, brachiocephalic vein or the superior vena cava. Regular surveillance venography (with and without subsequent PTA) was defined as that performed within 3–6 months after initial venography and PTA. The endpoints of follow-up included cessation of haemodialysis due to peritoneal dialysis or renal transplantation, creation of a new AV access on the contralateral arm or in either groin or permanent occlusion, stenting of the central vein lesion or patients lost to follow-up or death. Mid-term outcome is defined as 2 years from the initial PTA.

An angiographic significant central lesion is defined as more than 50% luminal loss. Technical success was defined as less than 30% residual stenosis after PTA. Primary patency of the central veins was defined as the time interval between the initial and next intervention. Primary assisted patency of the central vein was defined as the interval between the initial intervention and the date of permanent occlusion or stenting of the central vein lesion. Complications were classified in accordance with the Society of Interventional Radiology criteria.[3]

Technique

An initial central venogram was performed via a 23G cannula inserted into the upper limb fistula to document the location and degree of CVD. PTA would be attempted in the presence of a significant CVS or CVO. After gaining venous access via the appropriate upper limb or common femoral vein, a 4-Fr diagnostic catheter (Berenstein, Cordis, Warren, New Jersey, USA) and an 0.018–0.035-in hydrophilic guidewire (Terumo, Tokyo, Japan) were introduced to cross the lesion. PTA of the lesion was performed using standard techniques with an appropriately sized PTA balloon which was inflated until the lesion was effaced or up to the rated burst pressure, whichever was lower. The balloons used were sized to the adjacent normal venous segment and they ranged from 12 to 16mm and were of 40mm length (Powerflex, Cordis, Warren, New Jersey, USA; Atlas, Bard Peripheral Vascular, Tempe, Arizona, USA).

In chronic occlusions where antegrade or retrograde access alone was inadequate for PTA, a combined antegrade-retrograde approach was employed. In the latter technique, vascular sheaths were inserted antegradely into the upper arm dialysis circuit and in the appropriate common femoral vein. A suitable guide wire was first used to cross the CVO from either direction and exteriorised via the opposite sheath with the aid of a snare. Once through and through access was achieved, a small balloon was used for pre-dilatation. After which, PTA was performed with an optimally sized balloon. Prolonged inflations of up to 3 minutes were typically performed. A completion venogram was then procured to document the result post-PTA.

Statistical Analysis

Statistical analyses were performed using SPSS Version. 21. The data was reported as mean ± standard deviation or count (percentages). Primary and primary assisted patency rate of central veins was determined using Kaplan-Meier analysis and log rank test was used to compare patency rates between the 2 groups. Cox regression was performed to identify predictive factors that were associated with the central vein patency rates. Chi-square test and independent sample Student's t-test were used to compare categorical and continuous variables between the groups. The level of significance was set at 0.05.

Results

A total of 176 patients on haemodialysis presented with CVD during the 4-year study period, of which 52 patients had CVO and 124 patients had CVS. Among these patients, 7 patients had lesions that could not be traversed by a guidewire and PTA was not performed, 4 patients underwent stenting on their first intervention and 53 patients were lost to follow-up after initial PTA. Of the remaining 112 patients, 35 were in the CVO group and 77 in the CVS group.

The mean duration of follow-up was 16 ± 7.2 months for the CVO group and 16 ± 7.7 months for the CVS group. The mean number of PTA per patient in the first year was 3.7 ± 1.3 and 3.3 ± 1.1 for the CVO group and CVS group, respectively. The mean number of PTA over the 2-year follow-up period was 5.8 ± 2.7 and 5.0 ± 2.6 for the CVO group and CVS group, respectively.

The demographics and co-morbidities of both groups are summarised in Table 1. The 2 groups were not significantly different in terms of co-morbidities but there were significantly more male patients ($P = 0.03$) in the CVS group.

Table 1. Patients' Demographics and Risk Factors (Reported as N (%) for Categorical Variables and Mean ± SD for Continuous Variables)

	CVO (N = 35)	CVS (N = 77)	*P* value
Demographics			
Male	13 (37%)	46 (60%)	0.03
Female	22 (63%)	31 (40%)	0.03
Patient age (years)	63 ± 9.3	63 ± 9.8	0.46
Follow-up (months)	16 ± 7.2	16 ± 7.7	0.45
Number of PTA over 2 years	5.8 ± 2.7	5.0 ± 2.6	0.46
Number of PTA in 1st year	3.7 ± 1.3	3.3 ± 1.1	0.63
Comorbidities			
Diabetes	20 (57%)	41 (53%)	0.70
Hypertension	33 (94%)	76 (99%)	0.23
Coronary artery disease	14 (40%)	36 (47%)	0.51
Hyperlipidemia	32 (91%)	62 (81%)	0.15
History of smoking*	2 (7%)	7 (11%)	0.72
Access location			
Upper arm	28 (80%)	67 (87%)	0.34
Side of CVS/CVO			
Left	24 (69%)	41 (53%)	0.22
Right	11 (31%)	32 (42%)	0.22
Use of anti-platelets or anticoagulants	10 (29%)	31 (40%)	0.23
History of tunnelled CVC insertion*	31 (88%)	61 (89%)	0.86

* % computed based on available data

The most common indication for initial referral for PTA was swelling of the upper extremity (CVO, 43%; CVS, 48%, P >0.05) in both groups. The other indications and distribution of the central vein lesions are shown in Table 2. For both groups, the brachiocephalic vein (CVO, 97%; CVS, 68%, P = 0.001) was the most common site.

Outcome

The technical success rate of initial PTA was 77% for the CVO group and 73% for the CVS group (P = 0.6). We were only interested in determining the outcomes of patients who underwent our surveillance programme after successful initial PTA, so the 7 patients who had lesions that could not be crossed on initial presentation were excluded.

The 3-month primary patency of the central veins was 65% and 55% for the CVO and CVS group, respectively (P = 0.32) and the 6-month primary patency was 6% for both groups (P = 1.0).

The 6-month primary assisted patency of the central vein was 91% and 99% for the CVO and CVS groups, respectively (P = 0.03); the 1-year primary assisted patency was 88% and 99% for the CVO and CVS groups, respectively (P = 0.009). The 2-year primary assisted patency was 77% and 90%, respectively (P = 0.07). Log rank test showed significant difference in the overall primary assisted patency between the 2 groups (P = 0.048). This data is summarised in Table 3 and Figures 1A and 1B.

Table 2. Indication for Referral for Initial PTA and Distribution of Central Vein Lesions (Reported as N(%))

	CVO N = 35	CVS N = 77	*P* value
Indication			
Swelling	15 (43%)	37 (48%)	0.61
Malfunction access			
High venous pressure	2 (6%)	9 (12%)	0.50
Poor access flow	8 (23%)	12 (16%)	0.35
Bleeding post-dialysis	0 (0%)	1 (1%)	1.00
Thrombosis	2 (6%)	4 (5%)	1.00
Not specified	4 (11%)	6 (8%)	0.50
Asymptomatic	4 (11%)	8 (10%)	1.00
Distribution of lesions			
Subclavian vein	1 (3%)	21 (27%)	0.03
Brachiocephalic vein	34 (97%)	52 (68%)	0.001
Superior vena cava	0 (0%)	4 (5%)	0.31

Table 3. Primary and Primary Assisted Patency of Central Vein

	CVO	CVS	*P* value
Primary patency			0.45
3 months	65%	55%	0.32
6 months	6%	6%	1.0
Primary assisted patency			0.048
12 months	88%	99%	0.009
24 months	77%	90%	0.07

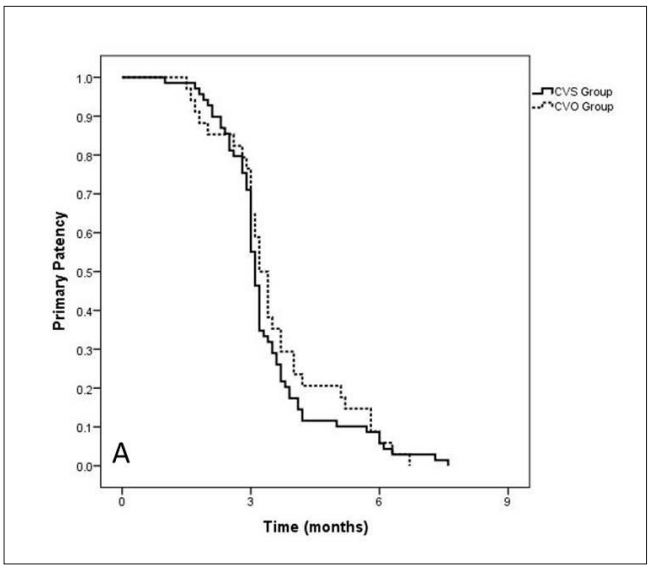

Fig. 1A. Primary patency of central veins.

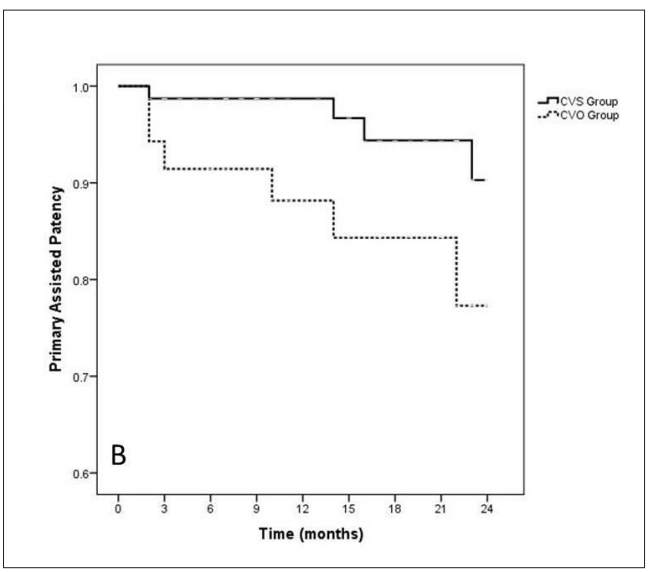

Fig. 1B. Primary assisted patency of central veins.

Multivariable analysis was performed on the following factors: age, gender, co-morbidities, history of tunnelled CVC use, location of AV haemodialysis access, side of lesion, and use of antiplatelet/anticoagulation medication did not yield any significant association in relation to the primary assisted patency.

The complication rates for both the CVO and CVS groups were low, with 1% or less directly related to PTA of the central veins. These complications were minor and, in all instances, managed conservatively. A total of 8 patients died within 30 days of the procedure, none of which were directly related to PTA. Three patients died from diabetic wound related sepsis, 3 from sequalae of their chronic renal disease, 1 from a cerebrovascular event and 1 from an acute cardiac event (Table 4).

At the end of the study period, 12 (34%) patients in the CVO group and 39 (51%) patients in the CVS group were on follow-up. Five (14%) patients in the CVO group and 3 (4%) patients in the CVS group underwent stenting of the central vein lesion or had permanent CVO. There were 4 (11%) patients and 11 (14%) patients in the CVO and CVS groups, respectively, who were lost to follow-up.

Table 4. Complications (Reported as N)

	CVO (Total no. of PTA = 202)	CVS (Total no. of PTA = 387)
Minor Complications		
Directly related to PTA of central vein		
Contrast extravasation	1	
Haematoma	1	2
Ruptured PTA balloon		1
Not directly related to PTA of central veins		
Inadvertent embolisation	1	
Contrast extravasation	1	6
Post angioplasty thrombosis		1
Dissection of vein		1
Ruptured vein		1
30-Day Mortality	2	6

Discussion

While CVD is a common problem that affects haemodialysis patients, the true prevalence of CVO is not known. The presence of CVO, if permanent, usually precludes the subsequent creation of new dialysis access on the ipsilateral upper limb.[4]

Current guidelines recommend stenting of CVD lesions for recurrent stenoses or stenoses that are refractory to PTA.[2] In our institution, stenting is less preferred as it can impede future endovascular and surgical treatment options when major venous junctions are stented. Unlike malignant CVS and CVO where there is consensus for stenting, the management of benign CVS and CVO, as in our study population, is still being debated.[5] In selected patients with permanent CVO and who have no other access site, the use of Haemodialysis Reliable Outflow (HeRO) graft (Merit Medical, Utah, USA) can serve as an alternative vascular access, circumventing the CVO.[6] However, this is considered a relatively new approach in the local setting. In view of the challenges related to CVO, we embarked on regular surveillance venography for our patients with CVD to prevent subsequent progression to CVO.

It is estimated that 50% of patients with significant CVD develop clinical symptoms.[7] This is similar to our study population where 48% of the patients with CVS and 43% of the patients with CVO were symptomatic at first presentation. The remainder of the patients presented with malfunctioning dialysis access.

Our initial PTA technical success rates were 77% and 73% in the CVO and CVS groups, respectively, comparable with the literature which ranged from 70–90%.[8–10] Of note, there were 7 patients with CVO lesions which could not be crossed at the initial PTA. If these 7 patients were included in the calculation, the initial technical success rate for PTA in patients who first presented with CVO, prior to entry into our surveillance programme, would have been significantly lower at 64%. In other words, CVO is technically more challenging to treat than CVS.

The primary patency of the central veins after PTA has been reported in the literature to be 49–63% and 29–55% at 3 and 6 months, respectively.[9,11–13] In our study, the primary patency for the CVO group was 65% and 6% at 3 and 6 months, respectively. The primary patency for the CVS group was 55% and 6% at 3 and 6 months, respectively. The fact that most of

our patients maintain primary patency at 3 months validated our strategy of not surveying them earlier than 3 months. Of note, our low primary patency rate at 6 months was due to our institutional practice of intervening as a result of our surveillance programme.

In a small study of 24 venograms with CVS, it has been shown that PTA was associated with rapid restenosis progression.[14] In another retrospective study, withholding PTA in asymptomatic patients who had CVS resulted in significantly higher central vein patency rates compared with symptomatic patients who were treated. The primary patency rate at 36 months for the asymptomatic and treated symptomatic groups were 67% and 18%, respectively.[10] These studies suggested that asymptomatic patients with CVS should not be treated. We recognise that restenosis is an inevitable outcome for most patients who have been treated with PTA, with endothelial proliferation as the main cause of restenosis.[8] However, the subject numbers are much smaller compared to our study and CVO was not addressed separately.

Several studies in the literature have reported their 1-year and 2-year primary assisted patency to be 73–82% and 56–62%, respectively (Table 5).[9,15–16] We achieved a higher primary assisted patency rate of 88–99% at 1-year and 77–90% at 2-years. In 2 comparable studies, the mean number of PTA per patient was 1.5 ± 1.0 and 2.0 ± 1.6, respectively, over a mean follow-up period of 1.8–3.3 years.[9,15] In our study, the mean number of PTA per patient was 5.8 ± 2.7 for the CVO group and 5.0 ± 2.6 for the CVS group over a mean follow-up period of 1.3 years. With our surveillance programme, we are therefore able to prolong patency of the central veins, albeit at the expense of an increased number of interventions.

In our study, the overall primary assisted patency of the central veins for the CVO and CVS groups were significantly different (overall, $P = 0.048$). This indicates that patients who initially presented with CVO deteriorated faster despite being on regular follow-up. Fourteen percent of our patients in the CVO group and 4% in the CVS group became permanently occluded or required stenting. In a study of 9 patients with CVO, Kim YC et al reported no significant difference in the primary assisted patency post-PTA between CVO and CVS.[15] In another study reporting the use of stent grafts in CVD, while not directly comparable, a significantly shorter primary patency was also found in patients with CVO than with CVS.[17]

There are several limitations in our study. Firstly, initial patient referral was based on individual physician's criteria. Secondly, the PTA technique among operators was not standardised. Thirdly, the measurable dialysis information was also not available. Further, the number of patients who were symptomatic during subsequent follow-up was not completely available as this was not consistently recorded. Lastly, the severity of the central vein lesions was determined only via imaging and no haemodynamic measurements were made. On the other hand, the major strengths of our study include a larger population size and CVO group which facilitated statistical analysis.

In conclusion, CVD remains a difficult problem in ESRF patients on haemodialysis and should be managed in a multidisciplinary manner. We have shown that high primary assisted patency rates can be achieved with an increased number of interventions. As CVO is harder to treat than CVS, pre-emptive PTA of CVS to prevent progression to CVO will preserve central vein patency. This will allow the ipsilateral upper limb to be used for dialysis access. Further cost-effectiveness studies should be performed to determine the true benefit of our strategy of surveillance venography for CVD.

Table 5. Summary of Assisted Primary Patency in Studies of Central Vein PTA

Study	Year	N	Initial success (%)	Primary assisted patency (%) at		
				6 months	12 months	24 months
Our study – CVO Group	-	35	77	91	88	77
Our study – CVS Group	-	77	73	99	99	90
Bakken et al[9]	2007	47	82	77	73	57
Kim et al[15]	2009	26	-	100	78	56
Ozyer et al[16]	2009	94	-	92	82	62

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Epidemiology and Factors Associated with Remission of Pemphigus Vulgaris and Foliaceus in Singapore

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Abstract

Background: Pemphigus is a chronic, relapsing immunobullous disease. There is limited data on the clinical course and prognostic factors of pemphigus in Asian patients. Methods: We conducted a retrospective cohort study of all newly diagnosed pemphigus vulgaris (PV) and pemphigus foliaceus (PF) patients seen at the National Skin Centre from 1 January 2004 to 31 December 2009. Demographic and clinical data on co-morbidities, treatment and remission were recorded. Mortality information was obtained from the National Registry of Diseases. Prognostic endpoint was overall remission at last visit. Results: Sixty-one patients (36 PV and 25 PF) were recruited. Among PV patients, higher initial prednisolone dose (*P* = 0.017) and the use of azathioprine (*P* = 0.028) were significantly associated with overall remission at last visit. However, higher desmoglein 1 antibody titres at diagnosis (*P* = 0.024) and the use of dapsone (*P* = 0.008) were negatively associated with overall remission at last visit. Among PF patients, only higher desmoglein 1 antibody titre at diagnosis (*P* = 0.041) was found to be associated with lower overall remission at last visit. There was no mortality during the 3-year follow-up period in both PV and PF. Conclusions: Higher initial prednisolone dose and the use of azathioprine in PV desmoglein 1 antibody titre at diagnosis in PV and PF might be prognostic markers for achieving remission. Use of dapsone was associated with lower overall remission in PV, but this might be confounded because dapsone was used as an adjuvant therapy in recalcitrant cases. Owing to study methodology and limitations, further evaluation is needed for better prognostication of pemphigus.

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Key words: Autoimmune blistering disease, Dermatology, Pemphigus foliaceus, Pemphigus vulgaris, Remission

Introduction

Pemphigus is an autoimmune disorder that causes immune-mediated blistering of the skin and mucous membranes. There are 2 major subtypes: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV and PF are characterised by intra-epidermal blister and acantholysis, resulting from damage caused by IgG autoantibodies directed against desmosomal glycoproteins, namely desmoglein 3 and/or desmoglein 1. On direct immunofluorescence (DIF), intercellular IgG deposits are found in the epidermis. PV is the most common intra-epidermal immunobullous disorder, with a variable incidence ranging from 0.76 per million per year in Finland[1] to 16.1 per million per year in Jerusalem.[2] PF is less common, occurring at 0.5 per million per year in Western Europe[3] to 6.7 per million per year in Tunisia.[4] In an earlier study from 1995 to 1997, PV and PF constitute 62% and 32%, respectively, of all pemphigus cases seen at the National Skin Centre, which is the major referral centre for immunobullous skin diseases in Singapore.[5]

Pemphigus has a chronic relapsing course, often requiring long-term immunosuppressants including systemic corticosteroids and other adjunctive

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agents. There are significant disease morbidity and mortality, with most data in Western and Middle Eastern countries.[1,4,6–10]

At present, there is limited data on the clinical course, prognostic factors and survival of Asian patients as compared to Western cohorts. w

Our primary aim was to describe and compare the demographics, clinical features, co-morbidities, treatment and disease outcomes of PV and PF in Singapore. We also sought to identify the prognostic factors affecting remission for PV and PF.

