Original Article

An 11-year Review of Dermatomyositis in Asian Patients

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Abstract

Introduction: Dermatomyositis (DM) is a multisystem inflammatory disease with a strong association with malignancy. We aimed to describe a series of Asian patients with DM and identify any significant clinical factors associated with malignancy. Materials and Methods: This was a retrospective review of a multi-racial cohort of 69 Asian patients diagnosed with DM over an 11-year period from 1996 to 2006. Results: Malignancy was detected in 15 out of 68 patients (22%), the most common of which was nasopharyngeal carcinoma (7 cases). Compared to the non-malignancy group, the malignancy-associated group was older and had more male patients. There were no statistically significant clinical, serological or laboratory factors associated with a higher risk of malignancy. Conclusion: This study highlights the importance of ongoing malignancy screening especially for nasopharyngeal carcinoma in Asian patients with DM.

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Key words: Malignancy, Myositis, Nasopharyngeal carcinoma, Photosensitivity

Introduction

Dermatomyositis (DM) is an acquired multisystem inflammatory disease with prominent, characteristic cutaneous manifestations and proximal muscle myopathy. A clinically distinct amyopathic variant with typical skin signs but no muscle disease had been described as well.[1,2]

Apart from systemic complications such as respiratory or oesophageal diseases, early recognition and treatment of this disease is of crucial importance because of its strong association with underlying malignancy in adult DM.[3-7] Malignancy has been reported to occur concurrently with, precede or follow the diagnosis of DM. This increased risk of cancer is highest within the first 3 years and declines with time, with malignancy reported up to 5 years after the diagnosis DM.[7-12] In Singapore, nasopharyngeal carcinoma had been found to be over-represented.[5,6]

The aims of this 11-year retrospective study were to describe a series of patients with this disease and to identify any significant clinical risk factors associated with malignancy.

Materials and Methods

All patients with a diagnosis of adult DM at the National Skin Centre (NSC), Singapore from 1996 to 2006 were identified from our electronic database and reviewed. The diagnosis was based on classical cutaneous features with a consistent skin biopsy.[9] Muscle involvement was evaluated based on the clinical assessment of proximal muscle weakness, laboratory markers (serum creatine kinase and aldolase) and electromyogram (EMG) or muscle biopsy, if indicated. Amyopathic DM was diagnosed if clinical and laboratory evidence of muscle involvement was absent for at least 6 months.

Malignancy screening was performed for all patients, based on our institution's guidelines. The standard screening investigations included a complete history and examination, laboratory investigations including: full blood count, renal and liver function tests, urinalysis, tumour markers (carcinoembryonic antigen, carbohydrate antigen 19-9, alpha-fetoprotein for all patients; cancer antigen 125 for females and prostate-specific antigen for males), stool for

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occult blood and chest x-ray. All patients were referred for ear, nose and throat evaluation including endoscopy of the posterior nasopharynx, Epstein-Barr virus (EBV) serology and post nasal space biopsy where indicated. In addition, all female patients were referred for gynaecological evaluation and breast examination, Pap smear, mammogram and pelvic ultrasound were performed. Gastrointestinal endoscopy and computed tomography (CT) imaging of the thorax, abdomen and pelvis were performed if indicated, based on clinical or laboratory findings.

A diagnosis of malignancy was obtained from the patient's medical records. Cases of juvenile dermatomyositis aged below 12 years were excluded. In addition, all patients were matched with the Singapore Cancer Registry, a nationwide registry established since 1968 for the capture of cancer cases in Singapore, to ensure a comprehensive capture of cancer occurrences within this population. Cases were deemed to be associated with malignancy if the diagnosis of DM had preceded or followed the malignancy by up to 5 years. The study was reviewed and approved by the institutional ethics committee.

Statistical Analysis

The strengths of the factor-cancer associations were measured by odds ratios (ORs) and their 95% confidence intervals (CIs), which were estimated by fitting unconditional logistic regression models and adjusting for age and gender in the models. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 17.0 (Chicago, IL, USA). Two-sided *P* values under 0.05 were considered statistically significant.

