Case Series

Cluster of *Staphylococcus aureus* and Dengue Co-infection in Singapore

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Abstract

Introduction: Singapore saw a resurgence of dengue infections in 2005. Concurrent bacterial co-infections in dengue is rare. Clinical Picture: We report a cluster of serious methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia or severe soft tissue infection in 5 epidemiologically linked construction workers presenting with dengue and non-resolving fever. Treatment: Surgical intervention was indicated in 4 of the 5 patients despite appropriate anti-staphylococcal therapy. Outcome: All but 1 patient were eventually discharged. Clonality and Panton-Valentine leucocidin genes were not demonstrated. Epidemiological investigations suggested that occupational contact dermatitis could have predisposed the patients to this opportunistic co-infection. Conclusion: Clinicians need to be vigilant to unusual manifestations of dengue which may signal a concomitant aetiology.

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Introduction

In recent years, Singapore has seen a resurgence of dengue fever despite the seemingly successful implementation of a nationwide *Aedes* mosquito control programme,[1] culminating in 9459 clinical and laboratory-confirmed dengue cases in 2004 and up to 13,653 cases in its 2005 dengue epidemic.[2]

Concurrent bacteraemia in patients with dengue fever (DF) is rarely reported.[3-7] These comprise mainly isolated case reports. We describe a cluster of 5 cases of methicillin-susceptible *Staphylococcus aureus* (MSSA) infection diagnosed in conjunction with DF at our institution, a tertiary dengue referral centre in Singapore.

Materials and Methods

From 4 May to 3 July 2005, we identified 5 foreign-national migrant workers from the same construction site (which was experiencing an ongoing dengue outbreak) who presented with clinical features and laboratory findings consistent with acute dengue infection but were subsequently found to be co-infected with MSSA. A systematic review of their clinical records was conducted.

Diagnosis of DF, dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) was made in accordance with World Health Organization (WHO) criteria[8] with a compatible clinical presentation. Initial assessment included complete blood count and serum biochemical measurements (electrolytes and liver function tests). Confirmatory testing was performed with either dengue-specific real-time polymerase chain reaction (RT-PCR) kit (RealArt™ Artus GmbH, Germany) or IgM and IgG capture enzyme-linked immunosorbent assay (ELISA) assay (Panbio, Queensland, Australia).[9] The MSSA isolates were cultured from blood and/or intraoperative tissue, and identified by morphology, colony characteristics, Staphaurex and positive tube coagulase test. Antibiotic susceptibility testing was performed using Clinical and Laboratory Standards Institute (CLSI) methodology.[10]

Molecular typing of isolates was performed via pulsed-field gel electrophoresis (PFGE) using restriction endonuclease SmaI.[11] Gel images were digitised using Molecular Analyst v1.6 (Bio-Rad) and analysed using Dice coefficient UPGMA (unweighted pair-group method with arithmetic averages), with a cut-off of 80% or greater

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similarity connoting relatedness of isolates.

In addition, the isolates were tested for the presence of Panton-Valentine leucocidin (PVL) genes.[12]

Approval for this study was granted by the institutional ethics review committee.

Case Reports

Case 1

A 36-year-old male construction worker was admitted with suspected dengue with 4 days of fever and rash. The admitting clinical and laboratory profiles are listed in Table 1. Serum dengue PCR was positive. By day 10 of the illness, his fever persisted and he complained of left testicular pain with overlying inflammation. A testicular ultrasound was notable for epididymo-orchitis. Follow-up computed tomographic scans demonstrated subcutaneous oedema involving the left scrotal wall. Urgent surgical exploration, on concerns of Fournier's gangrene, revealed purulent necrotising gangrene involving the scrotum and lower abdominal wall. Intraoperative tissue specimens isolated MSSA, although blood cultures were negative. The patient underwent several debridements and received an antimicrobial regimen consisting of empirical amoxicillin/clavulanate followed by high-dose cloxacillin.

Case 2

A 39-year-old presented with 3 days of fever, rash, mild leucopenia and thrombocytopenia. Dengue PCR was positive. His fever persisted past day 7, and he subsequently complained of right testicular and inguinal swelling. Surgical exploration demonstrated pus in the right scrotum and necrotic dartos muscle, with multiple gluteal, perineal and thigh abscesses, all requiring drainage. Blood and intraoperative tissue cultures were positive for MSSA. Treatment necessitated further debridements and appropriate antimicrobial therapy before discharge.