Methods

This was a retrospective cohort study. Our study cohort comprised all newly diagnosed Singaporean pemphigus patients seen at the National Skin Centre from 1 April 2004 to 31 December 2009. Patients with either PV or PF were recruited based on the following criteria: i) typical clinical findings of pemphigus; ii) histopathological findings of suprabasilar or subcorneal blister or acantholysis; iii) immunopathology – direct immunofluorescence (DIF) with intercellular deposition of IgG and/or complement 3 in the epidermis; iv) indirect immunofluorescence (IIF) findings with circulating intercellular IgG antibodies or v) positive serum desmoglein 3 and/or desmoglein 1 antibodies. Exclusion criteria included foreign patients as well as patients with other subtypes of pemphigus and any other immunobullous disorders. Desmoglein 3 and desmoglein 1 antibodies were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits (MBL Co. Ltd, Japan). Antibody levels ≥ 20 U/ml were interpreted as positive ELISA results.

Patients were identified through the National Skin Centre's electronic medical and histology records. Data collection was performed by reviewing the case records of the patients to obtain demographic data, medical history, clinical features, laboratory results, treatment details and disease status at last follow-up visit. Patients were then matched with the National Registry of Diseases Office (NRDO) death registry for verification of mortality status. This study was approved by the ethics committee of the National Healthcare Group, Singapore.

The disease status definition was based upon the consensus statement on definitions of disease activity and therapeutic response as proposed by the International Pemphigus Committee in 2008.[11] Remission status was defined at the last visit. Remission on minimal or off therapy was defined as the absence of new or established lesions, or presence of transient new lesions that healed within 1 week, while receiving minimal therapy (i.e. prednisolone ≤ 10 mg/day and/or minimal adjuvant therapy defined as half of the dose required to be defined as treatment failure), or off all systemic therapy, for at least 2 months. Remission during tapering of therapy was defined as the absence of new lesions that did not heal within one week while receiving more than minimal therapy for at least 2 months.

Statistical Analysis

Continuous variables were summarised using medians with ranges and were compared using Mann-Whitney U test. Categorical variables were summarised using counts with percentages and were compared using Fisher's exact test. Time to remission was examined using Cox proportional hazard model which is a time-to-event survival analysis that is able to deal with miss-to-follow-up data using censoring. Predictors with P-value < 0.2 from the univariate Cox proportional hazard model that did not cause convergence problem were included in the final multivariate model. Hazard ratios with 95% confidence intervals (CI) were reported. Significance was assessed at a level of 0.05. All statistical analyses were performed using IBM SPSS Statistics 24.

Results

Demographic and clinical features

A total of 36 patients with PV and 25 patients with PF were included in the study. There were 20 (55.6%) females and 16 (44.4%) males in the PV group, compared to 9 (36.0%) females and 16 (64.0%) males in the PF group (P = 0.193; Table 1). The median age at which PV was diagnosed was 53.7 years (range 22.3–86.9 years), similar to that of PF at 52.1 years (range 27.2–78.8 years). PV patients had a significantly longer median duration of follow-up (range) of 4.7 (0.2–8.4) years, compared to PF of 3.6 (0.0–8.5) years, P = 0.026. The ethnic distribution in patients with PV versus PF was similar: 24 (66.7%) versus 17 (68.0%) Chinese, 4 (11.1%) versus 3 (12.0%) Malay, 5 (13.9%) versus 4 (16.0%) Indian and 3 (8.3%) versus 1 (4.0%) of other ethnicities, P = 0.969. Generalised lesions (defined as affecting more than one body site, in contrast to localised pemphigus affecting only one body site) were predominant in both PV (94.4%) and PF (96.0%). Lesions were predominantly mucocutaneous (77.8%) in the PV group but cutaneous

Table 1. Clinical characteristics and treatment summary of PV and PF patients

	PV (n = 36)	PF (n = 25)	*P* value
Male	16 (44.4%)	16 (64.0%)	0.193
Female	20 (55.6%)	9 (36.0%)	
Median age of diagnosis, years	53.7 (22.3, 86.9)	52.1 (27.2, 78.8)	0.936
Median follow-up duration, years	4.7 (0.2, 8.4)	3.6 (0.0,8.5)	0.026
Race			
Chinese	24 (66.7%)	17 (68.0%)	0.969
Malay	4 (11.1%)	3 (12.0%)	
Indian	5 (13.9%)	4 (16.0%)	
Other	3 (8.3%)	1 (4.0%)	
Localised	2 (5.6%)	1 (4.0%)	1.000
Generalised	34 (94.4%)	24 (96.0%)	
Mucocutaneous involvement	28 (77.8%)	-	<0.00001
Cutaneous involvement	8 (22.2%)	25 (100%)	
Positive direct immunofluorescence	34 (94.4%)	25 (100%)	1.000
Missing	-	-	
Positive IIF	27 (87.1%)	18 (85.7%)	1.000
Missing	5	4	
IIF median titres	160 (20, 160)	160 (20, 160)	0.336
Dsg 1 antibody positivity at diagnosis	27 (87.1%)	21 (90.5%)	1.000
Missing	5	4	
Dsg 1 median antibody titre at diagnosis (IU/ml)	94 (4, 300)	137 (1, 283)	0.097
Dsg 3 antibody positivity at diagnosis	29 (93.5%)	2 (9.5%)	<0.00001
Missing	5	4	
Dsg 3 median antibody titre at diagnosis (IU/ml)	148 (1, 300)	36.25 (29, 43.5)	<0.00001
Co-morbidities	16 (44.4%)	11 (44.0%)	1.000
Hypertension	10 (27.8%)	5 (20.0%)	0.557
Hyperlipidemia	10 (27.8%)	3 (12.0%)	0.206
Diabetes mellitus	4 (11.1%)	2 (8.0%)	1.000
Stroke	2 (5.6%)	1 (4.0%)	1.000
Cardiovascular disease	3 (8.3%)	0 (0%)	0.262
Gastrointestinal disease	2 (5.6%)	0 (0%)	0.512
Prior malignancy	2 (5.6%)	0 (0%)	0.512
Renal disease	1 (2.8%)	1 (4.0%)	1.000
Lung disease	1 (2.8%)	0 (0%)	1.000
Thyroid disease	0 (0%)	0 (0%)	-
Remission during tapering of therapy at last visit	9 (25.0%)	5 (20.0%)	1.000
Remission on minimal/off therapy at last visit	23 (63.9%)	15 (60.0%)	
Corticosteroid only	12 (33.3%)	12 (48.0%)	0.294
Initial corticosteroid dose, mg/kg/day	0.7 (0.5, 1.0)	0.6 (0.4, 1.0)	
Median corticosteroid dose, mg/kg	40 (20,80)	30 (20,50)	
Use of other immunosuppressants	24 (66.7%)	13 (52.0%)	0.189
Azathioprine	19 (52.8%)	1 (4.0%)	<0.00001
Dapsone	10 (27.8%)	13 (52.0%)	0.175
Mycophenolate mofetil	3 (8.3%)	-	
Cyclophosphamide	2 (5.6%)	-	
Intravenous immunoglobulin	2 (5.6%)	-	
Rituximab	1 (2.8%)	-	

Results are presented as n (%) or median (minimum, maximum) Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus, IIF: indirect immunofluorescence, Dsg: desmoglein

in the PF group. There was no significant association between anti-desmoglein antibody titres and generalised versus localised disease, or mucocutaneous versus cutaneous disease.

Diagnosis

All patients had histological findings of suprabasilar and subcorneal blistering for PV and PF, respectively. In the PV group, 22 patients fulfilled all 5 diagnostic criteria (i–v) above, 13 fulfilled 4 criteria and 1 fulfilled 3 criteria. Almost all had positive DIF except for 2 PV patients who were diagnosed based on characteristic clinicopathological findings, positive IIF and desmoglein 3 titres. In the PF group, 16 patients fulfilled all 5 criteria, 7 fulfilled 4 criteria and 2 fulfilled 3 criteria.

There was no significant difference in IIF positivity between PV and PF patients: 87.1% (27/31) versus 85.7% (18/21), $P = 1.000$. Out of 31 PV and 21 PF patients who had desmoglein serologies sent at diagnosis, 87.1% and 90.5% had desmoglein 1 positivity, respectively ($P = 1.000$). Their median desmoglein 1 titres at diagnosis were 94 IU/ml versus 137 IU/ml $P = 0.097$). The PV group had a median desmoglein 3 titre at diagnosis of 148 IU/ml.

Associated Diseases

The most common co-morbidities in PV compared to PF were: hypertension (27.8% versus 20.0%), hyperlipidemia (27.8% versus 12.0%), diabetes mellitus (11.1% versus 8.0%) and stroke (5.6% versus 5.0%). Cardiovascular disease (8.3%), gastrointestinal disease (5.6%) and prior malignancy (5.6%) were present in the PV patients, but absent in the PF group.

Treatment Regimes

Systemic treatment for PV included combination therapy of oral corticosteroid (100%) and non-steroidal immunosuppressants (94.4%), comprising azathioprine (52.8%), dapsone (27.8%), mycophenolate mofetil (11.1%), cyclophosphamide (5.6%), intravenous immunoglobulin (5.6%) and rituximab (2.8%). The majority were started on systemic non-steroidal immunosuppressants in addition to oral corticosteroid to control the disease activity. Of note was the significantly greater use of azathioprine found in PV (52.8% versus only 4.0% in PF, $P < 0.00001$). However, dapsone was used in both PF (48.0%, $P = 0.175$) and PV (27.8%).

Only 33.3% PV patients were on oral corticosteroid monotherapy for the entire duration of disease with moderate to high initial dose of prednisolone (0.5 to 1 mg/kg/day) used to treat PV, at a mean initial dose of 0.7 mg/kg/day. Within this group, 16.7% had localised disease and 25.0% had no mucosal involvement, whereas all PV patients who received combination therapy had generalised disease, with 20.8% having no mucosal involvement. Comparatively, 48.0% of PF patients received prednisolone monotherapy for the entire duration of disease with a mean initial dose at 0.6 mg/kg/day (range 0.4 to 1 mg/kg/day). Ninety six percent of all PF patients had generalised cutaneous disease at presentation.

Remission Outcomes

There was no significant difference in time to overall remission at last visit between PF (median time to remission 3.95 years, 95% CI 3.27–5.45) and PV (median time to remission 4.91 years, 95% CI 4.14–6.18) ($P = 0.30$). The majority of PV and PF patients achieved disease control (Table 2). Four PV patients (11.1%) and 5 PF patients (20.0%) remained with active disease at the last follow-up. Amongst the PV patients with active disease, 3 (75.0%) were treated with combination therapy (2 with prednisolone and azathioprine, 1 with prednisolone, azathioprine, dapsone, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin, rituximab sequentially) and 1 with prednisolone monotherapy (1.1 kg/mg/day). In contrast, all 5 PF patients with active disease were treated with oral prednisolone monotherapy.

Twenty-three PV patients (63.9%) attained remission on minimal or off therapy at last visit compared to 15 PF patients (60.0%). Seventeen of these PV patients (73.9%) received combination therapy, most commonly with azathioprine (76.5%, n=13), followed by dapsone (41.2%, n=7), mycophenolate mofetil (11.8%, n=2), cyclophosphamide (5.9%, n=1) and intravenous immunoglobulin (5.9%, n=1). Nine of the above PF patients (60.0%) received combination therapy, most commonly with prednisolone and dapsone (88.9%, n=8) and 1 patient with prednisolone and azathioprine.

Survival

Using data from the national registry of deaths, we had complete verification of the death status of all patients. At 3 years of follow-up, all PV and PF patients were alive.

Table 2. Remission outcomes at last visit in PV and PF patients

	PV (n = 36)	PF (n = 25)
Median time to overall remission	4.91 years (95% CI: 4.14, 6.18)	3.95 years (95% CI: 3.27, 5.45)
Active disease	4 (11.1%)	5 (20.0%)
Corticosteroid monotherapy	1 (25.0%)	5 (100%)
Use of other immunosuppressants	3 (75.0%)	-
Azathioprine	2 (66.7%)	-
Azathioprine, dapsone, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin, rituximab sequentially	1 (33.3%)	-
Remission on minimal/off therapy	23 (63.9%)	15 (60.0%)
Corticosteroid monotherapy	6 (26.1 %)	6 (40.0%)
Use of other immunosuppressants	17 (73.9%)	9 (60.0 %)
Azathioprine	13 (76.5%)	1 (11.1%)
Dapsone	7 (41.2%)	8 (88.9%)
Mycophenolate mofetil	2 (11.8%)	-
Cyclophosphamide	1 (5.9%)	-
Intravenous immunoglobulin	1 (5.9%)	-

Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus
Median time to remission is the average time when 50% patients reach remission.

Factors Associated with Remission at Last Visit

In patients with PV, higher initial prednisolone dose (mg/kg/day) (hazard ratio 1.1, 95% CI 1.01–1.15, $P = 0.017$) and use of azathioprine (hazard ratio 10.05, 95% CI 1.28–78.64, $P = 0.028$) were predictive of attaining overall remission (Table 3). However, higher desmoglein 1 antibody titres at diagnosis (hazard ratio 0.98, 95% CI 0.95–0.99, $P = 0.024$) and the use of dapsone (hazard ratio 0.04, 95% CI 0.003–0.412, $P = 0.008$) were negatively associated with overall remission.

Among PF patients, only higher desmoglein 1 antibody titre at diagnosis (hazard ratio 0.97, 95% CI 0.94–0.99, $P = 0.041$) was negatively associated with achieving overall remission (Table 4). Although IIF titre was found to have a statistically significant P value = 0.014, both the hazard ratio and 95% CI closely overlapped with null.

Generalised versus localised disease (as a proxy marker of clinical severity) was not significantly associated with attaining overall remission in both PV and PF patients. Similarly, the presence of mucosal lesions in PV patients was not significantly associated with attaining overall remission.

Discussion

In the present study, we report on the clinical course, co-morbidities, treatment regimes and prognostic factors of pemphigus. PV was the more common subtype found in patients (56.2%), versus PF (43.8%), consistent with reported studies.[4–6,8–9,12–17] The mean age of diagnosis for PV (53.1 years) and PF (54.5 years) in our study was comparable to other studies in both Asian and western cohorts.[1,4,7–9,12–14,16–18] The female-to-male ratio of 1.3 among patients with PV was similar to that reported from China, Korea, India, Israel, Tunisia, Turkey, UK, France and Finland with an overall female predominance.[1,4–7,9–10,12–17,19–22] However, we noted a male preponderance (female-to-male ratio of 0.6) in patients with PF, which was evident in an earlier study of pemphigus in Singapore.[5] Several studies of PF in Israel, Brazil and India also had a female-to-male ratio of 0.5, 0.3 and 0.16, respectively.[9,17,23] Other studies have, however, reported a female predilection.[8,10,13,14] The reason for this female predominance is largely unexplained, although a female predominance is seen in other autoimmune diseases. In both PV and PF, there was no particular

Table 3. Results of univariate and multivariate analyses on attaining overall remission at last visit in PV

Risk factor	Univariate Analysis (Cox Regression)		Multivariate Analysis[1,2] (Cox Regression)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	1.01 (0.48, 2.15)	0.97	0.22 (0.02, 2.08)	0.19
Female				
Age, years	1.00 (9.97, 1.03)	0.87	1.05 (0.96, 1.15)	0.32
Ethnicity				
Chinese	0.82 (0.38, 1.79)	0.62	0.37 (0.07, 2.02)	0.25
Others				
Lesion distribution				
Localised	2.83 (0.65, 12.44)	0.17	3.40 (0.09, 130.98)	0.51
Generalised				
Mucosal lesions				
Present	1.45 (0.62, 3.40)	0.39	2.58 (0.22, 30.29)	0.45
Absent				
IIF titre	1.00 (0.99, 1.01)	0.55	1.00 (0.97, 1.02)	0.85
Initial corticosteroid dose (mg/day)	1.01 (0.98, 1.03)	0.68	**1.08 (1.01, 1.15)**	**0.017**
Desmoglein 1 titre at diagnosis (IU/ml)	1.00 (0.99, 1.01)	0.84	**0.98 (0.95, 0.99)**	**0.024**
Desmoglein 3 titre at diagnosis (IU/ml)	1.00 (1.00, 1.01)	0.59	1.02 (1.00, 1.04)	0.036
Azathioprine				
Yes	1.68 (0.81, 3.50)	0.17	**10.05 (1.28, 78.64)**	**0.028**
No				
Dapsone				
Yes	0.51 (0.23, 1.16)	0.11	**0.04 (0.003, 0.41)**	**0.008**
No				
Mycophenolate mofetil				
Yes	0.92 (0.22, 3.94)	0.91	17.44 (0.99 – 306.57)	0.05
No				
Hypertension				
Yes	0.88 (0.40, 1.93)	0.76	2.55 (0.11, 59.02)	0.56
No				
Diabetes				
Yes	0.50 (0.15, 1.69)	0.26	4.13 (0.11, 157.27)	0.45
No				

[1]Variables significant *at P* < 0.2 in the univariate analysis were considered for inclusion in the final multivariate analysis
[2]For each risk factor, the last group is the reference group for calculating the hazard ratio in the Cox regression analysis
Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus, IIF: indirect immunofluorescence

Table 4. Results of univariate and multivariate analyses on attaining overall remission at last visit in PF

Risk factor	Univariate Analysis (Cox Regression)		Multivariate Analysis (Cox Regression) [1,2]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	1.41 (0.56, 3.52)	0.47	0.23 (0.02, 3.03)	0.27
Female				
Age, years	1.02 (0.98, 1.05)	0.34	1.05 (0.95, 1.17)	0.34
Ethnicity				
Chinese	0.49 (0.17 to 1.42)	0.19	-	-
Others				
Lesion distribution				
Localised	1.28 (0.17, 10.00)	0.81	-	-
Generalised				
IIF titre	1.01 (1.00, 1.02)	0.01	1.04 (1.00, 1.07)	0.014
Initial corticosteroid dose (mg/day)	0.96 (0.92, 1.01)	0.08	1.08 (0.94, 1.24)	0.304
Desmoglein 1 titre at diagnosis (IU/ml)	1.00 (0.99, 1.01)	0.85	**0.97 (0.94, 0.99)**	**0.041**
Azathioprine				
Yes	0.04 (0.00, 21.77)	0.31	-	-
No				
Dapsone				
Yes	1.55 (0.60, 3.97)	0.36	0.85 (0.08, 9.74)	0.90
No				
Hypertension				
Yes	1.23 (0.44, 3.46)	0.70	0.71 (0.06, 8.32)	0.79
No				
Diabetes				
Yes	3.92 (0.79, 17.60)	0.10	-	-
No				
Hyperlipidemia				
Yes	5.07 (1.18, 21.77)	0.03	-	-
No				

[1]Variables significant *at* $P < 0.2$ in the univariate analysis were considered for inclusion in the final multivariate analysis
[2]For each risk factor, the last group is the reference group for calculating the hazard ratio in the Cox regression analysis
Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus, IIF: indirect immunofluorescence

racial predilection, with the distribution similar to the national racial demographics. Mucocutaneous involvement was seen in 77.8% patients with PV at initial presentation, in keeping with earlier studies.[9–10,12–13,15–16,19–20]

We note that Indians (13.9% in PV and 16.0% in PF) may be over-represented in our study. The ethnic composition of Singapore's resident population from 2008 to 2018 was about 74% Chinese, 13% Malays, 9% Indians and 3% Others. The reason for this is unclear, but we postulate that this may be due to our small sample size.