Results

Demographics and Clinical Signs

A total of 68 patients with the diagnosis of DM were identified. Out of these 68 patients studied, there were 47 female and 21 male patients giving a female to male ratio of 2.2:1. There were 62 Chinese (91.2%), 2 Malay (2.9%), 1 Indian (1.5%) and 3 of other races (4.4%). Their age ranged from 13 to 83 years, with a mean age of 50 years.

The mean duration of disease prior of diagnosis of DM was 6.3 months (range, 1 to 47 months). Patients were followed up for a mean duration of 24.7 months (range, 0.25 to 155 months). The linkage with the Singapore Cancer Registry identified all cancer incidences among the patients up to June 2009.

The commonest clinical signs in our series were Gottron's papules/sign (72.1%), a photodistributed rash (70.8%) and heliotrope rash (57.4%). The other common cutaneous signs were nail fold telangiectasia (51.5%) and poikiloderma (47.1%), followed by itch/excoriations (44.1%), malar erythema (26.5%), alopecia (17.6%), vasculitic lesions (17.6%) and ragged cuticles (16.2%). Two patients had calcinosis and 1 patient had vesiculo-bullous lesions.

Muscle Involvement

Muscle involvement was detected in varying degrees of severity, ranging from clinical complaints of muscle weakness, biochemical evidence of elevated muscle enzymes, and confirmed muscle involvement based on abnormal EMG and/or muscle biopsy reports.

Three main groups of patients were identified: 38 patients (55.9%) presented with clinical proximal muscle weakness; 24 of these 38 patients had laboratory or histological evidence of myositis (elevated muscle enzymes or abnormal EMG/muscle biopsy). Twelve (17.6%) patients had no clinical muscle weakness but had laboratory evidence of myositis (abnormal muscle enzymes and/or EMG), 18 (26.5%) were truly amyopathic with no clinical weakness or laboratory evidence of myositis.

Associated Malignancy

Overall, malignancies were detected in 15 patients (22%), the most common of which was nasopharyngeal carcinoma (NPC) (46.7 %). Other malignancies that were detected were colorectal, hepatocellular, breast, uterine and ovarian carcinomas (Table 1). The diagnosis of malignancy was made preceding the diagnosis of DM in 5 cases and concurrently or shortly after diagnosis of DM in 10 cases (mean = 9.7 months; range, 1 to 32 months). Table 2

Table 1. Diagnosis and Type of Malignancy Associated with Dermatomyositis

Type of Malignancy	No. of cases (%)	Diagnosis of Malignancy
Nasopharyngeal carcinoma	7 (46.7)	1 preceded DM (6 months) 3 concurrent 3 followed DM (32 months, 18 months, 8 months)
Colorectal carcinoma	3 (20)	2 preceded DM (24 months, 5 months) 1 followed DM (6 months)
Hepatocellular carcinoma	1 (6.7)	Followed DM (1 month)
Breast carcinoma	2 (13.3)	Preceded DM (2 months, 2 months)
Uterine	1 (6.7)	Followed DM (1 month)
Ovarian	1 (6.7)	Followed DM (2 months)

Table 2. Clinical Features in Malignancy versus Non-malignancy Associated Dermatomyositis