Case 3

A 39-year-old was admitted with clinical presentation and laboratory findings consistent with DHF, confirmed by dengue PCR and ELISA. By day 9, he had a non-resolving fever and complained of chest pain. A chest radiograph revealed nodular pulmonary infiltrates. Blood cultures isolated MSSA; the presence of concurrent skin and pulmonary lesions raised concerns of septic emboli. He deteriorated and was transferred to the intensive care unit, requiring mechanical ventilation for acute respiratory distress syndrome. Transesophageal echocardiography (TEE) revealed global hypokinesia with 20% ejection fraction; no vegetations were visualised. He made steady improvement, and was discharged after receiving cloxacillin treatment for a month.

Case 4

A 43-year-old admitted with 5 days of fever, myalgia and positive dengue PCR. By day 8, he had left thigh induration with persistent temperature. Magnetic resonance imaging revealed a 9x8 cm thigh abscess necessitating operative drainage. Blood and operative cultures were positive for MSSA. He further developed multiple chest wall, iliopsoas and prostatic microabscesses by day 12 of illness despite cloxacillin. The patient insisted on discharge against medical advice on day 13.

Case 5

A 42-year-old presented with clinical dengue and positive dengue PCR plus serology. On day 8, erythema was noted over the dorsum right hand (site of recent intravenous cannula). Intravenous cefazolin was initiated. With progressive cellulitis, surgical exploration revealed pus and soft tissue necrosis over the proximal forearm. Blood and wound cultures grew MSSA. He received appropriate antibiotics, required 2 further debridements and a split-thickness skin graft for wound closure.

All patients had denied intravenous drug abuse. Random toxicology screens for 2 of the patients were negative for substances of abuse. With the exception of Case 4, all patients had either transthoracic echocardiography (TTE) or TEE which did not detect any vegetations. Table 1 summarises the presentation and clinical course of the 5 patients with dengue-*S. aureus* co-infection.

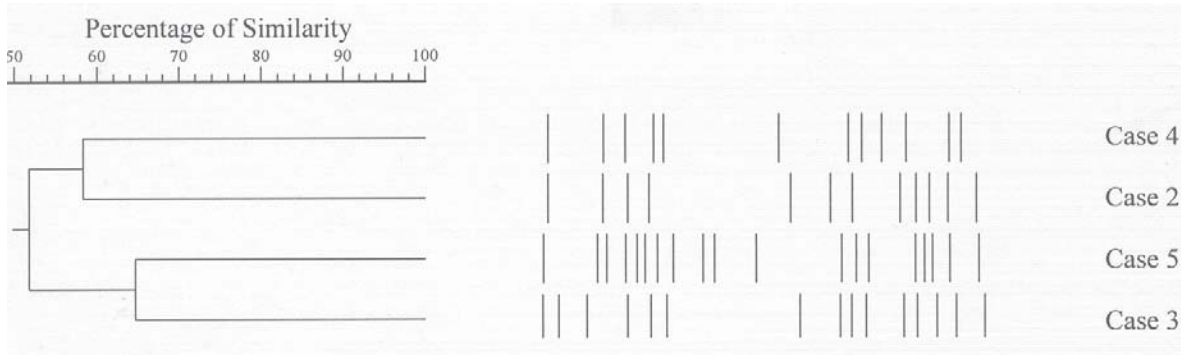

Fig. 1. Dendrogram based on PFGE profiles of the *S. aureus* blood isolates analysed using Dice co-efficient UPGMA. Tissue isolate from index case 1 was not archived prior to emergence of the subsequent cases in the cluster.

Table 1. Characteristics and Clinical Course of 5 Patients Admitted with Dengue *Staphylococcus aureus* Co-infection