In terms of co-morbidities, we noted more patients with PV having hyperlipidaemia (27.8%) compared to patients with PF (17.9%), although this was not statistically significant. The prevalence of hypercholesterolemia in Singapore was reported to be 17.4% in 2010.[24] Other studies have also reported similar associations with hypertension, diabetes and hyperlipidaemia.[5,8,12,15,25–26] None of the pemphigus patients in our study was reported to have thyroid disorders, contrary to previous reports.[9,15,19,25,26] Two PV patients had prior malignancy of nasopharyngeal cancer and breast ductal carcinoma in situ, respectively. Although previous studies[27] had suggested an association of PV with internal malignancy, no significant association was found in our study.

The overall remission on minimal or off therapy at last visit was 63.9% for PV patients and 60.7% for PF patients in our study, comparable to between the 50% rate reported for complete remission off therapy[6,28] and the 70–80% reported for complete remission on minimal therapy.[29] Another study reported higher remission on minimal or off therapy at 70% and 83% for PV and PF patients, respectively.[17]

There was no significant difference in the initial median corticosteroid dose or remission between PV and PF in our study, although PV patients had a significantly longer follow-up period. This is in contrast to the earlier study in Singapore where PV was shown to be a more severe disease than PF, as indicated by the higher dose of corticosteroids required for disease control, longer duration to achieve complete remission and longer follow-up period.[5] However, other studies have reported that PV and PF follow a similar clinical course and prognosis.[8,10,14,20] Significantly, more than half of PV patients were treated with azathioprine compared to only 7.1% of PF patients. Azathioprine is a well-established choice of adjuvant treatment for management of PV.[30–31]

All patients in our study had completed 3 years of survival as verified with the national registry of death records. An earlier study conducted at the National Skin Centre, Singapore, from 1995 to 1997 saw a 12% mortality in the 3-year period.[5] A French study reported 1-, 2- and 5-year survival at 90%, 85% and 82%, respectively.[6] However, other studies have found lower mortality. A Korean study showed mortality to be 6.5% among 199 PV and PF patients during a 16-year follow-up period from 1993 to 2008,[13] with the commonest cause of death being sepsis. In a study in Thailand, there was only 2.4% mortality from 1993 to 1999 (only among the PV patients), resulting from sepsis as a complication of high-dose corticosteroids.[14] Another study in Israel[7] also found mortality rate to have decreased from 22% during 1960 to 1980, to 10% during 1976 to 2004, and none of the deaths was directly related to pemphigus or complication of treatment (mainly cancer (occurring years after diagnosis of pemphigus) and ischemic heart disease). It was suggested that the increased use of adjuvant therapy[32] and improved management of disease and treatment side-effects contributed to this finding. The better survival rate in our study may be attributed to the use of moderate dose of corticosteroids and increased use of adjuvant non-steroid immunosuppressants prescribed in our centre. The trend for improved survival is also corroborated by a recent study in India, which observed only 1 death from pulmonary embolism, over an average of 2.7 years of follow-up (0.01% mortality) during 1991–2013.[17]

We have tried to evaluate factors associated with remission in this study. However, as this was a retrospective study, definitive documentation of certain endpoints of pemphigus (for instance, transient new lesions healing within a week), which are primarily derived for use in prospective trials, was not possible in all cases. Thus, the following discussion regarding prognostic factors needs to be considered in this light.

We found that age,[8,17] gender,[8,17,20] ethnicity and mucosal involvement[17,20] were not prognostic factors for remission, similar to various studies, although some other groups have found that age,[6,7,20,22] ethnicity,[7,20,33] and initial mucosal involvement[6,7,8,21,32,34] had an impact on prognosis.

Patients with PV and PF who had higher desmoglein 1 antibody levels at diagnosis in our study had significantly lower overall remission at last visit.

A previous study of survival prognosis demonstrated that PV patients with higher anti-desmoglein 1 antibodies achieved a lower overall survival, although this was not reflected among patients with PF.[22] We postulate that increased desmoglein 1 titres may reflect increased disease severity, with higher resistance to therapy and longer time to attain remission. Desmoglein 3+/1+ profile in PV patients has been associated with more severe disease, with additional desmoglein 1 predicting severe cutaneous involvement in additional to mucosal involvement.[35]

In another study, high desmoglein 3 antibody levels at baseline (>100), as compared to 0–29 (negative) and 30–100 (low-medium level), were indeed associated with a longer total disease duration.[20] However, our study did not demonstrate an association between desmoglein 3 antibody levels and remission at last visit, possibly because most of our PV patients (86.2%) had high absolute desmoglein 3 antibody levels (>100) at diagnosis, so this may have restricted the evaluation of a relationship. Further studies are needed to evaluate the roles of desmoglein 3 and 1 as prognostic markers.

Our data also indicated that an initial higher prednisolone dose and use of azathioprine were associated with achieving overall remission at last visit for PV patients. However, we did not control for the tapering schedule of corticosteroids and disease duration in our analysis. Hence, their prognostic impact on remission might be confounded. One study comparing high dose oral prednisone versus low dose prednisone plus azathioprine did report significantly longer time for disease control and remission with the latter group.[36] However, other studies revealed no improvement in disease duration or time to remission with high doses of prednisolone, possibly owing to the associated morbidity.[17,20,32] Co-administration of azathioprine was found to reduce the cumulative corticosteroid dose and displayed a superior steroid-sparing effect compared to mycophenolate mofetil.[30, 37, 38] However, another study showed that prednisolone alone allowed earlier complete remission than prednisolone with adjuvant treatment among patients with PF,[13] although this was confounded by the difference in initial disease severity.

The use of dapsone among PV patients was negatively associated with overall remission at last visit in our study. However, this association might be confounded because dapsone was used as an adjuvant treatment in recalcitrant cases, in combination with other agents, instead of being first-line therapy. Out of the 8 PV patients who received dapsone (whilst on concomitant oral corticosteroid), 3 had received azathioprine earlier (2 of whom had recalcitrant disease requiring subsequent use of other adjuvant therapy) and 3 had received dapsone as an initial steroid-sparing treatment before requiring azathioprine.

The strengths of this study include comprehensive patient data capture at a national dermatology referral centre, detailed recorded information including co-morbidities, long-term follow-up and complete verification of 3-year mortality status with the national registry of deaths.

The limitations include the small sample size and retrospective nature of the study, in which specific impact of disease severity or combination of immunosuppressive agents on prognosis could not be evaluated. Disease severity was not assessed as this was a retrospective study and there was no published validated severity scoring system at the time of study initiation. While treatment protocols were standardised as far as possible, selection bias of treatment including physician preference, patient characteristics and co-morbidities would be expected. Factors including the tapering schedule of corticosteroids and disease duration were also not controlled for in our analysis.

In conclusion, this is a long-term follow-up study illustrating the clinical characteristics and their influence on prognosis of Asian PV and PF patients. Higher initial prednisolone dose and use of azathioprine in PV as well as lower desmoglein 1 antibody titre at diagnosis in PV and PF might be prognostic markers for achieving remission. The use of dapsone was associated with lower overall remission in PV but this might be confounded because dapsone was used as an adjuvant therapy in recalcitrant cases, instead of being first-line therapy. Overall, owing to the study methodology and limitations, further evaluation is needed for better prognostication of pemphigus.

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Review Article

Current Status of Laparoscopic and Robotic Pancreatic Surgery and Its Adoption in Singapore

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Abstract

Despite the potential clinical advantages offered by laparoscopic pancreatic surgery (LPS), the main obstacle to its widespread adoption is the technically demanding nature of the procedure and its steep learning curve. LPS and robotic pancreatic surgery (RPS) have been proven to result in superior short-term perioperative outcomes and equivalent long-term oncological outcomes compared to the conventional open approach, with the caveat that they are performed by expert surgeons who have been trained to perform such procedures. The primary challenge faced by most pancreatic surgeons is the steep learning curve associated with these complex procedures and the need to undergo surgical training, especially with regards to laparoscopic and robotic pancreaticoduodenectomy. Current evidence suggests that RPS may help to shorten the lengthy learning curve required for LPS. More robust evidence—in the form of large randomised controlled trials—is needed to determine whether LPS and RPS can be safely adopted universally.

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Introduction

Pancreatic surgery is considered one of the most complicated and treacherous procedures in the abdominal cavity since it is associated with high morbidity and mortality rates.[1,2] Even with major advancements in surgical technique and perioperative care, the morbidity rate of pancreatic surgery in high-volume expert centres remains high at >50% even as its mortality rate drops to <5%.[1–3] Consequently, despite the "revolution"— minimally invasive surgery (MIS)—in abdominal surgery that took place in the 1990s and early 21st Century, the adoption and practice of MIS in pancreatic surgeries remain limited.

Laparoscopic surgery is associated with several inherent limitations, including diminished haptic feedback, reduced dexterity and decreased natural hand-eye coordination. Any attempt to perform surgery on a patient while observing a 2-dimensional screen is counter-intuitive and compromises hand-eye coordination (fulcrum effect).[4,5] Furthermore, laparoscopic instruments have a limited range of motion, diminished dexterity and may augment physiological tremor. Consequently, robotic surgery was introduced to overcome the limitations posed by laparoscopic surgery.[6,7] Until recently, the only robotic-assisted surgical platform that was widely available

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around the world was the Da Vinci system offered by Intuitive Surgical, Inc. (Sunnyvale, CA, USA) which offered the advantages of a 3-dimensional view (that offsets the loss of hand-eye coordination in laparoscopic surgery), 7 degrees of freedom that replicate human movement with superior dexterity, elimination of physiological tremor and ergonomic comfort.[4,5] In theory, the advantages of this robotic platform would translate into superior fine suturing and dissection that are frequently required in major pancreatic surgery, especially pancreaticoduodenectomy (PD).[8,9]

Although the first laparoscopic pancreatic surgery (LPS) was performed in the early 1990s,[10] the adoption of LPS remained slow; it was only in the past decade that a significant increase in the adoption of LPS by surgeons from around the world was observed.[11] Compared to the open approach, LPS is reported to provide the added benefits of smaller incisions with better cosmetic results, lower level of postoperative pain and estimated blood loss, shorter hospital stay and recovery time with equivalent morbidity and overall mortality rate.[12–18] It is, however, important to emphasise that most of the evidence that supported the use of LPS is limited to retrospective case-control studies,[12–18] and only 4 randomised controlled trials (RCT) had been performed to date.[19–22]

Despite the clinical advantages offered by LPS, the major obstacle to its widespread adoption is the technically demanding nature of the procedure and its steep learning curve.[23] This is attributed to the retroperitoneal location of the organ, its proximity to major vasculature and high propensity for complications such as pancreatic fistula and bleeding. Moreover, major pancreatic surgeries are relatively rare procedures in most tertiary health institutions, making it difficult for many surgeons to obtain sufficient case volume to attain proficiency.

Distal Pancreatectomy

Distal pancreatectomy (DP) is performed for tumours or pathologies that involve the body and tail of the pancreas.[2] For technical reasons, a concomitant splenectomy is also performed since the splenic artery and vein are closely related to the pancreas with many small branches and tributaries that communicate between the pancreas and these vessels. Since DP is technically more simple to perform than PD, laparoscopic distal pancreatectomy (LDP) is therefore more widely performed than laparoscopic pancreaticoduodenectomy (LPD).[5] DP has been proposed as an ideal surgical procedure for MIS as unlike PD, it does not require any complex reconstruction.[5,24]

Nonetheless, as a minimally invasive procedure, LDP remains technically challenging and complex, and has been reported to be associated with an open conversion rate of up to 38% by even reputable high-volume tertiary centres.[25] Studies have shown that LDP offers several advantages over open surgery, especially in short-term perioperative outcomes including less postoperative pain, quicker recovery and decreased blood loss.[12–14,26,27] However, most of these studies were retrospective case-control series. In the only RCT (LEOPARD) that compared minimally invasive DP and open DP by the Dutch Pancreatic Cancer Group, Rooij et al found that the former was significantly associated with decreased blood loss and reduced time to functional recovery at the expense of longer operating time.[21] Similarly, a recent large international cohort study that analysed 1562 minimally invasive DP with 18% open conversion vs 1359 open DP from the American College of Surgeons National Quality Improvement Program demonstrated a risk reduction rate of 11% in composite major morbidity.[27]

Although DP is commonly performed with *en bloc* splenectomy, recent studies have recommended spleen preservation since it reduces the risk of postsplenectomy infection and thrombocytosis, haematologic abnormalities and overall morbidity.[28,29] Most pancreatic surgeons concur that the spleen should be preserved as far as possible in benign and borderline malignant neoplasms,[5,22] and 2 techniques have been described for spleen-preserving DP: 1) in the Warshaw technique, the splenic artery and vein are resected, leaving only the short gastric vessels for perfusion of the spleen; and 2) in the Kimura technique, the splenic vessels are spared.[5] Technically, splenic vessel preservation procedures are more demanding since they require meticulous separation of the splenic vessels from the pancreatic parenchyma and ligation of numerous branches of the splenic vessels supplying the pancreas. Consequently, operating time and blood loss tend to be higher. The Warshaw technique, however, is associated with a higher incidence of splenic infarction and left-sided portal hypertension with gastric varices.[24]

Numerous retrospective studies have shown that a major advantage of robotic distal pancreatectomy (RDP) over LDP is that it offers superior spleen preservation rate.[25–34] It is hypothesised that improved dexterity of the robotic system facilitates suturing in

tight spaces and more accurate control of the splenic tributaries, thereby allowing more accurate dissection of splenic vessels from the pancreatic parenchyma.[4,5] These advantages improve the rate of spleen and splenic vessel preservation in DP.

Another advantage of the robotic platform is the lower open conversion rate to open surgery compared to laparoscopic surgery, especially during the learning phase.[35] Conversion to the open procedure is undesirable since it mitigates the advantages of MIS, resulting in increased operating time, intraoperative blood loss and need for blood transfusion, higher complication rates and longer hospital stay.[25,26,36] It is, however, important to emphasise that no RCT has been performed to compare LDP with RDP, and that numerous confounding factors—such as selection bias and learning curve—could have accounted for the findings of these non-randomised studies.

Pancreaticoduodenectomy

Tumours that are located in the periampullary region require formal resection via PD. As a result of the highly complex manipulations that are required during resection and anastomoses thereafter, the minimally invasive surgical approach is only performed by a few pancreatic surgeons in high-volume centres.[37–42] In 1994, Gagner et al[10] reported the first study of LPD; however, the steep learning curve of LPD led to its slow adoption compared to LDP. Even today, the practice of MIS in PD is limited and remains controversial, given the technical complexity of the procedure and lack of perceived advantages over the open approach.

A few large series of LPD[37–9] and robotic pancreaticoduodenectomy (RPD)[40,41] from high-volume centres had reported excellent results associated with MIS. To the best of our knowledge, 3 RCT[19,20,22] had evaluated short-term outcomes of LPD against open PD, but with mixed results. While 2 single-centre RCT from India and Spain[19,20] reported short-term benefits associated with LPD including decreased blood loss and shorter hospital stay at the expense of longer operating time, a multicentre RCT from the Netherlands was forced to cease prematurely over concerns of safety after a high mortality rate was observed in the MIS arm.[22] The findings of these 3 studies suggested that LPD offers advantages over the open approach only when it is performed by experienced surgeons; when LPD is performed by inexperienced surgeons, higher morbidity and even mortality may result.[22] These findings were corroborated by other single-centre retrospective studies that demonstrated the advantages of MIS when it is performed by more experienced centres, and increased morbidity when MIS is undertaken by less experienced centres.[43]

There is growing evidence that robotic pancreatic surgery (RPS) is potentially superior to LPS, especially for more complex procedures such as PD. A recent multicentre study in North America had shown that RPS was associated with a lower open conversion rate than LPS for both DP and PD.[44] Another multicentre study in the United States demonstrated that RPS could be practised safely and yielded similar anastomotic and overall complications rates compared to the open approach even during the initial learning phase.[45] The superior steadiness, precision and dexterity associated with the robotic platform allow fine, accurate dissection and suturing in confined spaces.[4,8,9] These advantages of the robotic platform will potentially shorten the learning curve for the performance of complex anastomoses in minimally invasive pancreaticoduodenectomy (MIPD) such as pancreatoenteric anastomoses and hepaticojejunostomy compared to conventional laparoscopy. This is especially relevant to minimally invasive hepatopancreatobiliary surgeons who practise in countries that have a small population, and who will never acquire the experience and surgical volumes that surgeons in more populous countries such as China and the United States will have.

Learning Curve in LPS and RPS

A major obstacle to the widespread adoption of minimally invasive pancreatic surgery (MIPS)—especially MIPD—is its steep learning curve.[46] In the literature, several authors have addressed the learning curve of LDP. Depending on the outcome measure, it was reported to be as low as from 10–15 procedures[47,48] for open conversion and up to 40 procedures for reduction in operating time.[49] The learning curve of RDP was reported to be shorter than LDP,[50] with 2 studies[51,52] reporting a learning curve of only 5–10 cases for reduction in operating time.

For LPD, a single-surgeon study[53] that used cumulative sum (CUSUM) chart analysis reported a minimum of 40 procedures before the learning curve—in terms of operating time and blood loss—was completed. Another study from South Korea reported improvements in operating time and postoperative morbidity after approximately 30–60 procedures.[54]

Several studies have analysed the learning curve of RPD. The learning curve of a surgeon—in terms of operating time—was reported to range from between 10–33 procedures.[52,55] For institutions, the learning curve—in terms of blood loss and conversion rate—was shown to improve after 20 procedures, and 20–80 procedures were needed before an improvement in operating time was seen.[56–8]

The varied findings of different studies have highlighted the difficulty in defining the learning curve of a surgical procedure including MIPS. Various factors can affect this "magic number", including the statistical method used (such as CUSUM), outcome measure (such as blood loss, operating time, morbidity and conversion rate), single surgeon vs institutional data, study cohort size and the surgeon's proficiency and experience in MIS and open surgery.[46] Consequently, it is almost impossible to determine the exact number of procedures that are required to complete the learning curve in order to achieve proficiency. It is also very unlikely that the personal learning curves of surgeons will be uniform across indivduals.[46]

The inverse association between institution volume and surgical outcomes is well documented in complex surgeries such as pancreatic surgery.[23,59,60] The volume-outcome effect is seen in MIPS, especially MIPD.[61,62] Current data suggest that MIPD is associated with higher mortality in centres that perform <10 cases a year.[23,46,61,62] This finding is especially relevant to many institutions whose pancreatic centres do not see a high volume of procedures, unlike those in China and the United States. To bridge the wide gulf between the open approach and MIPD, several surgeons have proposed a hybrid technique for the learning curve. This technique is shown to be a safe approach that allows surgeons to make the transition from open PD to MIPD.[63–6]

Limitations of RPS

Despite the theoretical and potential advantages that robotic surgery offers, its widespread use is limited by its high cost that has curtailed accessibility to the robotic platform.[8] Globally, only a few centres[4,15,31] have reported their experiences with RPS. The high cost of acquiring and maintaining this platform has meant that few surgeons from around the world have regular access to this technology for training purposes. This has led to a lack of familiarity and experience with RPS, and few surgeons are willing to attempt complicated robotic procedures such as RPS. It is worthwhile to highlight that with increased adoption and competition, the costs of new technological applications or devices are likely to decrease exponentially with the passage of time.

LPS and RPS in Singapore

In Singapore, the practice of MIPS had grown in the last decade although most pancreatic surgeries are still being performed using the conventional open approach. Earlier studies had reported exclusively on DP but not PD. In 2009, the first study on LPS was published after it reported on 3 patients who underwent spleen-preserving DP.[67] Subsequently, larger series on LDP and RDP were published.[33,68] In 2016, the first study on RPS was published after it reported on 3 cases of spleen-saving, vessel-preserving DP in the Singapore General Hospital (SGH).[29] In a subsequent update in 2018, SGH reported on its experience with 30 RPS: the open conversion rate was only 3.3% and the major (Clavien-Dindo grade >2) morbidity rate was 23.3% with no mortality. [4] These findings established the feasibility and safety of RPS.