	Malignancy Associated (n = 15)	Non-malignancy Associated (n = 53)
Demographics		
Age	range, 43 to 81 (mean = 57)	range, 13 to 83 (mean = 49)
Female: Male ratio	1 : 3	2.53 : 1
Cutaneous signs		
Photodistributed rash	11 (73%)	35 (66%)
Heliotrope rash	10 (67%)	29 (55%)
Gottron's papules/sign	10 (67%)	39 (74%)
Nail fold telangiectasia	8 (53%)	27 (51%)
Poikiloderma	8 (53%)	24 (45%)
Itch/excoriations	6 (40%)	24 (45%)
Malar erythema	5 (33%)	13 (25%)
Alopecia	2 (13%)	10 (19%)
Vasculitic lesions	2 (13%)	10 (19%)
Muscle involvement		
Clinical muscle weakness	5 (33%)	33 (62.3%)
Myositis (clinical and/or laboratory evidence)	9 (60%)	41 (77.4%)
Laboratory tests		
Positive ANA	8/14 (57.1%)	25/44 (56.8%)
Elevated ESR (mm/h) (Elevated if >10 in males and >20 in females)	8/13 (61.5%)	21/37 (56.8%)
Histology		
Interface dermatitis	11/14 (78.6%)	30/47 (63.8%)
Positive direct immunofluorescence	2/9 (22.2%)	13/39 (33.3%)

compares between patients with and without malignancy. There were no statistically significant predictive factors for higher risk of malignancy in patients with DM (all *P* values >0.05), in terms of demographics, cutaneous signs, muscle involvement, laboratory tests and histology.

Autoimmune Markers

Anti-nuclear antibody (ANA) was positive in 33 out of 58 tested patients, with similar positivity rates in patients with associated malignancies (57.1%) and those without malignancy (56.8%).

Other autoimmune markers that were positive include anti-dsDNA (3/36, 8.3%), anti-Jo1 (1/37, 2.7%), anti-Ro (2/26, 7.7%) and anti-Mi2 (1/25, 4%). All the above markers except for anti-Jo1 were positive only in DM patients without associated malignancy.

Discussion

This case series reports a large multi-racial cohort of Asian patients with DM seen at NSC, the largest tertiary outpatient dermatological centre in Singapore. Similar to previous local studies, this study suggested that Chinese had a higher association with DM than other races.[5,6] Chinese patients comprised 91.2% of this study cohort, which is higher than proportion of Chinese in general population (75.2%) and patients seen at the NSC (78%). The female to male ratio in this study (2.2:1) is higher than that of the general population (1:1).[13] The trend towards female predilection as well a mean age of above 45 years of age is in agreement with other Western series.[14,15]

Reported malignancy prevalence rates in the literature ranged from 15% to 60%.[5,6,16-20] In this series, we performed a comprehensive search using linkage with the Singapore Cancer Registry and found a positive cancer association in 22% of patients, most common cancer being NPC (46.7%). DM is associated with a wide range of malignancy including breast, lung, colorectal cancer commonly, with no particular predilection in the Caucasian population.[3,4] In the Asian populations, however, previous dermatomyositis studies done in Singapore, Hong Kong and Taiwan concurred that NPC was the commonest associated malignancy.[5,6,17,19,20] The relative incidence of NPC in the DM studies from such at-risk populations for NPC is disproportionately higher than that of commoner malignancies such as colorectal, lung and breast cancer.

NPC is the 6th most common cancer among males in Singapore with an annual incidence of 5.5%.[21] Out of the 7 patients NPC in this series, there were 4 males and 3 females, with a mean age of 49.5 years. EBV infection is a well-established aetiological factor NPC. Although no virus has been found to be a direct causative factor for DM, previous studies have shown that disease flares and may be associated with underlying opportunistic viral infections due to herpes simplex virus and cytomegalovirus (CMV).[22,23] It would be interesting to further investigate if EBV may be involved in the pathogenesis of DM with underlying NPC.