Data	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	36	39	39	43	42
Gender	Male	Male	Male	Male	Male
Duration of stay in Singapore	9 months	7 months	6 years	Unknown	1 year
Date of admission (mm/dd/yy)	5/4/05	6/17/05	6/22/05	6/15/05	7/3/05
Duration of fever on admission	4 days	3 days	5 days	5 days	3 days
Other symptoms on admission	Rash, giddiness	Vomiting, rash	Rash	Vomiting, myalgia	Nausea, myalgia
Day of hospitalisation C/S (+)	HD 6	HD 6	HD 3	HD 4	HD 6
Day of fever when C/S (+)	Day 10	Day 9	Day 8	Day 9	Day 9
Laboratory tests on admission					
White blood cell ($x10^9$/L)	1.9	3.9	1.3	2.6	1.8
Neutrophil (%)	73	83	71	73	62
Lymphocyte (%)	19	9	17	19	23
Haemoglobin (g/dL)	17.5	13.7	16.2	14	16
Haematocrit (%)	49.7	40.8	47.3	41.4	48.3
Platelet ($x10^9$/L)	93	98	92	110	88
Nadir platelet count ($x10^9$/L)	27	26	21	9	37
Date of platelet nadir (mm/dd/yy)	5/7/05	6/21/05	6/25/05	6/19/05	7/6/05
Day of illness at nadir	Day 7	Day 7	Day 8	Day 9	Day 6
Dengue PCR result	Positive	Positive	Positive	Positive	Positive
Date of DF PCR (mm/dd/yy)	5/5/05	6/18/05	6/23/05	6/16/05	7/4/05
Dengue Ig M result	Negative	N/A	Negative	N/A	Positive
Dengue Ig G result	Negative	N/A	Positive	N/A	Positive
Date of dengue serology (mm/dd/yy)	5/5/05	N/A	7/8/05	N/A	7/11/05
Clinical diagnosis: DF/DHF	DF	DF	DHF	DF	DF
Date of first culture with MSSA (mm/dd/yy)	5/10/05	6/23/05	6/25/05	6/19/05	7/9/05
Blood culture for MSSA	Negative	Positive	Positive	Positive	Positive
Sites of infection	Skin and soft tissue	Skin and soft tissue, blood	Skin, blood	Skin and soft tissue, blood	Skin and soft tissue, blood
Abscess locations	Fournier's gangrene: scrotum, abdominal wall	Gluteal, perineum, thigh	Lung	Left thigh, chest wall prostate, psoas	Right hand
Skin	Nil documented	Nil documented	Abrasions, eczema	Nil documented	Eczema
Echocardiography results	Nil vegetations	Nil vegetations	EF 20%, nil vegetations	Declined	Nil vegetations
Clinical outcome	Improved	Improved	Improved	Discharged against medical advice	Improved
Duration of hospitalisation (days)	38	26	37	7	33

DF: dengue fever; DHF: dengue haemorrhagic fever; C/S (+): Culture positive; EF: ejection fraction; HD: Hospital Day; MSSA: methicillin-susceptible *S. aureus*; N/A: not available; PCR: polymerase chain reaction

Molecular Analysis

The 4 MSSA blood isolates analysed were not related (Fig. 1). PVL genes were not detected in any of the 5 isolates.

Discussion

Bacteraemia with dengue co-infection is rare. To date, only about 20 cases have been reported in the literature. These isolated and sporadic cases generally involved Gram-

negative *Enterobacteriaceae* species;[4-7] with only 1 reported case of *S. aureus* co-infection.[3] Our cluster of 5 patients with severe *S. aureus* co-infection arising from the same worksite amongst approximately 4000 DF/DHF cases admitted to our institution in 2005, makes it difficult to disregard an epidemiological link even though molecular analysis did not demonstrate clonality.

Following notification to local health authorities, a field epidemiology team dispatched to the worksite noted a preponderance of eczematous dermatitis amongst the construction workers. Exposure to cement with ungloved hands was postulated to be the most likely cause, leading to breaches to skin integrity as a portal of entry for *Staphylococcal* infection. However, the team was unable to obtain permission to perform nasal and skin swabs to detect *S.aureus* carriage from these workers.

The exact point of acquisition of *S. aureus* infection or bacteraemia cannot be definitively ascertained. Bacterial blood cultures were not routinely performed in the clinical setting of a viral infection. The possibility of co-infection was considered when fever persisted beyond the anticipated period characteristic of dengue fever or with notable skin/soft tissue manifestations in our patients. Clinical and epidemiological findings suggest a community source rather than nosocomial acquisition of MSSA. Nonetheless, the lack of clonality of MSSA suggests a temporally acquired susceptibility to staphylococcal infections in general rather than co-infection by a hypervirulent and/or hyper-transmissible MSSA clone.

The question of whether dengue infection does modulate the immune system in predisposition to other infections is of interest. Viruses like measles, influenza and cytomegalovirus are known to induce transient in-vitro and in-vivo immunosuppression of cell-mediated responses.[13,14] Impaired T-cell proliferation in acute dengue infection has been reported.[15] Studies demonstrating disruption of endothelial lining by dengue virus may suggest a possible opportunistic mechanism exacerbated by disruption of skin integrity from exogenous eczema.[16]

As the dengue upsurge continues in Southeast Asia, clinicians will inevitably encounter unusual manifestations of the disease in the course of their practice, amongst which a prolonged fever of more than a week may be an important clue for concomitant or alternative causes of infection. Though challenging, it is imperative to remain vigilant for alternative infections before ascribing this to a variant presentation.

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