In recent years, several case series on LPD and RPD were published. In 2019, SGH reported its first case series of 7 RPD.[66] In a subsequent report of 27 cases of LPD and RPD,[9] it found that the robotic approach allowed surgeons to make the transition from the hybrid approach to the totally MIS approach more quickly in their learning curves. In the same year, Tan et al[65] reported their experience with laparoscopic-assisted pancreaticoduodenectomy (hybrid approach) and described it as a bridge to the totally MIS approach.

Recently, SGH reported its initial experience with 150 MIPS.[69] It found a rapid growth in the practice of MIS in the past 6–7 years and >90% of procedures were performed since 2012. It also noted an increase in the number of complex MIPS that were performed such as LPD and RPD. In their recent study on robotic hepatopancreatobiliary surgery in Singapore, Lee et al[70] reported that as of February 2018, 46 RPS—including 18 RPD—were performed in 2 institutions across Singapore.

Although the number of MIPS is increasing,[69] most procedures—especially LPD and RPD—are routinely performed by a small number of surgeons. In a small country such as Singapore, the primary challenge faced by pancreatic surgeons is the steep learning curve of these complex procedures and their low numbers. Possible solutions may include centralisation of major pancreatic surgeries in a single centre and the adoption of robotic surgery that has been shown to shorten the learning curve, especially in PD.[71] Institutions that

have been performing MIPS should be supported and incentivised to encourage more institutions and pancreatic surgeons to practise MIPS. The introduction of dedicated and structured training programmes and availability of expert proctors are also critical to promote LPS and RPS.[23]

Conclusion

LPS and RPS are rapidly gaining acceptance and practice from around the world and will undoubtedly become the gold standard in pancreatic surgery in the near future, especially in high-volume pancreatic surgery centres. More large and robust RCT are needed to determine whether LPS and RPS can be safely practised globally.

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Commentary

Autism Spectrum Disorder and COVID-19: Helping Caregivers Navigate the Pandemic

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The coronavirus disease 2019 (COVID-19) pandemic has disrupted societies globally. As of 11 May 2020, 53 children have been infected with COVID-19 in Singapore (Ministry of Health, Singapore, unpublished data). Children generally have mild disease,[1] although there is emerging literature on paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Less well reported is the impact of COVID-19 on the daily lives and psychology of children. This article highlights the implications of COVID-19 on an especially vulnerable population of children - children with autism spectrum disorder (ASD). ASD is a developmental disorder characterised by impaired social communication, language, and restricted stereotypic behaviour with rigidities. ASD is prevalent. It is estimated that 50,000 individuals are affected by ASD in Singapore.[2] Healthcare professionals are likely to encounter persons with ASD in their routine practice. Based on our experience in our developmental and behavioural paediatrics practice, caregivers experience significant challenges in managing children with ASD during this pandemic. Children with ASD are having difficulties adjusting to change and feeling anxious, whilst caregivers themselves are worried and fatigued. This article aims to be a resource for healthcare professionals in supporting these families. Strategies depicted are based on behavioural management principles used for ASD – promoting structure, use of antecedent strategies and positive reinforcement of desirable behaviours.

Sharing of Information

Children with ASD are cognisant about changes in their environment. A trusted caregiver should explain these changes to the child in a developmentally appropriate manner and focus on providing reassurance for the child. As these children have relative visual strengths, the use of visual supports[3] may help the child understand the situation better. For those who are younger, have lower language or cognitive abilities, videos and social stories with pictures will be helpful. For children who use language, caregivers can start by asking their child what he/she already knows, what questions he/she may have, and then supplement or correct their understanding accordingly. The dialogue should be direct as these children might not be able to infer from vague messages. For example, instead of saying, "There is a virus and it's dangerous to go outside", consider saying "Staying at home will reduce the chances of getting sick". Knowledge sharing should happen regularly for caregivers to address new concerns that may arise. Exposure to COVID-19 related media exposure should be monitored and restricted.

Coping with Change

Individuals with ASD prefer routines and may have difficulty adjusting to changes. However, during this period, changes are common. To help children cope with change, caregivers should maintain a child's daily routine. When this is not possible, pre-empt the child about any change and adopt a new routine while allowing time for the child to adapt to it. A visual schedule of the day's routine will help the child know what to expect and transit between activities. Timers can further provide children with visual and auditory cues. Allocated time and space for various activities (e.g. mealtime, learning, play) will help the child understand specific events better. For less verbal children, the TEACCH (Treatment and Education of Autistic and Communication related handicapped Children) method of using actual items to help children conceptualise a routine is helpful. Empower the child by giving them control over small decisions, like choosing a preferred type of meal. Pique their

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motivation to new measures like hand washing and mask wearing by proposing these as methods they can protect themselves with.

Adjusting to New Routines

New routines like hand washing, use of masks, social distancing, restricted outdoor access and home-based learning are new norms. Children with ASD may have difficulties grasping the reason for these practices and in understanding that his/her caregiver is now also a teacher. In addition, home environments may not be conducive for learning if they are too sensory stimulating or if siblings are distracting.

Caregivers should introduce new routines in a positive manner. It is more effective to tell children what to do, than what not to do. Caregivers should use instructions like "hands by your side", instead of "don't touch your face". For younger or less verbal children, keep the message simple by using keywords, direct demonstration or visual aids. For example, to promote hand hygiene, the caregiver can use a hand gesture indicating hand washing coupled with a verbal cue. To help children maintain adequate distance from others, teach them to stretch out both their arms to use that as a physical boundary. Use of social stories can aid in explaining these concepts. Caregivers could use a reward system to reinforce compliance to desirable behaviours.

Maintaining Connections with Loved Ones

Restrictions in movement between households can result in children being unable to interact with familiar caregivers. The absence of familiar caregivers like teachers and grandparents can make children feel anxious. Caregivers could help families maintain social connections via telephone or video calls, and use a visual countdown to represent when these reunions can take place in-person.

Self-care of Caregivers

Caregivers of children with ASD experience more stress.[4] Further, for a parent raising a child with ASD, the risk of self-neglect is higher. Parents often postpone their own needs for their children and family. With increased parenting, coupled with work from home demands during this pandemic, this stress is likely to be exacerbated. Parents of children with ASD already feel socially isolated at baseline; social distancing during this pandemic could aggravate the sense of loneliness. It is important for caregivers to take care of themselves. A caregiver's health and well-being is directly related to the quality of care they can provide their children. Specific to COVID-19, parental anxiety can also lead to children worrying more.

Caregivers need to first ensure that they are caring for themselves physically with adequate nutrition and rest. Next, they need to practice emotional self-care by acknowledging and addressing emotional burdens they are experiencing. Thirdly, they should practice spiritual self-care, through a process of doing something they enjoy. This can be by taking scheduled short breaks from parenting, or making time for hobbies. Using hobbies as activities which the parent and child can do together may be helpful. Caregivers should not feel guilty for offering their children some screen time during this period. Actively seeking help for both emotional and tangible support (for example, caring for the child) is encouraged, as is seeking help from professionals when feeling overwhelmed.

Risk factors for increased stress include: having more than one child with a disability, disadvantaged socioeconomic status, children with severe ASD who require constant supervision and assistance for activities of daily living, children with disrupted sleep, and caregivers with little social support.[5] Using the resources in Figure 1, physicians can reach out to these families and offer support.

Managing the Child's Anxiety

Children with ASD are are at a higher risk of having anxiety.[6] Language impairment may limit communication of emotions and make their anxiety harder to detect. Anxiety is likely to be exacerbated in a pandemic setting.[7] Anxiety in these children may manifest as tantrums, challenging behaviours,

1. Enabling guide – Latest information on Coronavirus Disease 2019
2. NUH COVID-19 Resources for Parents and Caregivers
3. MOH Special Care Kit – Resources to support individuals with special needs for COVID-19 related healthcare encounters
4. Let's fight COVID-19 together with Superhero me
5. KKH COVID-19 Care Resources
6. Singapore National Care Hotline
7. Tinkle Friend Hotline by the Singapore Children's Society

Fig. 1. COVID-19 community resources for persons with special needs in Singapore

distractedness, separation anxiety, trouble eating or sleeping, behavioural regression and/or increase in repetitive behaviours. These changes are reactions to disruptions faced, and are likely transient. Children should be encouraged to express their feelings verbally, or through writing, drawing, or play. Caregivers should be good listeners and avoid 'playing down' a child's fears as this can exacerbate the anxiety. Older children with ASD may benefit from mindfulness practice.[8] This can include being mindful of their behaviours, and learning coping and calming skills. Parents can help by modelling these practices. When required, help from psychologists/psychiatrists should be sought. Cognitive behavioural therapy[9] is a widely accepted psychological approach for treating anxiety in children who use words to communicate. In some cases, medication can be helpful.

Conclusion

Healthcare professionals should be aware that caregivers of children with ASD face additional challenges during this pandemic. We have outlined strategies that can provide support to these families. In view of the immense stress some families endure, healthcare professionals should be vigilant about family violence, to enquire about family stress levels and make violence screening a part of every assessment. Look for mood disorders in caregivers and unusual fearfulness in children. Reaching out to vulnerable families proactively when there are no appointments in the near future can help avert violence. With know-how, healthcare professionals can help families with persons with ASD better manage this challenging COVID-19 period.

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Commentary

Otolaryngology Surgery in Time of COVID-19—What PPE to Use When?

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) on 11 March 2020.[1] As otolaryngologists (ENT surgeons) manage various conditions involving the upper airway, they are at particular risk of contracting the disease, especially during performance of procedures on the nose, mouth, pharynx and larynx. We wish to share the policies on personal protective equipment (PPE) instituted by the Department of Otorhinolaryngology, Tan Tock Seng Hospital (TTSH), Singapore in consultation with the National Centre for Infectious Diseases (NCID). NCID is the designated frontline healthcare facility to treat patients with COVID-19 in Singapore. It is physically linked to TTSH, the designated hospital that treated Severe Acute Respiratory Syndrome (SARS) in 2003. Our otolaryngology department provides outpatient and inpatient services to both TTSH (1500 bed capacity) and NCID (330 bed capacity), the largest inpatient healthcare facility in the island nation.

Background

Our understanding of how SARS-CoV-2 is transmitted is based on our experience from the SARS outbreak in 2003,[2–3] combined with early data from Wuhan, Hubei, People's Republic of China, as well as our present experience with COVID-19.[4–6] Based on current information, SARS CoV-2 is transmitted mainly via respiratory droplets. While there is no conclusive evidence of airborne transmission, it is possible that aerosol-generating procedures such as tracheal intubation, can transmit the virus.[7,8] A recent paper described that aerosolised SARS CoV-2 can last up to 3 hours in the air and even longer on various surfaces.[9] A point to note is that this study was performed using a Goldberg drum that was not ventilated, and thus may not reflect real world situations. Other possible modes of transmission include contact, fomites and fecal-oral route.[10]

Singapore diagnosed her first case of COVID-19 on 23 January 2020 and reported her first local transmission on 7 February 2020.[11,12] At the time of writing, we have 25346 confirmed cases with 21 deaths. Anecdotal reports from various countries including China, Italy and Iran have noted that ENT surgeons and ophthalmologists are infected at higher rates as compared to other specialties.[13] This may be due to the nature of the ENT work and the proximity to the routes of viral transmission. According to an original Chinese press article, this increased rate of infection may be due to the lack of PPE used by both these specialties during the initial outbreak.[13]

As an otolaryngology department providing services to NCID that manages the majority of COVID-19 cases in Singapore, we need to ensure that personal protective measures are well instituted. Transmission of disease from patient to healthcare worker (HCW) or amongst HCWs can rapidly paralyse the healthcare system. After consulting the Department of Infectious Diseases at NCID and studying the best available evidence, we describe below the infection control measures adopted by our department during this pandemic.

Systemic Measures

In Singapore, the Disease Outbreak Response System Condition (DORSCON) framework is used to guide the country's response to outbreaks. The alert was raised to Orange on 7 February 2020.[14] National-level measures include border control, contact tracing, social distancing, regular temperature taking and hand hygiene. Hospital-level measures include postponement

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of non-urgent or non-essential surgeries and outpatient appointments, cancellation of non-essential large group meetings, limiting the number of hospital visitors, declaration of travel history and symptoms, and last but not least a moratorium on all vacation leave (local and overseas) for medical staff. Increased frequency of environmental cleaning and decontamination was also instituted across various venues within the hospital, not only the patient care areas but also all common areas. Early studies showed these measures to be effective in removing SARS CoV-2 particles.[10]

In addition, specific measures adopted by the operating theatre (OT) included Level 2 PPE for all personnel performing intubation and extubation, which are considered Aerosol Generating Procedures. Non-participating personnel vacate the OT during these procedures. All OTs in TTSH and NCID use a multitude of engineering features to ensure that air exchanges occur more than 20 times per hour and the air undergoes high-efficiency particulate air (HEPA) filtration. Further details adopted by our OT are similar to what was described in an article published by the anaesthesia departments of Singapore General Hospital and Sengkang General Hospital.[15]

At the time of writing, elective pre-operative testing of COVID-19 has not been recommended in Singapore. One reason could be the need to maximise the impact of testing within a finite capacity. However, as the pandemic appears to be a long-drawn battle, it is possible that pre-operative testing may be done in the future to allow for some resumption of business-as-usual. The Singapore government has recently ramped up the testing capacity, perhaps with this in mind.

Personal Protective Equipment (PPE) Recommendation

We divide PPE into 3 levels:

Level 1: Surgical mask, eye protection, disposable gloves, gown, surgical cap

Level 2: Fitted N95 mask (National Institute of Occupational Safety and Health (NIOSH)-certified N95 respirators), eye protection, disposable gloves, gown, surgical cap

Level 3: Powered Air-Purifying Respirator (PAPR), eye protection, disposable gloves, gown, surgical cap, shoe covers

Table 1 summarises the recommended levels of PPE per ENT procedure type based on the risk of transmission. The rationale for these recommendations is explained below.

Table 1: Recommended level of personal protective equipment (PPE) per otolaryngology procedure type

Type of procedure	General public	Patients suspected** or diagnosed with COVID-19
Airway procedures	Level 2	Level 3
Oropharyngeal procedures	Level 2	Level 3
Sinonasal procedures	Level 2	Level 3
Otological procedures that require drilling	Level 2	Level 3
Otological procedures that do not require drilling	Level 1	Level 2
Head and neck procedures that require access of the upper aerodigestive tract*	Level 2	Level 3
Head and neck procedures that do not require access of the upper aerodigestive tract	Level 1	Level 2

Level 1 – Surgical mask, eye protection, disposable gloves, gown and surgical cap
Level 2 – Fitted N95 mask (National Institute of Occupational Safety and Health (NOISH)-certified N95 respirators), eye protection, disposable gloves, gown, surgical cap
Level 3 – Powered Air-Purifying Respiratory (PAPR), eye protection, disposable gloves, gown, surgical cap, shoe covers

*Upper aerodigestive tract refers to nasal cavity, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and cervical trachea
**A suspected patient is defined by the Ministry of Health, Singapore based on the presence of acute respiratory symptoms or infective changes on chest imaging, in association with travel outside of Singapore or to hotspots of COVID-19 outbreak in Singapore, or contact with a confirmed COVID-19 patient. The exact details of this definition evolve according to the epidemiology of COVID-19 in Singapore. The reader may refer to www.moh.gov.sg for information.

Procedures Performed in OT Under General Anaesthesia

1. Airway Procedures

Recommendation: Level 2 PPE for general public, Level 3 PPE for patients suspected or diagnosed with COVID-19

Examples of airway procedures performed in the OT are tracheostomy, endolaryngeal microsurgery and laryngoscopy. These procedures, especially tracheostomy, are considered by the World Health Organization as Aerosol Generating Procedures (AGP).[17] We recommend Level 2 PPE because it significantly reduces the risk of transmission of SARS to HCWs during AGP.[18] However, if a patient is confirmed or suspected of having COVID-19 (based on Singapore Ministry of Health's definition which changes as the pandemic evolves) and requires urgent surgery, we advise Level 3 PPE for additional precaution. Certain techniques such as complete apnoea during insertion of the tracheostomy tube can be employed to further decrease the risk of viral transmission through reducing the amount of aerosol generation. The British Laryngological Association has also recommended that intubation be preferred over jet ventilation.[19] Similarly, in our unit, we avoided jet ventilation and considered a surgical airway as an alternative if access to a challenging airway is required during this pandemic.

2. Oropharyngeal Procedures

Recommendation: Level 2 PPE for general public, Level 3 PPE for patients suspected or diagnosed with COVID-19

Tonsillectomy, palate and tongue base surgeries are performed in this anatomical region. These are considered as potentially aerosol generating. Therefore, our recommendation is Level 2 PPE. Given the nature of the surgeries in this category, it is unlikely that they will need to be done urgently in a COVID-19 case. If an unexpectedly urgent oropharyngeal surgery becomes indicated in a confirmed or suspected COVID-19 patient, the procedure should be performed with Level 3 PPE.

3. Otological Procedures

Recommendation: Level 2 PPE for the general public if drilling is involved, Level 1 if no drilling. Level 3 PPE for patients suspected or diagnosed with COVID-19 if drilling is involved, Level 2 if no drilling

Otological procedures such as tympanoplasty and mastoidectomy involve cutting and suctioning within the enclosed middle ear and drilling of mastoid air cells. Mastoid air cells contain respiratory columnar epithelium.[20] To our knowledge, there are no studies to confirm the presence of SARS CoV-2 virus particles in the mastoid despite the presence of respiratory epithelium. However, drilling of the mastoid bone can result in aerosolisation around the operative field, increasing the risk of transmission. This is differentiated from nasal endoscopic drilling where drilling and suctioning occur within a relatively enclosed space. Therefore, our recommendation is Level 2 PPE if drilling is involved and Level 1 PPE if no drilling involved, for example in a myringoplasty. The level of PPE should be increased by 1 if the operation is performed on a suspected or confirmed COVID-19 patient.

4. Sinonasal Procedures

Recommendation: Level 2 PPE for the general public, Level 3 PPE for patients suspected or diagnosed with COVID-19

Examples of sinonasal procedures are septoplasty, inferior turbinoplasties, Functional Endoscopic Sinus Surgery (FESS) and endonasal skull base surgeries such as transphenoidal resection of pituitary adenomas. These are procedures involving cutting, debriding, suctioning of mucosa and bone within an enclosed cavity. There is uncertainty surrounding the optimal PPE for sinonasal procedures. A commentary recently published by Stanford University School of Medicine, based on information from anecdotal reports and personal correspondence from various international colleagues, highlighted that N95 masks might not be sufficient in preventing the transmission of COVID-19 and that endoscopic nasal surgery has the highest risk of spreading the infection.[21] However, a team of neurosurgeons from Wuhan suggested that the transmission of COVID-19 to HCWs from a patient who underwent endonasal endoscopic pituitary adenoma resection that occurred post-operatively, was attributed to insufficient personal airway protection.[22]

The Stanford commentary also mentioned that a neurosurgeon in Wuhan stated N95 masks alone were insufficient in preventing the transmission of COVID-19 to HCWs, and the situation only improved after the use of PAPR. However, N95 masks have been shown to effectively prevent transmission of SARS to HCW,[23,24] and the N95 respirator is only one component of the PPE. Other measures such as the technique of donning

and doffing a PPE to avoid self-contamination, and environmental decontamination,[10] are equally important. Prolonged usage of the same PPE may also reduce its effectiveness.

On the other hand, the same commentary[21] also mentioned that the viral load is higher in nasal samples compared to throat samples. This is concerning because powered instruments such as microdebriders or endoscopic drills are often used during sinonasal procedures, and may result in aerosolisation. However, a recent study from Boston showed that microdebriders did not cause aerosolisation, in contrast to endoscopic drills.[25] Furthermore, the use of these instruments takes place within the relatively enclosed sinonasal cavity. With closed-circuit suction available, aerosolisation may be limited as compared to that in an open cavity.