In agreement with previous studies, this series found a trend towards an older age at diagnosis and male gender in the malignancy group.[16,19] Although there were no statistically significant clinical features, including myositis, that were predictive or associated with malignancy, several interesting clinical cases were noted. One patient had a recalcitrant course with severe cutaneous manifestations despite heavy immunosuppressive therapy and was diagnosed to have NPC 32 months after the diagnosis of DM, despite initial negative

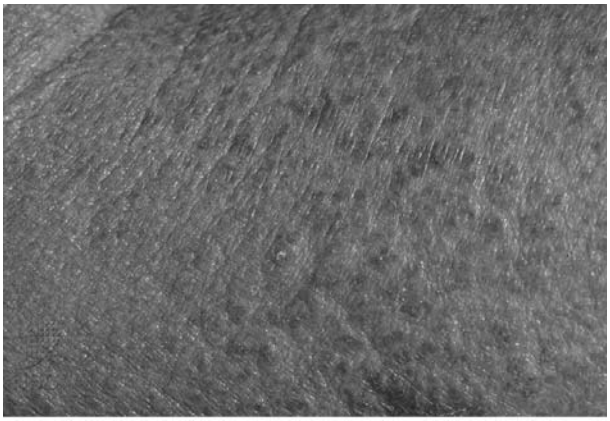

Fig. 1. Prominent hyperkeratotic papules over the extensor aspects of the forearms and dorsa of the hands in a patient with NPC.

screening. Another patient with NPC had florid cutaneous manifestations with prominent hyperkeratotic papules over the extensor aspects of the forearms and dorsa of the hands (Fig. 1). These cases highlight the importance of judicious malignancy screening particularly in DM cases with atypical or extensive cutaneous symptoms. This is in agreement with previous report of malignancy being associated in DM with severe cutaneous findings such as skin necrosis, hyperkeratotic follicular papules and vesiculo-bullous lesions.[7,24-26] The vesiculo-bullous variant has been proposed as a marker of poor prognosis and aggressive internal malignancy, in particular gynaecological malignancies.[7,26] Other findings such as periungal erythema, skin necrosis and persistently raised erythrocyte sedimentation rate have been previously reported as markers of underlying cancer.[3,8]

While ANA positivity was found to be similar in both the malignancy and non-malignancy group, it is interesting to note that other more specific autoimmune markers such as anti-Mi2, anti-dsDNA and anti-Ro antibodies were only positive in the non-malignancy group, except for one patient with DM and uterine cancer who was also positive for anti-Jo1. This suggests that these autoimmune markers are more likely to be positive in DM patients without malignancy. To the best of our knowledge, no previous studies have studied the predictive value of these autoimmune markers to help distinguish between malignancy and non-malignancy associated DM.

The limitations of this study included a relatively small sample size and short follow-up period. Given its retrospective nature, data collection was limited to case records and investigations were not standardised across all patients. Details on the clinical course and treatment of patients were not analysed. In addition, as NSC is primarily an outpatient facility, the profile of DM patients may differ from that seen by hospital-based dermatologists, rheumatologists or internists. Sparsa et al[3] reported that the prevalence of malignancy in DM patients observed by internists was higher than that seen by dermatologists. This difference was attributed to a more aggressive cancer-screening policy as well as a relatively sicker patient profile seen by internists in such in-patient settings.

We recommend a thorough malignancy screen for all adult patients diagnosed with dermatomyositis: (i) a complete history and examination, including endoscopy of the posterior nasopharynx, (ii) laboratory investigations including a full blood count, renal panel, liver function test, tumour markers (EBV IgA panel, CEA, CA19-9, AFP, CA 125 for females and PSA for males), stool for occult blood, PAP smear for females, and (iii) radiological evaluation: CXR, CT abdomen and pelvis, pelvic ultrasound and mammogram for females.

Conclusions

In summary, malignancy was associated in up to a quarter of patients with DM. No single clinical sign or marker was associated with malignancy and vigilant screening for malignancy in all DM patients is essential, especially in patients with florid skin symptoms, including atypical features such as hyperkeratosis or vesiculo-bullous lesions. In Asian patients, NPC is the commonest associated malignancy. Serum EBV IgA titres have been shown to be a potentially useful tumour marker for NPC screening and should be considered as part of the routine screening for Asian DM patients.[27] While most cancers were detected within 8 months of DM diagnosis, screening for at least 3 years is indicated.

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