When considering PPE recommendations by various guidelines, there is a significant country-to-country variation in disease burden, community spread, systemic and hospital protective equipment, and availability of COVID-19 testing capability. Based on the evidence that is currently available, we recommend that Level 2 PPE is adequate when performing sinonasal procedures on the general public. Furthermore, with systemic infection control measures in place at the level of the hospital and the community, as well as the fact that sinonasal procedures are performed endoscopically within an enclosed cavity, there is a possibility that Level 1 PPE may be sufficient for such surgeries on the general public. However, until more evidence emerges, escalation of PPE to Level 3 is recommended when performing sinonasal procedures on patients diagnosed with or suspected to have COVID-19, in order to minimise the risk of viral transmission to HCWs.

5. Head and Neck Procedures not Requiring Access of the Upper Aerodigestive Tract

Recommendations: Level 1 PPE for the general public, Level 2 PPE for patients suspected or diagnosed with COVID-19

The upper aerodigestive tract refers to the nasal cavity, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and cervical trachea. Head and neck procedures such as thyroidectomy, parotidectomy and neck dissection, do not require access through these sites. Thus, Level 1 PPE should suffice after intubation. Level 2 PPE is recommended in patients diagnosed with or suspected to have COVID-19 to minimise the risk of transmission to HCWs. Of note, the use of energy devices that vaporises tissue should be discouraged as it can potentially aerosolise viral particles that may be present in the patient's bloodstream. Viremia was detected in SARS patients,[26,27] which is also caused by a coronavirus, raising the possibility of viremia in COVID-19 patients.

6. Head and Neck Procedures Requiring Access of the Upper Aerodigestive Tract

Recommendations: Level 2 PPE for the general public, Level 3 PPE for patients suspected or diagnosed with COVID-19

These procedures include maxillectomy, glossectomy, mandibulectomy, nasopharyngectomy, oropharyngectomy, hypopharyngectomy, laryngectomy and laryngopharyngectomy. The HCWs involved face prolonged risk of exposure to respiratory aerosol and should be well protected. We recommend Level 2 PPE when operating on the general public and Level 3 PPE when operating on patients suspected or diagnosed with COVID-19, consistent with our recommendations above for site-specific procedures.

Eye Protection

The conjunctiva may be potential portals of infection.[16] The definition of eye protection may vary from safety glasses to face shields to air-tight goggles. There is insufficient evidence regarding their relative superiority. However, in procedures with a high risk of splash or aerosolisation, air-tight goggles can be considered.

Outpatient Clinic Procedures

Since a variety of outpatient procedures performed in the otorhinolaryngology clinics have a high risk of aerosolisation, we recommend deferring all non-urgent high-risk procedures during a pandemic. But if such procedures become essential for patient care, appropriate PPE should be worn.

Flexible nasolaryngoscopy, stroboscopy and related procedures such as injection medialisation and tracheostomy tube change are considered high risk procedures. If the procedure cannot be deferred, it should be performed with Level 2 PPE in a designated room which can be subsequently decontaminated. This room should have air ventilation systems and HEPA filters similar to that of the OTs. Diagnostic rigid nasoendoscopy, and associated procedures such as

topical anaesthetic spray, nasal biopsy or intervention can be performed with Level 2 PPE. Aural toilet and other otological procedures such as myringotomy and grommet tube insertion can be performed using Level 1 PPE. However, as the cough reflex may be triggered during such procedures, a surgical mask for the patient to wear is advised.

Ancillary Measures

Proper fitting of N95 masks, the correct use and disposal of PPE and meticulous hand hygiene are also crucial in infection control.

Conclusion

In a pandemic, situations evolve quickly, and each country's healthcare system will face its unique set of challenges and limitations. The level of available evidence regarding the appropriate PPE against COVID-19 for various ENT procedures is still low. Our recommendations are formulated based on the setup and resources available to our unit at TTSH and NCID as well as currently available evidence. Our recommendations cannot be taken in isolation without considering the overall load and containment of the disease in the community, the availability of PPE for all HCWs in the country, and training of HCWs in the correct use and safe disposal of PPE. We are heartened that the global medical fraternity is banding together to fight this scourge upon its people. Rapid communications are important for us to review and change our practices so as to better protect our colleagues and patients.

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Inflammatory Markers in COVID-19

Dear Editor

As the cataclysmic repercussion of COVID-19 continues to spread across the globe, it is imperative to explore for markers that can be used to monitor disease severity in COVID-19 patients. Previous studies have suggested that Interleukin-6 (IL-6) and acute phase reactants such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, procalcitonin (PCT), fibrin degradation product (FDP), D-dimer were elevated in patients more severely affected by COVID-19[1] and H1N1.[2] These markers can be explored to predict the prognosis in COVID-19 patients in the initial stages so that aggressive and specific therapeutic interventions can be adopted timely.

A novel coronavirus disease COVID-19 emerged from Wuhan, China in 2019. Since then it has caused massive loss of lives. More than 5.86 million people have been affected and more than 360,000 patients have succumbed to the illness.[3] SARS-CoV-2, the virus that causes COVID-19, belongs to the family of beta coronavirus and is postulated to have been spread from bats to humans, and later mutations have enabled it to transmit from human to human.[4,5] In the past decade, 2 other zoonotic coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), have been reported to damage the respiratory tract and cause severe outbreaks and deaths.[4,5]

The clinical spectrum of the disease ranges from being asymptomatic to full blown acute respiratory distress syndrome (ARDS).[6,7] The body's immune system, age and inherent comorbidities determine the varied presentation of the disease. Though the exact pathogenesis of COVID-19 remains elusive to mankind, the studies previously done on other coronavirus such as SARS-CoV have demonstrated release of a considerable amount of pro-inflammatory cytokines resulting in a cytokine storm syndrome.[8] Cytokine storm syndrome is a diverse set of conditions of pleotropic causation associated with exuberant systemic inflammation, multi-organ failure, hyperferritinemia and high mortality.[9] At present, due to a lack of reliable markers, the monitoring of COVID-19 patients relies mainly on the observation of clinical parameters. The aim of this study is to evaluate the role of various inflammatory markers which have been used earlier in lung injury assessment in SARS-CoV and MERS-CoV.[10]

Method

All consecutive patients with confirmed COVID-19 infection admitted to Sawai Mansingh (SMS) Hospital, Rajasthan, India, from 1 March to 1 April 2020 were enrolled. Their clinical profile, management and outcomes were monitored. Patients were divided into severe and non-severe categories. Severe category was defined when any one of the following criteria was met:

1) Dyspnea, respiratory rate ≥30/min
2) Oxygen saturation by pulse oximeter ≤93% in resting state
3) Partial pressure of arterial oxygen (PaO_2) to fraction inspired oxygen (FiO_2) ratio ≤300 mm Hg

The medical records of patients were analysed for epidemiological (demographics and exposure history), clinical (signs, symptoms and underlying comorbidities), and laboratory parameters, besides radiological characteristics (CT scan and X-ray findings), treatment (antiviral therapy, antibiotics, respiratory support) and outcome data. This data was obtained from history given by patients and with data collection forms from electronic medical records.

Besides baseline investigations like blood cell count, liver function tests, renal function tests, quantitative assessment of LDH, serum ferritin, procalcitonin, CRP, FDP, D-dimer and IL-6 was also done and values >250 U/L for LDH, >270 ng/ml for serum ferritin, >0.5 ng/ml for procalcitonin, >5mg/dl for CRP, >5ug/ml for FDP, >0.5 ug/dl for D-dimer and >7 pg/ml for IL-6 were considered abnormal. These investigations were done on the day when the patient was admitted as a case of COVID-19 (Day 0) and on Day 7.

Oropharyngeal swab specimens were collected for extracting SARS-CoV-2 RNA from suspected

COVID-19 patients and placed into a collection tube containing virus transport medium (VTM) for extraction of total RNA. RT-PCR assay for SARS-CoV-2 was conducted by viral nucleic acid detection kit based on the recommendation by National Institute of Virology, Pune, India. Proportions for categorical variables were compared by the Fisher's Exact test.

Discussion

Forty-eight COVID-19 patients were included in this study. The mean age of patients in the severe category was 57.5 years, and in non-severe category 37.9 years. Male patients comprised 66.7% of total patients. Of the 48 patients, 32 (66.7%) were asymptomatic. In patients who were symptomatic, cough (87.5%) was the most common symptom followed by fever (81.3%), myalgia (50%), headache (43.8%) and 6 patients (37.5%) had dyspnea. Four out of 6 patients requiring oxygen support had underlying comorbidities such as COPD (chronic obstructive pulmonary disease), diabetes mellitus, hypertension, hypothyroidism, CAD (coronary artery disease), CKD (chronic kidney disease).

Evaluation of the haemogram in severe category patients revealed that 83.3% patients had lymphopenia, 16.7% had thrombocytopenia and 16.7% had eosinopenia. In the non-severe category, there were 19% patients who had lymphopenia, 9.5% thrombocytopenia, 16.7% eosinopenia (Table 1).

Table 1. Laboratory Findings of COVID-19 Patients

Laboratory findings	All patients (n=48)	Non-severe (n=42)	Severe (n=6)	P value
Blood cell count				
Lymphopenia				
WBC <1.5*10^9/L, n (%)	13 (27.0)	8 (19.0)	5 (83.3)	<0.05
Thrombocytopenia				
Platelets <1.4*10^9/L, n (%)	5 (10.4)	4 (9.5)	1 (16.7)	0.503
Eosinopenia				
Eosinophils <1% of total WBC, n (%)	8 (16.7)	7 (16.7)	1 (16.7)	>0.05
CRP (mg/dl), median (range)	3.3 (1.4-8.9)	2.95 (1.4-6.0)	7.2 (4.4-8.9)	
>5 mg/L, n (%)	7 (14.6)	2 (4.7)	5 (83.3)	<0.05
Procalcitonin (ng/ml), median (range)	0.3 (0.1-1.2)	0.2(0.1-0.6)	0.8 (0.4-1.2)	
>0.5 ng/L, n (%)	6 (12.5)	1 (2.4)	5 (83.3)	<0.05
LDH (U/L), median (range)	320 (112-1221)	310 (112-711)	881 (439-1221)	
>460 U/L, n (%)	8 (16.7)	3 (7.1)	5 (83.3)	<0.05
SGOT (U/L), median (range)	31.5 (10-110)	28 (10-72)	67 (59 -110)	
>40 U/L, n (%)	11 (22.9)	6 (14.3)	5 (83.3)	<0.05
SGPT (U/L), median (range)	33.2(15-122)	27 (15-55)	68 (52-122)	
>40 U/L, n (%)	11 (22.9)	6 (14.3)	5 (83.3)	<0.05
FDP (ug/ml), median (range)	3.3 (1.6-9.1)	3.1(1.6-5.2)	6.95(4.2-9.1)	
>5 ug/ml, n (%)	6 (12.5)	1 (2.4)	5 (83.3)	<0.05
D-dimer (ug/ml), median (range)	0.3(0.1-1.7)	0.27(0.1-0.6)	1.3(0.2-1.7)	
>0.5 ug/ml, n (%)	6 (12.5)	1 (2.4)	5 (83.3)	<0.05
Ferritin (ng/ml), median (range)	64.5 (18-1120)	53(18-670)	893 (112-1120)	
>270 ng/ml, n (%)	8	3 (7.1)	5 (83.3)	<0.05
IL-6 (pg/ml), median (range)	5.1(2.3-512)	4.8 (2.3-6.8)	68.5 (12-512)	
>7 pg/ml, n (%)	6 (12.5)	0 (0)	6 (100.0)	<0.05

Overall, 22.9% patients had deranged liver function tests while 83.3% patients in the severe category had elevated SGOT/SGPT levels.

Inflammatory markers were predominantly increased in patients in the severe category namely CRP (83.3%), procalcitonin (83.3%), LDH (83.3%), serum ferritin (83.3%), FDP (83.3%), D-dimer levels (83.3%) and IL-6 (100%) (Table 1). The levels of inflammatory markers were significantly increased at the time of admission in patients in severe category. The median duration of performing these tests from the onset of symptoms was 7.5 days (range 6–14 days). Patients in the non-severe category had lower IL-6 levels and other inflammatory markers at the time of admission and took lesser time to get a first sample negative and had lesser symptoms.

In comparison, the mean duration of getting first and second COVID-19 sample negative from positive was 8 days and 9.2 days respectively in severe category. In patients who could maintain saturation at room air it was 7.7 days and 9.2 days respectively (Table 2). Only 1 patient who could not maintain saturation at room air was first given Bilevel Positive Airway Pressure (BiPaP) and later required a ventilator while others were able to maintain oxygen saturation with the help of nasal prongs or oxygen masks. One patient who eventually needed intubation had a very high spike (>500pg/ml) of IL-6.

In our study, more males were infected (66.7%) by SARS-CoV-2 probably due to more frequent foreign travels in pursuit of education and employment. This was lower than that reported by Chen et al[11] and Huang et al[12] where male patients comprised 73% of the enrolled cases, and higher than that reported by Wang et al (54.3%).[13] The mean age of patients in the study was 40.4 years, which is a decade younger than that reported by Wang et al[13] (56.0 years), Chen et al[11] (55.5 years) and closest to that reported by Huang et al[12] (49.0 years). The mean age of patients in the severe category was 57.5 years as compared to 37.9 years in the non-severe category, thus demonstrating that older patients were at greater risk of lung injury requiring ventilator support. Previous studies have demonstrated that lymphopenia and cytokine storm is associated with more severe infection by coronavirus.[14, 15]

In our study, 83.3% patients belonging to the severe category had elevated CRP, LDH, ferritin, PCT, FDP and D-dimer while they were elevated in <5% patients belonging to the non-severe category. These laboratory parameters were elevated in most of the patients in the severe category and showed an overlap with each

Table 2. Management and Outcome of Patients Requiring Oxygen Support

Age, Sex	Treatment			Oxygen support				COVID-19 Tests		
	Lopinavir/ Ritonavir	Chloroquine	Oseltamivir	Low flow O_2 mask	High flow O_2 mask	Non-invasive ventilation	Invasive ventilation	1st Positive	1st Negative	2nd Negative
67, M	✓	✓	✓	×	×	✓	✓	Mar 2	Mar 14	Mar 15
85, M	✓	✓	✓	✓	×	×	×	Mar 10	Mar 14	Mar 15
38, M	✓	✓	✓	✓	×	×	×	Mar 20	Mar 28	Mar 29
37, M	✓	✓	✓	×	✓	×	×	Mar 18	Mar 28	Mar 29
58, M	✓	✓	✓	✓	×	×	×	Mar 25	Mar 30	Mar 31
60, M	×	×	×	×	✓	×	×	Mar 30	-	-

Table 3. Laboratory Parameters of Patients at Day 0 and Day 7

Age, Sex	Days from onset of symptoms to admission (Day 0)	LDH (230-460 U/L)		CRP (0.0-5 mg/L)		Ferritin (12-270 ng/ml)		PCT (0.0-0.5 ng/ml)		FDP (0-5 ug/ml)		D-dimer (0-0.5 ug/ml)		IL-6 (0-7 pg/ml)	
		Day 0	Day 7	Day 0	Day 7	Day 0	Day 7	Day 0	Day 7	Day 0	Day 7	Day 0	Day 7	Day 0	Day 7
67, M	13	**1221**	1453	**8.9**	10.2	**1050**	1500	**1.2**	2.2	**9.1**	15	**1.5**	2.2	**512**	700
85, M	14	**1098**	687	**7.4**	5.1	**898**	787	**0.98**	0.5	**7.2**	4.1	**1.2**	0.7	**34**	50
38, M	7	**982**	788	**6.8**	3.4	**888**	563	**0.78**	0.21	**6.9**	3.2	**0.8**	0.3	**12**	8
37, M	6	**780**	800	**7**	3.5	**1120**	232	**0.77**	0.09	**7**	3.2	**1.4**	0.2	**72**	11
58, M	8	**439**	231	**4.4**	2.2	**800**	321	**0.4**	0.12	**4.2**	2.1	**0.2**	0.25	**75**	10
60, M	7	**515**	333	**8.3**	3.9	**112**	70	**0.72**	0.49	**6.3**	4.8	**1.7**	0.3	**65**	70

other, indicating that if one single parameter could be developed to identify the patients at highest risk of mortality, then other parameters may not be done so as to conserve resources and decrease the costs of conducting these tests. The elevation in inflammatory markers in our study was more than that reported by Liu et al[16] where CRP, LDH, D-dimer were elevated in 85.5%, 65.2%, 65.2% patients respectively in the severe category.

Paquette et al[2] reported that IL-6 concentrations were found to be significantly higher in H1N1 patients who required critical care support compared to patients who did not. Also, IL-6 levels were higher in patients who died (22.2%) compared to survivors (77.8%). Similarly, Liu et al[16] reported that among the COVID-19 patients in whom IL-6 was assessed before and after treatment, significant decrease in IL-6 and improved CT assessment was found in 81.3% patients after treatment. In our study, we found that IL-6 was elevated in all patients belonging to the severe category while none of the patients belonging to the non-severe category had increased IL-6. These results indicate that IL-6 and other inflammatory markers may be valuable parameters in monitoring disease severity in COVID-19 patients.

Conclusion

The clinical spectrum of COVID-19 ranges from being asymptomatic to ARDS. Severely affected patients are characterised by cytokine release syndrome. Laboratory parameters such as IL-6 and other markers of inflammation such as CRP, PCT, ferritin, LDH, FDP and D-dimer can be used in monitoring severity of disease in COVID-19 patients instead of COVID-19 affected patients patients. Targeting IL-6 may be useful in treating the cytokine storm in severely affected individuals. However, more research is needed for the suitability of IL-6 as a therapeutic target and disease severity biomarker. Our study covered only the early COVID-19 cases of North India, but a larger sample size would be needed to conclusively establish the role of dynamic changes to the markers of the disease.

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Letter to the Editor

COVID-19: Critical Role of Angiotensin 1-7 in ACE2 Modulation

Dear Editor,

With the declaration of Novel Coronavirus Disease 2019 (COVID-19) as pandemic by World Health Organization (WHO), many countries have taken drastic measure to enforce movement control to curb COVID-19 outbreak. On 23 January 2020, it was reported that Malaysia had 4 patients suspected to have contracted the COVID-19. On the same day, Singapore confirmed its first case of COVID-19.[1] The first confirmed COVID-19 case reported in Malaysia was on 24 January 2020. To date, WHO has reported a total of 5.6 million confirmed cases, with 353,373 confirmed deaths among 216 countries around the world.[2] Current evidence suggests that COVID-19 patients could develop rapidly worsening respiratory failure and acute respiratory distress syndrome (ARDS).[3]

Similar to SAR-Cov (Severe Acute Respiratory Syndrome Coronavirus), COVID-19 is believed to be using the same entry point of Angiotensin Converting Enzyme 2 (ACE2) into the human host cells.[4,5] ACE2 is a carboxymonopeptidase that cleaves at the carboxy-terminal (C-terminal) end of a protein or peptide [6], and is expressed on respiratory and intestinal epithelial cells, endothelial cells, renal tubule cells and immune cells.[6–10] Tipnis et al (2000) also reported that the mammalian homologue of ACE has implications on cardiovascular and renal function.[11] Up to 96% of ACE2 is available as membrane-bound enzyme, and the minority of ACE2 (1–4%) presents as a soluble form in blood, urine, and other body fluids.[12,13] Additionally, the latest study by Wan et al (2020) reported that COVID-19 uses the same receptor-binding motif, as SAR-Cov that directly contacts with ACE2.[14]

There is an intrinsically high renin angiotensin system (RAS) activity in the lungs, creating a relatively higher concentration of ACE2 in the organ. Interestingly, Angiotensin Converting Enzyme (ACE) inhibitors, which are commonly prescribed for hypertension treatment, antagonise specifically the effect of ACE, but not ACE2. [15] ACE2 plays an important role in RAS, by converting Angiotensin II to Angiotensin 1-7 (Ang-(1-7)).[6,16] The formation of Ang-(1-7) is the requisite biologic effects of ACE2 to Angiotensin II.[17,18] Nonetheless, Angiotensin I is also converted to Ang-(1-7) via endopeptidases.[19] Ang-(1-7) provides vasoprotective effects by stimulating nitric oxide production and reduces reactive oxygen species' production.[20] The disequilibrium of RAS has a significant role in COVID-19 as it is involved in the modulation of the inflammatory response in the lungs. It may seem counter intuitive, but upregulation and higher levels of Ang-(1-7) as well as ACE2 were observed in patients receiving ACE inhibitors or even Angiotensin Receptor Blocker (ARB).[14,21] Of note is the fact that augmentation of ACE2 activity, as backed by animal in vivo study, could offer vasodilation, anti-oxidant, anti-inflammation and lung protective effect.[22]

Evidence has shown diabetic and hypertensive patients are susceptible to COVID-19 and face higher mortality rates.[23] The use of ACE inhibitors and ARB over the expression of ACE2 is debatable until the latest study indicated that these two antihypertensive drugs could increase the mortality rate of patients with COVID-19.[24] The arguable use of ACE inhibitors and ARB is further supported by Cure and Cumhur (2020), with the rising concern over cardiac arrhythmias and myocarditis events, provoked by increased cardiac ACE2 levels caused by both antihypertensive drugs and thus enhancing the penetration of SARS-CoV-2 into the heart tissue.[25]

However, evidence has shown that ACE2 is not inhibited by ACE inhibitor because ACE and ACE2 are different enzymes.[26] Literature has shown that ACE2 is consistently increased by ARB especially in cardiac tissue and renal vasculature, but at high doses.[26,27] Of note is a China study reported which lower mortality rate in COVID-19 hypertensive patients treated with ACE inhibitor/ ARB (adjusted HR, 0.30; 95%CI, 0.12-0.70; $P = 0.01$).[28] To date, there is no solid evidence to support discontinuation of the use of ACE inhibitor and ARB in COVID-19 patients.[29] With the lack of evidence to support the possible

protective effect of ACE2 augmentation rendered by ACE Inhibitor/ ARB, the downstream metabolite of ACE2, Ang-(1-7), provides the possible clue to this dynamic responsiveness.

Hypothetically, as a negative feedback effect, ACE2 level should decrease with elevation of Ang-(1-7) in RAS (Fig. 1). Compared to ACE2, Ang-(1-7) is the downstream metabolite that could exert vasodilation and anti-inflammation effect when it binds to Mas receptor.[30–32] Despite functioning as a receptor for Ang-(1-7), Mas has important physiological actions in biological active peptide by providing a clear molecular basis.[34] Treatment with Ang-(1-7) has significantly reduced levels of proinflammatory cytokines, oxidative stress and macrophage infiltration in the lungs.[32] If this hypothesis is proven, the anti-inflammation and lung protective effect could be warranted with the increase concentration of external Ang-(1-7) albeit with the reduced ACE2 as host cell for SARS-CoV-2. Therefore, the spread of COVID-19 could be diminished with the reduction in the amount of ACE2 which act as host cells. "Emerging and re-emerging infections" seems to be the current trend, and the threat of infections is unlikely to be eradicated abruptly.[35] Further inroads with broader approaches involving biological agents should be considered to mitigate COVID-19. A proof of concept study would provide the much-needed evidence to support this postulation.

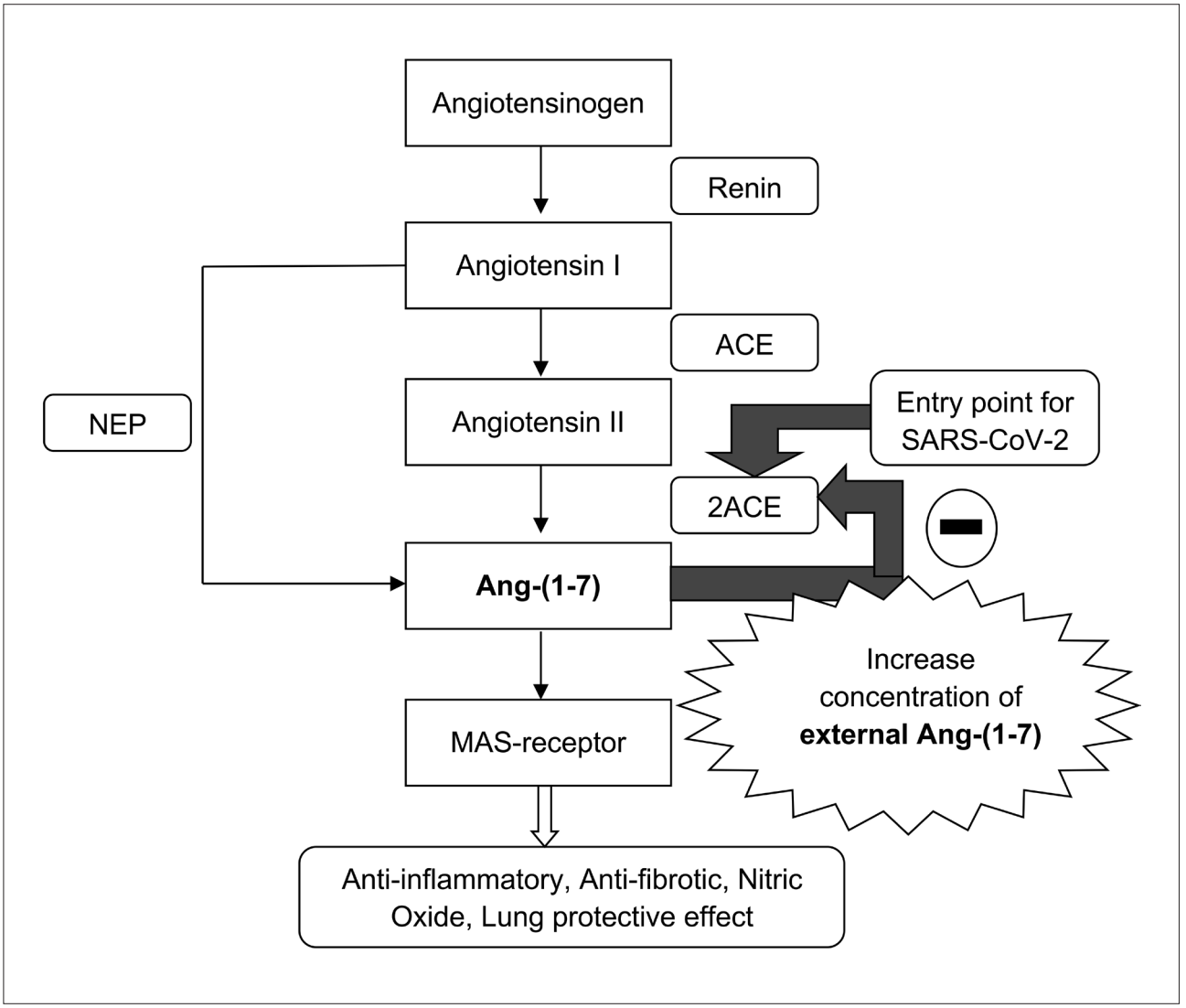

Figure 1. Negative feedback effect of Angiotensin 1-7 [Ang-(1-7)] in Renin Angiotensin System (RAS).

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Post-Critical Care COVID-19 Patient Benefits from a Robotic Patient-Guided Suspension System for Pulmonary Rehabilitation

Dear Editor,

The first case of coronavirus disease 2019 (COVID-19) in Singapore was diagnosed on 23 January 2020. As the number of COVID-19 cases increased in Singapore,[1] the healthcare system has had to manage more critical care patients and the sequelae of such prolonged, severe illness. In the rehabilitation of post-critical care COVID-19 patients, aspects of both pulmonary as well as neuromuscular rehabilitation exist. It is interesting that our patient who experienced frequent exertional desaturation benefitted from the use of a robotic patient-guided suspension system for mobilisation.

Written informed consent was obtained from the patient. No approval was sought from Institutional Review Board as this was a case report. Our patient is a 61-year old Chinese male who was pre-morbidly well when he presented to his general practitioner with symptoms of fever and dry cough on 11 March 2020 (Day 2 of illness). He was treated with oral antibiotics but did not improve. He presented at our acute care hospital on Day 9 with a persistent cough and new-onset breathlessness. Chest radiograph revealed a left-sided pneumonia (Figure 1) and he was treated with meropenem, azithromycin, as well as oseltamivir. He deteriorated the next day and was intubated for acute respiratory distress syndrome (ARDS) complicated by type 1 respiratory failure. He tested positive for the SARS-CoV-2 virus by PCR testing, and was started on lopinavir/ritonavir (Kaletra) as well as interferon beta-1b. Due to side effects, treatment was switched to hydroxychloroquine. Six days of intravenous methylprednisolone for refractory wheeze was administered with clinical response. After mechanical ventilation for 15 days, he was extubated on Day 24.

He was referred for inpatient rehabilitation on Day 30, after 2 negative COVID-19 swab results. He was oxygen-independent at rest but could only speak in phrases, and had exertional dyspnoea as well as resting tachycardia. Range of motion was full throughout and manual muscle testing via the Medical Research Council muscle scale (MRC) demonstrated a power of 4 in all limbs, but with poor endurance, and muscular atrophy in the lower limbs was noted. Peripheral sensation was intact and he had no areflexia or hyporeflexia that would suggest critical illness polyneuropathy. The patient also had poor truncal control and dynamic standing balance. He fatigued easily on sit-to-stand tasks, required supervision for transfers, and could only walk 4m with contact-assistance from therapists before he desaturated. The motor aspect of his Functional Independence Measure (Motor FIM) was scored as 59 (out of a total of 91 points).

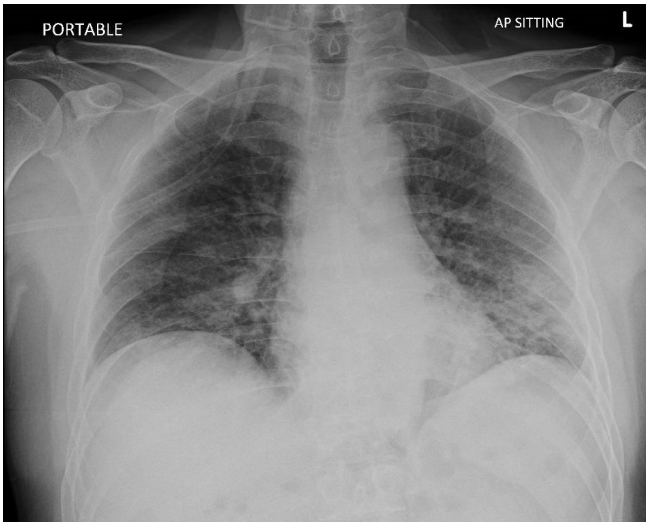

Figure 1: Patient's chest X-ray on admission

He continued to have anxiety symptoms but no further passive suicidal ideations from his stay in critical care. He scored 4 on the anxiety component of the Hospital Anxiety and Depression Scale (HADS-A), and 6 on the depression component (HADS-D).

Upon transfer to our rehabilitation unit on Day 31, he was assessed by a multidisciplinary team. He continued daily conventional physiotherapy and occupational therapy as tolerated. A dietician reviewed him for 4 kg weight loss (from 72 kg) during the

illness and prescribed Ensure milk supplement as well as vitamins. Our patient had recurrent thoughts about his intensive care unit (ICU) stay, but did not exhibit symptoms of post-traumatic stress disorder (PTSD). He feared being ostracised upon discharge and his anxiety about breathlessness was exacerbated by fears of virus re-activation. A mental health therapist engaged him in relaxation techniques and cognitive reframing.

It is becoming known that cardiovascular involvement is common in patients with severe COVID-19, and cardiomyopathy resulting from myocarditis, profound systemic inflammation, or microvascular dysfunction is associated with a worse prognosis.[2] As the patient had resting tachycardia and was planned for an increased intensity of rehabilitation, we organised cardiac enzymes and echocardiography to rule out cardiovascular disease – these were found to be normal. He then began training with the Andago V2.0 robot (Hocoma) which is a dynamic patient-guided suspension system for overground walking. Initial support requirements were 2.5 kg partial weights bilaterally (minimal weight support amounting to 5 kg in total) with 2 L/min supplemental oxygen via intranasal cannula. He achieved a distance of 302 m on his first session which lasted half an hour. After 6 consecutive sessions of robotic gait training (also conducted through the weekend), he ambulated 368 m, with 2.5 kg weight supports, without any further oxygen support (Figure 2).

The patient was discharged on Day 44 of his illness, after 13 days of inpatient rehabilitation. On discharge, he was walking independently without gait aids, and was independent in basic activities of daily living. His 6-minute walk test distance was 232 m and 10-meter walk test speed was 5.7 s with a gait speed of 1.87 m/s. HADS-A was reduced to 0 and HADS-D to 2. The patient achieved his goal of community ambulation.

Discussion

The patient presented to the acute care hospital on Day 9 of symptoms and was subsequently diagnosed with COVID-19 infection. In early March, testing was not as widely available and only selected patients with persistent symptoms were tested.[3] Current statistics suggest that up to 6% of COVID-19-infected patients may require ICU stay and intubation.[4] During the earlier phase of the outbreak in Singapore, the proportion of patients developing respiratory failure and needing mechanical ventilation was 15%.[5] This patient deteriorated on Day 10 of illness as was similar to what has been described.[6] Besides ARDS, patients could suffer from shock, myocardial dysfunction, and acute kidney injury.[4] Central nervous system involvement includes dysgeusia, hyposmia, altered consciousness levels, and neuropsychological manifestations. Critical illness myopathy and neuropathy, as well as other neurological syndromes such as Guillain-Barré syndrome have also been reported.[7] This could potentially amount to substantial disability and the rehabilitative needs in many severely-affected countries such as Italy have been shown to be great.[7]

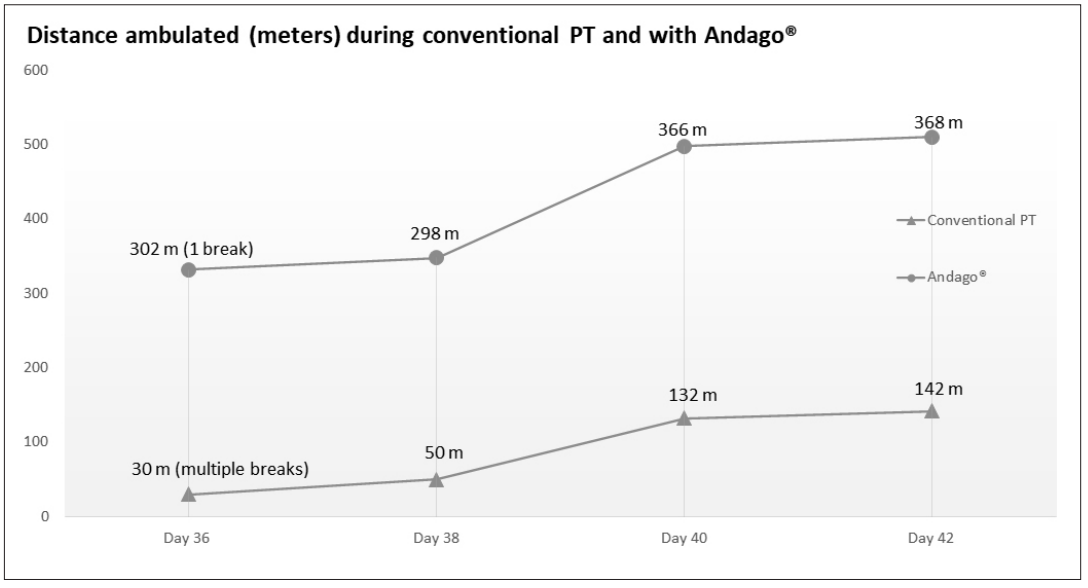

Figure 2: Comparison of distance ambulated using conventional physiotherapy and Andago

The rehabilitation of a post-critical care patient with COVID-19 requires a multidisciplinary approach. Besides the 2 main areas that require rehabilitation, namely pulmonary and neuromuscular rehabilitation,[8] other areas include nutrition and mental health. Of particular concern in these patients are the severe respiratory impairments that may preclude them from intensive therapies.[9]

Our patient desaturated early during activity and that impacted the intensity of the rehabilitation that he could tolerate. From our previous experience with Andago for another pulmonary rehabilitation patient,[10] we applied this robotic therapy which provided partial weight support, taking away the need for t herapists to support the patient. The Andago is a relatively-new robotic device that is classified in the category of patient-guided suspension systems[11] (Figure 3). It has sensors and control algorithms to assist with propulsion and manoeuvring of the frame, adjustments to maintain patient stability, and also assists with weightbearing. Patients are not confined to a fixed area and are allowed to walk overground as well as explore the environment. For patients with a Functional Ambulatory Classification (FAC) of 2, usually only 1 therapist is needed to control the device and monitor the patient. In this first experience of applying Andago for a post-critical care COVID-19 patient, the physician was present during the first session to ensure that it was suitable and that the patient could tolerate the treatment. During the session, with minimal supplemental oxygen (1 L/min), the patient was able to ambulate 10 times the distance covered during conventional therapy. Many pulmonary rehabilitation patients experience a vicious cycle of early desaturation, limited mobility, and further deconditioning, limiting them to low rehabilitation intensities. We believe that the partial weight support helped the patient to reduce the work of carrying his body forward during ambulation. In our case, robotic therapy enabled our patient to walk much further than he otherwise could with conventional therapy, breaking out of the vicious cycle and building endurance, physical balance, as well as confidence. Achieving an unaided distance of 142 m at discharge meant that he was able to walk to a car, facilitating community mobility and further independent reconditioning.

The Andago robot was preferred to other available devices such as treadmills with ceiling hoists and end-effector robots for 3 main reasons. Firstly, the patient is able to select his gait speed and is able to stop walking whenever he needs a break. Secondly, there is close proximity to the therapist as compared to treadmills and end-effector devices, which allowed the patient to sit down on a chair to rest immediately after the harness was easily unclipped from the suspension system, without having to take any additional steps should he get breathless. Thirdly, the patient is not static and is allowed to explore the environment with Andago. This in itself was therapeutic to the patient who had been in isolation for weeks prior to transfer to inpatient rehabilitation. Andago has not been applied to COVID-19 patients from around the world based on available literature, and its use in pulmonary rehabilitation is a novelty in itself.[10]

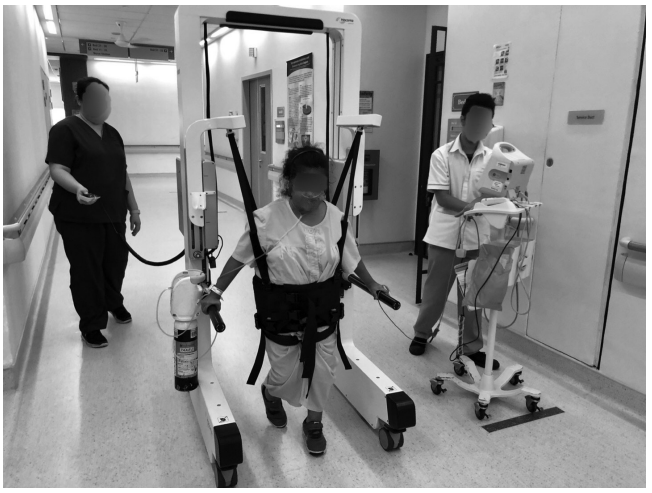

Figure 3: A patient using Andago® for pulmonary rehabilitation

This device may be beneficial in the pulmonary rehabilitation of patients who face early desaturation and dyspnoea post-severe infection. Post-infectious patients with COVID-19, H1N1, and other influenza-type pneumonias, as well as those with chronic restrictive lung disease may benefit from this intervention.[10] To be suitable for this device, patients need to be ambulating with minimal-assistance (FAC 2), or demonstrate motor power of more than anti-gravity in the lower limbs (MRC >3). This device may be useful in dealing with a high volume of patients transferring out of ICU post-COVID-19 infection or in other future pandemics as it increases the intensity of rehabilitation while reducing the manpower and physical burden on therapists to support the patient during ambulation.

The Andago is also suitable for use as an adjunct in neurorehabilitation by allowing patients to achieve more repetitions of the gait cycle thereby increasing their functional gains[12] (as illustrated similarly by our patient, Figure 2).

We have also learnt that there is a need for better psychological support in patients recovering from severe COVID-19 infections due to both societal and self-perceived stigmata, as well as uncertainty over the disease course, especially in the earlier phase of the illness where they remain in isolation. In the recovery phase, symptoms of PTSD should be monitored. The involvement of mental health therapists in early phases of the illness, and the use of innovative approaches such as tele-rehabilitation for isolated patients, should likewise be considered.[13]

Conclusion

In view of the global pandemic of COVID-19, the healthcare system should be poised to manage more post-critical care patients, as well as the sequelae of prolonged severe illness. Our experience in treating this post-critical care patient with COVID-19 involved a multidisciplinary team. Innovative treatment approaches, such as robotic therapies that are traditionally used more commonly for neurological impairments arising from stroke and spinal cord injuries, may prove beneficial in the pulmonary rehabilitation of post-critical care COVID-19 patients as well. More evidence may be gathered as more patients utilise this device.

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Outcomes of Surgically Treated Fingertip Injuries in Migrant Workers

Dear Editor,

Singapore employs more than 284,900 migrant construction workers.[1] Although safety training has been mandated to reduce the likelihood of workplace injuries, more than 12,000 workplace injuries have been reported in migrant construction workers in the latest statutory report.[2] We conducted a retrospective review of prospectively collected outcomes of surgically treated fingertip injuries in migrant workers at our tertiary teaching hospital between January 2015 to December 2015. Patients were included if they were (i) migrant construction workers, (ii) sustained a fingertip injury, (iii) underwent surgical treatment and, (iv) completed a minimum of 6 months follow-up. Participants were excluded if they had polytrauma or a concomitant fracture proximal to the fingertip. The study was approved by the SingHealth Institutional Review Board (CIRB 2016/2938).

Outcome measures included the total active motion (TAM), defined as the sum of active metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) arc of motion of an individual digit.[3] Outcomes were categorised as per the American Society for Surgery of the Hand (ASSH) into excellent (100%), good (>75%), fair (>50%) and poor (<50%) based on the comparison of the TAM in the affected digit, to the contralateral hand or norm of 260 degrees.[4]

Fifty-two injuries were analysed, with all sustained at the workplace. Demographic and perioperative data are presented in Table 1. The demographic characteristics of our patient cohort is similar to previous epidemiological studies on migrant workers in Singapore.[5]The mean preoperative TAM was 167 ± 62 degrees. Following surgery and a mean 9.3 ± 7.0 weeks of rehabilitation, the mean final TAM improved to 211 ± 57 degrees, corresponding to an outcome of "good". Eleven patients (21%) achieved "excellent" outcomes, 27 (52%) achieved "good" outcomes, 9 (17%) achieved "fair" outcomes and 5 (10%) achieved "poor" outcomes. Despite the majority

Table 1. Patient Demographics and Perioperative Data

Data (n = 52)	**Measures**
Mean age ± SD, years	32.4 ± 7.6
Number of males (%)	47 (90)
Number of right-handed individuals (%)	50 (96)
Number of dominant hand injuries (%)	31 (60)
Number of injuries sustained at workplace (%)	52 (100)
Mean preoperative total active motion ± SD, degrees	167 ± 62
Digit involved, n (%)	
Thumb	11 (21)
Index finger	13 (25)
Middle finger	16 (31)
Ring finger	6 (12)
Little finger	6 (11)
Tissue involved, n (%)	
Bone	27 (52)
Soft tissue	18 (35)
Tendon	7 (13)
Diagnosis classification, n (%)	
Open laceration	14 (27)
Open tuft fracture	13 (25)
Phalangeal fracture	13 (25)
Traumatic amputation	12 (23)
Type of surgery performed, n (%)	
Nail bed repair	11 (21)
Open reduction and internal fixation	11 (21)
Tendon repair	7 (14)
Wound debridement and amputation	23 (44)
Mean days from admission to surgery ± SD, days	1.6 ± 1.9
Mean length of hospitalisation ± SD, days	2.9 ± 1.5
Mean duration of hospitalisation leave ± SD, days	12.4 ± 15.8
Mean duration of rehabilitation ± SD, weeks	9.3 ± 7.0
Mean number of therapy sessions attended ± SD	6.5 ± 4.2
Mean number of therapy sessions per week ± SD	0.9 ± 0.5

having excellent or good outcomes, only 10 out of 52 patients (19%) returned to work after recovery. Multiple regression analyses found that initial TAM was the only significant predictor for the final TAM (P <0.0001) and for achieving "excellent" or "good" ASSH categories (P <0.0001). There were no good predictors for change in TAM. Number of days from admission to surgery was the only significant predictor for return to work status (P = 0.05).

A stable, mobile and sensate fingertip is important to the overall function of the hand. Although fingertip injuries are unlikely to be life-threatening, they can result in permanent impairment[6] and a detrimental effect on quality of life and independence.[7,8] This is especially significant amongst workers whose livelihood depends on the use of their hands, and is reflected by the low percentage of patients who returned to work after recovery.

A novel finding in our study is that preoperative TAM is a significant predictor of postoperative TAM and predictor of "good" and "excellent" postoperative outcomes. This information will be useful for preoperative counselling, managing of expectations and setting of postoperative rehabilitation targets.

Early treatment after fingertip injury is one of the prerogatives for successful treatment. Our findings are in concordance, showing that earlier treatment was a significant predictor of return to work status. Apart from early surgical treatment, early return to work may potentially be beneficial. Hung et al studied 28 adult male subjects who suffered from work related finger amputation and reported better rehabilitative outcomes if patients who returned to work early after the treatment, started working with decreased workload which would be gradually increased over time[9].

In our study, despite satisfactory improvements of TAM, only 10 out of 52 patients (19%) returned to work. This contrasts with Cabral et al who conducted a cross-sectional of 35 workers, mostly low-educated, with various hand injuries, and reported an 85.7% return to work rate, with the majority of injured employed in the same industry.[10] This may allude to non-medical factors driving the failure to return to work. One such factor may be premature termination, as the cost to replace a worker may be lower than the burden of medical treatment and rehabilitation. This could be compounded by the inability to manage disability at the workplace.

Although we used prospectively collected data, our study is still prone to bias due to its retrospective nature. We also did not have data related to reasons on low return to work status. Further studies exploring reasons for the low return to work rate will help to shed light on the interplay between factors such as the socio-economic status of workers, country of origin, nature of employment and type of contract.

To the authors' knowledge, this is the first study evaluating the functional outcomes and return to work status in migrant construction workers with fingertip injuries following surgery. Migrant workers are an integral part of our society, contributing to Singapore's development and economic growth. Improving care for this population would include reducing workplace injuries, optimising surgical timing, technique and postoperative rehabilitation, as well as addressing the patient's ability to return to functional employment.

Acknowledgement

We would like to extend our sincere appreciation to the team at Singapore Chief Residency Programme and HealthServe for inspiring this work on migrant workers. We would also like to thank the silent heroes in our community, the migrant workers themselves for contributing to nation building.

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Letter to the Editor

The Role of Social Media during the COVID-19 Pandemic

Dear Editor,

With the widespread implementation of social-distancing measures, the coronavirus disease (COVID-19) pandemic has resulted in an exponential increase in screen time for everyone. Personal and professional lives have merged through platforms such as Facebook, Twitter and Instagram, unified in isolation. By listing the ways in which social media has been used during the pandemic locally and globally, we hope to inspire readers to leverage on social media in employing novel methods in medical education, research, patient care and staff support. We also present potential pitfalls based on current literature.

Spearheading Education and Research

To circumvent the restrictions placed upon traditional face-to-face pedagogical methods, students and educators have been utilising social media for medical education. Twitter has been used to create global networks of information by facilitating academic forums and developing scholarly work through crowdsourcing.[1] To solicit real time knowledge, the hashtag #FOAMed (Free Open Access Medical Education) is also increasingly being used by the online medical community to collaborate and share best practices at a rate faster than large international organisations.[1]

Social media encourages brevity — it is commonly superseded by punchy tweets and visual-heavy content. By condensing daily statistics and evolving measures into nuggets of information that are easily disseminated to both the public and healthcare institutions, infographics effectively associate data with decreased cognitive load and stronger reader preferences. In Hong Kong, an infographic for airway management for suspected COVID-19 patients was distributed via Twitter and WeChat, supporting healthcare workers (HCWs) across multiple countries.[2]

Social media can also be used in the field of disease epidemiology. Twitter messages, particularly when location services are tagged can provide real-time approximations of disease prevalence without the delay of scheduled official releases.[3] The trending of key words can reflect public concerns, giving authorities a sense of public sentiments. By mining data from Sino Weibo, public officials in Wuhan, China, were able to identify the elderly as a vulnerable population and subsequently directed the appropriate support resources.[4] Any research in infectious disease in today's age of digital globalisation would be incomplete without tapping into the power of technology and social media for its development.[5]

Unfortunately, the qualities of social media such as its extensive penetrance and speed of information transmission have ironically led to the rapid proliferation of fake news through its various platforms. A recent study found that 27.5% of the most watched YouTube videos about COVID-19 included misinformation, reaching 62 million views globally.[6] Such falsehood engender widespread public anxiety, life-threatening self-medication and non-compliance to COVID-19 measures.[6] The influence of social media is so strong that the World Health Organisation has set up an Information Network for Epidemics aimed at tackling the "infodemic" by correcting and controlling the spread of false information.[7] Measures include educating the public on indiscriminate dissemination of fake news as well as ensuring the availability of official sources of information to allow verification of online content.

Patient Care and Staff Support

The cessation of physical interactions during this pandemic has undermined how we practice patient-centred care, defined by in-person interaction. By tapping unto social media's diverse tools either in the form of audio or text, HCWs can facilitate virtual communication between isolated and sometimes dying patients with their loved ones, thereby comforting patients and supporting their bereaved family and friends.[8]

Social media can also provide emotional support for frontline HCWs who face significant psychological distress due to increased workload, social isolation, stigmatisation as well as concerns about being sources of infection to self and family members.[9] In Wuhan, WeChat was used to provide support to frontline workers with issues of grief and burnout.[10] Locally, senior management staff regularly spread messages of encouragement to all frontline workers within and beyond the healthcare sector via digital avenues (see Figure 1). Through regulated digital applications, social workers and therapists can also set up and promote peer support groups (see Figure 2). These platforms are important in creating safe spaces for HCWs to express strong emotions as they navigate complex issues of grief, uncertainties and ethical dilemmas relating to their duty of care to patients (see Figure 3).[11] Through social media, members of the public are also able to express appreciation towards HCWs and dispel any misconceptions about them, strengthening solidarity among HCWs and the community.

However, despite its promises, social media remains an unfamiliar platform to HCWs who may report a lack of technical knowledge in accessing social media.[12] Some HCWs perceive social media to be inefficient and a burden that takes away time and resources from their primary duties. Some also worry about damage to their professional image, with potential lawsuits for violations of personal and professional boundaries.[13] An holistic collaboration between the respective stakeholders such as government bodies, hospital administrators, HCWs as well as various healthcare-related community groups is thus necessary to encourage and optimise the use of social media. In fact, given the borderless nature of such infectious disease outbreaks, an

Fig. 1. An Instagram post showing appreciation to unsung heroes labouring during the COVID-19 pandemic.
(Reference: Nusmedicine. The COVID-19 Chronicles. Instagram; 2020)

Fig. 2. Students from Duke-NUS Medical School encouraging the healthcare staff on the frontlines of COVID-19 via a video posted on Instagram.
(Reference: Singhealthmedicalhumanities. True colours. Instagram; 2020)

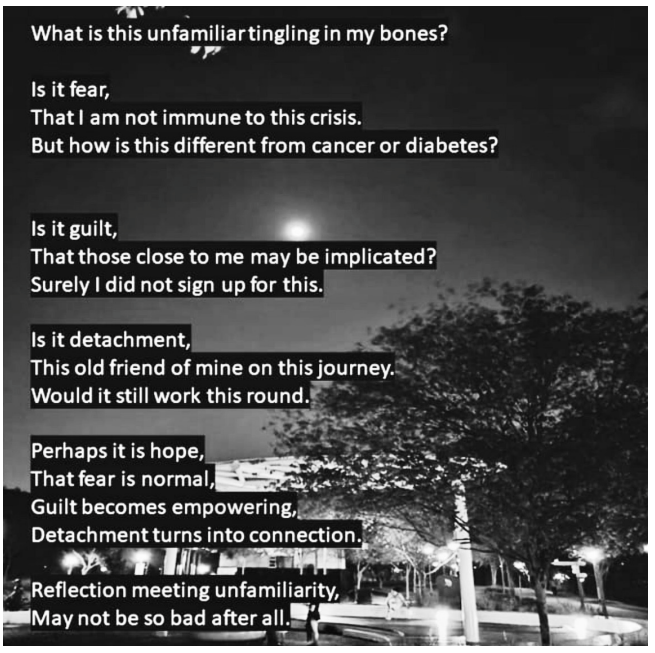

Fig. 3. An example of poetry expressing ineffable and heartfelt emotions during stressful periods on Instagram.
(Reference: Singhealthmedicalhumanities. Poem. 2020)

international effort of social media utilisation is also of utmost importance.[14] Only when multiple levels of society see the relevance of social media and are unitedly reassured about its safety, can it gain traction to mitigate the adverse impacts of any healthcare crisis, especially one as contagious as COVID-19.

Conclusion

What is clearly emerging form this current pandemic is the imminent acceleration of information technology (IT) infrastructure development and digitalisation across all sectors worldwide.[15] The potential of social media in healthcare is no longer something we can put aside; its systematic development, together with its utilisation for the good of our patients and fellow colleagues, is warranted.

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Rationale for a Singapore Transthyretin Amyloidosis Registry

Dear Editor,

Amyloidosis is a protein mis-folding disorder, occurring when serum proteins mis-fold into unstable monomers which then self-aggregate into beta-pleated sheets of insoluble amyloid fibrils.[1] The abnormal deposition of these fibrils in end-organs eventually result in organ dysfunction. Light chain (AL) amyloidosis and transthyretin (TTR) amyloidosis are the most common forms of amyloidosis seen in clinical practice. AL amyloidosis is a plasma cell dyscrasia, resulting from abnormal production of monoclonal immunoglobulin light chains by an abnormal clone of plasma cells. As such, the mainstay of treatment for AL amyloidosis is the obliteration of the plasma cell clone using chemotherapy, or stem cell transplantation.

On the other hand, TTR amyloidosis results from mis-folding of native TTR protein, which is produced in the liver. TTR is a tetrameric transporter protein produced by the liver and is ubiquitous in the blood stream. However, TTR amyloidosis occurs when these TTR tetramers dissociate and mis-fold into beta-pleated amyloid fibrils, which deposit in end-organs. This condition can either be secondary to an underlying genetic mutation resulting in unstable TTR tetramers, termed hereditary transthyretin amyloidosis (hATTR), or occur in the absence of apparent genetic mutation, term 'wide-type' amyloidosis (wtATTR).

TTR amyloidosis is a multi-systemic disease, with natural history and organs of involvement differing slightly between hATTR and wtATTR. wtATTR is a disease predominantly affecting elderly men, with cardiomyopathy, carpal tunnel syndrome and spinal canal stenosis as the main presenting pathologies.[2]

hATTR, occurring in younger patients, presents with a higher incidence of gait instability, gastrointestinal symptoms, urinary incontinence and neuropathic pain, compared to wtATTR.[3] These clinical manifestations result in significant morbidity and mortality. Disease-modifying treatment, therefore, can potentially have a greater impact on this group of patients, improving their functional status, quality of life and preventing premature death. Another important aspect of hATTR is the impact on future generations. Identifying the genetic mutation in affected individuals can aid in screening or even genetic testing in first-degree relatives. While there is currently no guideline for the management of asymptomatic carriers of hATTR mutations, the knowledge gained from a disease registry can represent the first step in trying to address the many ethical challenges in managing this complex genetic disease, not only for the affected individual, but also for the family.

Renewed Interests in Transthyretin Amyloidosis

The past 5 to 10 years have truly been a renaissance period for TTR amyloidosis. Previously thought to be a benign disease affecting elderly men who died with, instead of from, the disease, we are experiencing a paradigm shift in how we understand this condition. We have gained much insight into the epidemiology of TTR amyloidosis and learnt much about how to diagnose this condition. More importantly, specific therapeutic agents have been developed for the treatment of TTR amyloidosis.

In epidemiological studies, it has been found that TTR amyloidosis is much more prevalent that we thought, and most likely under-diagnosed. In autopsy studies, 25% of individuals aged 85 and above were found to have TTR amyloid fibrils in the myocardium.[4] Specific to cardiomyopathy phenotype (ATTR-CM), up to 13% of patients with the diagnosis of 'heart failure with preserved ejection fraction' (HFpEF) were found to have TTR amyloidosis as the underlying pathology.[5] ATTR-CM is also increasingly being diagnosed in younger patients, with some patients having severe symptoms and even receiving heart transplantation as treatment for their heart failure.[6]

There has also been increasing awareness about the multi-systemic manifestation of TTR amyloidosis. Carpal tunnel syndrome was present in up to 68% of patients diagnosed with wtATTR, preceding the diagnosis of amyloidosis by 1 to 14 years.[7] In a histological analysis of patients who underwent carpal tunnel surgery, 10% of surgical specimens were positive for amyloid deposits.[8] Some of these patients were subsequently diagnosed with ATTR-CM.

There has also been a radical shift in how ATTR-CM is being diagnosed. Previously, every patient had to undergo tissue (commonly endomyocardial) biopsy for the diagnosis of ATTR-CM. However, the current diagnostic algorithm proposes the ultilisation of technetium-based scintigraphy to replace invasive cardiac biopsy in diagnosing ATTR-CM. In patients with increased cardiac uptake on scintigraphy and absence of monoclonal proteins in the serum or urine, non-invasive testing had a 100% specificity and a 100% positive-predictive value, when compared against the gold standard of endomyocardial biopsy.[9]

Epidemiology and diagnostics aside, all this knowledge would have been meaningless if nothing can be done for patients after clinching the diagnosis. That would have been true 5 years ago. Various compounds for the treatment of TTR amyloidosis are now available, targeting different checkpoints of the disease process. Most of these compounds were initially studied in patients with familial amyloid polyneuropathy (FAP), showing encouraging outcomes. Studies of these novel treatment options have since been extended to patients with ATTR-CM. Patisiran and inotersan inhibit TTR production at hepatocyte nucleus level. They have been shown to retard neurological deterioration and improve quality of life in FAP.[10,11] Tafamidis is a stabiliser of TTR tetramers, preventing dissociation into monomers which then form the insoluble fibrils. In patients with ATTR-CM, tafamidis reduced all-cause mortality compared to placebo over 5 years, becoming the first disease modifying treatment for patients with ATTR-CM.[12] Antibodies targeting serum amyloid P (SAP) have also shown promise in early phase studies, in promoting macrophage-mediated clearance of end-organ amyloid fibrils.[13] Of all the novel compounds mentioned, tafamidis has now obtained the Health Sciences Authority (HSA)'s approval for use in TTR amyloidosis, making it the first amyloidosis-specific therapy available in Singapore.

Need for Data in Transthyretin Amyloidosis

While TTR amyloidosis is not a new disease, it has suffered from years of neglect, mainly from the belief that nothing can be done for these patients. We do not have local data for the genotype, phenotype and natural history of TTR amyloidosis in the multi-ethnic Singaporean population. This is especially important, given our aging population and the impending silver tsunami facing our healthcare system.

wtATTR-CM is still predominantly seen in older patients. Diagnosing this condition in this population is notoriously difficult, given the high prevalence of hypertension, diabetes mellitus and chronic kidney disease. These conditions often affect the myocardium and mimic ATTR-CM on cardiac imaging.

From the health economics point of view, choosing the right patient population for disease-modifying treatment is also of paramount importance. Given the often-prohibitive costs of drugs in the treatment of TTR amyloidosis, financial assistance is nearly always required for patients started on these drugs. Only by knowing the natural history of this disease in our local population can we identify the patients who will derive the most benefits from receiving disease-modifying drug treatment, as healthcare resources are limited.

Besides disease modifying drugs, organ transplantation represents the only other viable treatment option for TTR amyloidosis. In hATTR, liver transplantation can result in the cessation of the mutant TTR protein production and has been performed in patients with FAP. However, pre-transplant neurological symptoms typically remain. This treatment modality has been shown to be most beneficial in patients with the Val30Met mutation, as liver recipients with other hATTR mutations frequently show progression of cardiomyopathy despite transplantation.[14] While heart transplantation has been performed in patients with advanced ATTR-CM, low organ availability in Singapore remains an issue. A local patient with advanced ATTR-CM has been implanted with a durable left ventricular assist device but that remains an expensive therapeutic option which is not readily accessible.[15] With the genotype and phenotype data available in the registry, we hope to provide guidance

in selecting patients for organ transplantation, even comparing the cost-effectiveness of transplantation versus disease-modifying drug treatment.

Lastly, from the research standpoint, the increased global interest in TTR amyloidosis provides exciting opportunities for clinicians with interest in TTR amyloidosis. Data collected from our local patients will allow us to potentially collaborate with other established amyloid registries, such as the THAOS (Transthyretin Amyloidosis Outcomes Survey) registry, to compare the characteristics of world-wide patients and our Southeast Asian cohort.[3]

A Singapore Transthyretin Amyloidosis Registry

Singapore's small size, well-connected healthcare systems and widespread use of healthcare informatics provide us with a unique advantage in starting a comprehensive registry, capturing patients diagnosed with this relatively uncommon condition. Although not every institution has scintigraphy and genetic testing capabilities, our island is small enough for inter-institutional collaboration, ensuring patients receive the right diagnosis and treatment no matter which part of the island they are residing in. With accurate diagnosis and data-capturing of as many patients with TTR amyloidosis into a registry, we can answer many questions about the characteristics, natural history and even genotype of our local TTR amyloidosis population. This will be a long-term multi-disciplinary endeavour, involving cardiologists, neurologists, haematologists, nuclear physicians, pathologists and geneticists with special interests in TTR amyloidosis.

Initial efforts will be focused on answering questions about the epidemiology of TTR amyloidosis in Singapore, factor contributing in delays in diagnosis, optimal diagnostic modalities/ algorithms for our local population and the impact of comorbid conditions on these patients. Subsequently, we aim to examine the different management strategies for these patients, identifying the group of patients who derive the most benefit from expensive disease-modifying treatment. Lastly, we hope to study the long-term natural history of our local TTR amyloidosis patients — those who receive disease-modifying treatment as well as in those who do not.

Conclusion

The field of amyloidosis has been given a new lease of life over the past 5 years, especially transthyretin amyloidosis. New non-invasive algorithms have been developed for diagnosing this condition and, for the first time, evidence-based treatment with proven benefits can be offered to TTR amyloidosis patients. The approval of the first disease-modifying drug by the HSA is truly a promising start, as we await other treatment agents to complete their trial and potentially enter the local scene. A national effort will be definitely important for us to better understand the characteristics of our local TTR amyloidosis patients, potentially developing a local screening and diagnostic algorithm best suited to our unique healthcare infrastructure. Lastly, it provides us a platform to hop onto the global research bandwagon, with the eventual aim of establishing Singapore as a regional centre of excellence for TTR amyloidosis treatment and research.

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Initial Experiences of Laboratory Diagnosis of Coronavirus Disease 2019 (COVID-19) in Singapore General Hospital

Dear Editor,

On 31 December 2019, the World Health Organization (WHO) was alerted to the emergence of a novel zoonotic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China.[1] Shortly thereafter, Corman et al published a reverse transcription polymerase chain reaction (PCR) protocol for SARS-CoV-2 on 13 January 2020.[2] The Department of Molecular Pathology in the Singapore General Hospital put this test into service on 23 January 2020 and was the first to detect the coronavirus disease 2019 (COVID-19) in a patient in Singapore on the same day. The test was clinically validated against the patient's travel history, presenting signs and symptoms and chest radiograph findings. It was also validated against a confirmatory in-house test performed by the National Public Health Laboratory. Although positive controls were provided by the European Virus Archive Global, to avoid any delay in getting the controls shipped to Singapore, a severe acute respiratory syndrome coronavirus extract was used as a positive control since we were aware that the E gene in both viruses would be detected by the assay.

By 29 February 2020, a total of 3079 tests were performed on 1945 patients; 74 positive results were found in 13 COVID-19 patients. As countries from around the world ramp up tests for COVID-19, we believe our experience is useful for both clinicians and laboratories alike.

For sample collection, a deliberate choice was made to use dry Dacron swabs with no media because these were more likely to be still readily available during a pandemic. When swabs in media were accepted, those with smaller media volumes (1 mL) resulted in better sensitivity from less sample dilution.

Most of the samples that were received were oropharyngeal swabs. In our experience, swab yields are extremely operator-dependent. For example, a physician was still able to take swabs that were PCR-positive from 2 patients who had 2–4 days of intervening negative PCR after swabs were taken by other physicians. There were also cases when interjacent swabs were negative but were followed by strong positive results, such as in 1 patient who had consumed food and drinks before a negative sample was found. This variability may account for some of the apparent intermittent viral ribonucleic acid (RNA) detection previously reported elsewhere.[3] In our experience, patients can remain swab-positive for up to 25 days. Hence, adequate training in sample collection is just as critical as having a well-optimised assay. It is also important to collect multiple samples from the same patient.

For RNA extraction, easyMAG (bioMérieux, Marcy-l'Étoile, France) was used because the virus inactivation/lysis step can take place in biosafety cabinets before extraction resumed in automated extractors. It is important to note that not all commonly used lysis buffers are able to effectively inactivate viruses.[4]

To prioritise assay sensitivity, larger extraction volume input (500 μL) and lower eluate output (25 μL) were chosen, although this had to be balanced against higher PCR inhibition risks. An RNA internal control is therefore important and should be incorporated into the extraction step. This protocol may not work on media other than phosphate-buffered saline.

Initially, the WHO protocol was followed by screening for the E gene (95% limit of detection [LOD] 16 copies/reaction) and running a confirmatory test with ORF1ab or RdRp gene assay. However, detection of RdRp is not reliable when the E gene threshold cycle value is >30. We have since switched the confirmatory assay to ORF1b-NSP-14 (95% LOD 31 copies/reaction) which has much better sensitivity.[5]

Unexpectedly, contaminated primers and probes from reputable manufacturers were encountered repeatedly because they were also producing synthetic E gene oligonucleotides for use in assay validation or as positive controls. This has implications for laboratory-developed tests and rigorous testing of each

new lot is advisable. All low positive results should be repeated and concurrently with another equally sensitive target such as ORF1b-NSP-14. Laboratories can also select manufacturers—TIB Molbiol GmbH (Berlin, Germany) in our case—that produce only primer probes, not synthetic oligonucleotides.

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Not Another Rodent Ulcer

A 45-year-old Chinese sewage pipe repairman with a longstanding history of untreated human immunodeficiency virus (HIV) infection presented with a 3-month history of multiple ulcers with red papules on his face. The lesions did not improve with oral co-amoxiclav. He reported high-grade fever and weight loss of 8 kg over the preceding 3 months. He had stayed for 2 weeks in Chiang Rai, Thailand 5 months prior to his presentation. Clinical examination revealed two irregular, deep, large ulcers on his forehead and left cheek with multiple erythematous papules on his face (Figures 1 and 2). He also had widespread cervical and axillary lymphadenopathy. Skin biopsies taken from the edge of the forehead ulcer are as shown (Figures 3A and 3B).

What is your diagnosis?

A. Syphilitic chancre
B. Ecthyma gangrenosum
C. Disseminated talaromycosis
D. Pyoderma gangrenosum
E. Squamous cell carcinoma

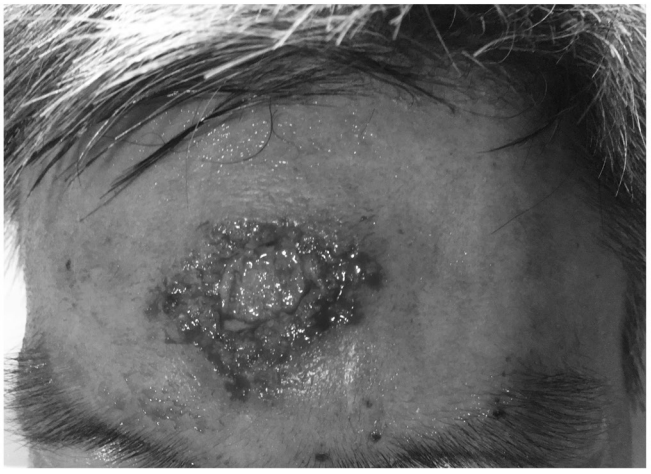

Fig. 1. Clinical photograph showing a central forehead ulcer with irregular undermined edge and granulation tissue at base of ulcer. Crusted erythematous papules are seen along the left eyebrow.

Findings and Diagnosis

The clinical photographs show two large ulcers with haemoserous crusting and multiple erythematous papules on the face. The patient reported that the ulcers initially begun as small erythematous papules, which enlarged and ulcerated subsequently. There were also ulcers noted on the soft palate and pharynx, as well as multiple excoriated papules on the patient's limbs.

Investigations revealed leucopenia [2.2 x 10^9/L; normal 4-11 x 10^9/L], lymphopenia [0.25 x 10^9/L;

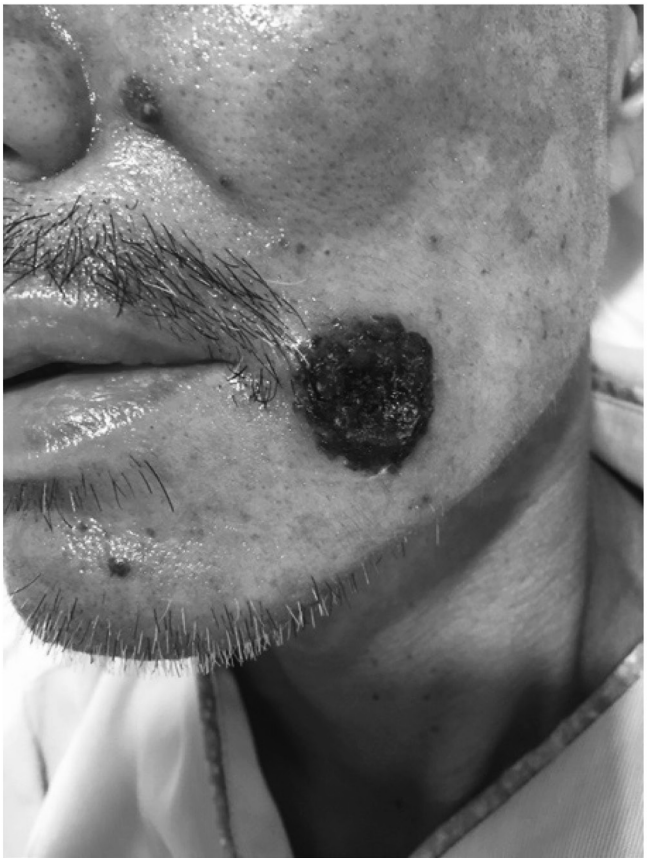

Fig. 2. Erythematous papules with central umbilication on the left nasolabial fold and chin are seen within the vicinity of a large left cheek ulcer topped with a haemoserous crust

Correct answer: C

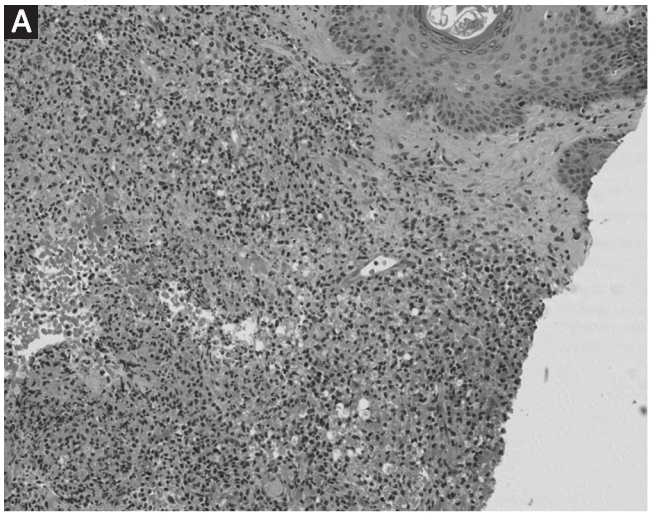

Fig. 3A. Hematoxylin and eosin stain of an incisional biopsy from the edge of the forehead ulcer (Original magnification x100).

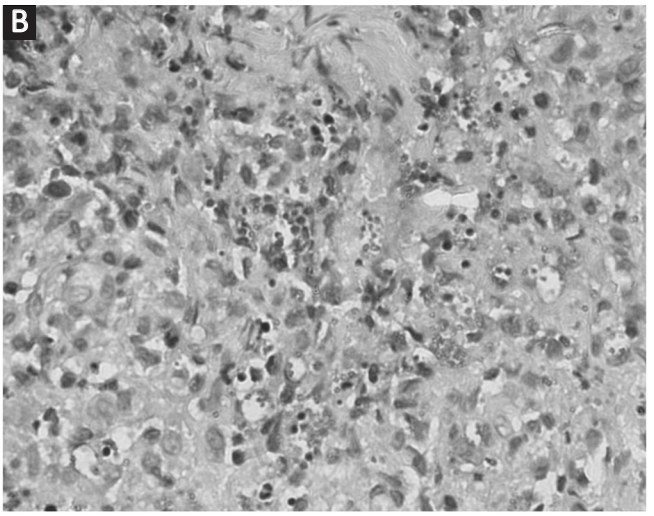

Fig. 3B. The same specimen stained with Periodic acid-Schiff stain (Original magnification x 400).

normal 0.9-3.3 x 10^9/L], CD4 count <20cells/μL, and a HIV viral load of 693,600 copies/ml suggestive of advanced HIV. The rapid plasma reagin (RPR) was non-reactive and syphilis line immunoassay (LIA) IgG was 12 RU/mL (negative). Computed tomographic (CT) imaging showed soft tissue thickening in the posterior nasal space and bilateral cervical, supraclavicular, axillary and intra-abdominal lymphadenopathy. There were scattered centrilobular nodules present in both lungs.

Histopathologic examination of the edge of the forehead ulcer revealed a dense dermal infiltrate of foamy histiocytes and multinucleated giant cells containing ovoid organisms, which stained positive on Grocott's methenamine silver (GMS) and periodic-acid Schiff (PAS). The overlying epidermis showed compact hyperkeratosis with no atypia. Gram stain did not show any bacteria. Blood cultures and biopsies of the forehead ulcer, posterior nasal space and cervical lymph nodes grew talaromyces marneffei, supporting a diagnosis of disseminated talaromycosis infection. Herpes simplex virus PCR swab and tissue mycobacterial culture from the ulcer were negative. Blood sample for cytomegalovirus PCR also returned negative.

He was commenced on abacavir 600mg/lamivudine 300mg once daily and dolutegravir 50mg once daily for HIV and initiated on intravenous amphotericin 5mg/kg/day for disseminated talaromycosis. Amphotericin was switched to intravenous voriconazole 4mg/kg every 12-hourly due to acute kidney injury. His cutaneous lesions resolved after a total of 29 days of systemic antifungals. Seven months later, he was admitted for abdominal pain, ascites and pleural effusion. Interval CT thorax, abdomen and pelvis confirmed persistence of lymphadenopathy. Cytological examination of peritoneal fluid and pleural aspirate as well as bone marrow biopsy confirmed diagnosis of plasmablastic lymphoma. Bone marrow and peritoneal fluid cultures were negative. He was switched to oral itraconazole 200mg twice daily after resolution of cutaneous lesions to prevent a relapse of talaromycosis. However, due to non-compliance to his HIV medications and clinic visits, his CD4 count remained low and he eventually demised from his lymphoma.

Discussion

Disseminated talaromycosis is an Acquired Immune Deficiency Syndrome (AIDS) defining illness which presents with multiple acneiform or umbilicated facial papules in an immunocompromised patient with a CD4 count lower than 100 cells/μL.[1] Other uncommon cutaneous presentations include facial ulcers, orogenital ulcers, panniculitis and Sweet Syndrome. Non-cutaneous manifestations may include fever, weight loss, lymphadenopathy, hepatosplenomegaly and arthritis.[1]

Talaromycosis marneffei, previously known as penicilliosis marneffei, is transmitted through the inhalation of the infectious conidia from a soil reservoir and should be considered in an immunosuppressed patient who presents with fever, weight loss and

multiple facial lesions after returning from an endemic region such as Thailand, Vietnam, and China.[2]

A diffuse dermal infiltrate comprising of foamy histiocytes or multiple granulomata containing unicellular round-ovoid organisms highlighted by GMS or PAS stains[2,3] as our patient's case depicts, is consistent with cutaneous talaromycosis. The extracellular elongated cells with centrally located transverse septa highlighted by GMS stain is useful in distinguishing T. marneffei from histoplasma capsulatum infection.[3] Blastomycosis, cryptococcosis and molluscum contagiosum are other differential diagnosis to consider for facial erythematous papules with central umbilication. Tissue or blood fungal culture with speciation of the fungal organism confirms the diagnosis.[2,3]

The key differential diagnoses to consider for non-healing facial ulcers in an immunocompromised host include ecthyma gangrenosum, atypical mycobacterial, syphilitic cutaneous gumma, cytomegalovirus, herpes simplex infections, atypical pyoderma gangrenosum and squamous cell carcinoma.

Ecthyma gangrenosum typically presents with a necrotic ulcer on the buttocks and lower extremities. The commonest aetiology is due to pseudomonas aeruginosa, however other angio-invasive organisms such as escherichia coli and mucor have been implicated.[4] The absence of necrotizing haemorrhagic vasculitis[4] or bacteria on Gram stain make ecthyma gangrenosum an improbable differential diagnosis.

Extragenital syphilitic chancre and cutaneous gumma would be unlikely in view of the negative syphilis line immunoassay and RPR titre. The typical histological findings of superficial and deep dermal infiltrate of plasma cells and endothelial swelling as seen in syphilis were not present in our biopsy.

Pyoderma gangrenosum in patients with HIV more commonly involves the perineum. Moreover, our patient's facial ulcer biopsy lacked the dense neutrophilic dermal infiltrate as would be anticipated in pyoderma gangrenosum.

Squamous cell carcinoma can present as cutaneous ulcers on sun-exposed areas such as the face. However, the lack of dysplastic keratinocytes with invasion into the dermis layer seen on histopathological examination makes it an incorrect diagnosis in this case.

Expeditious treatment with broad-spectrum antifungal agents such as intravenous amphotericin is imperative if disseminated talaromycosis is suspected. Treatment with amphotericin B has been shown to confer a survival benefit compared to intravenous itraconazole for disseminated talaromycosis. Mortality as high as 75% has been reported if treatment is delayed.[5]

Patients with disseminated talaromycosis as an AIDS-defining illness should also be commenced on antiretroviral therapy and secondary prophylaxis with oral itraconazole or voriconazole until the CD4 count is sustained at more than 100cells/μL.[2]

This case illustrates the diagnostic dilemma faced by clinicians treating HIV-positive patients with non-healing cutaneous ulcers and highlights the importance of a detailed physical examination and an accurate patient travel history.

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