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INVASIVE *STAPHYLOCOCCUS AUREUS* INFECTION IN AN AFRICAN ADOLESCENT: CASE REPORT
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SUMMARY

***Staphylococcus aureus* remains an important cause of mortality, in the community and health care set-ups. *S. aureus* strains with genes encoding lethal toxins and culture negative sepsis augment the diagnostic challenge in resource limited settings. With a growing rate of resistance to the causative bacteria and atypical clinical presentations, a high index of suspicion, appropriate knowledge of the intricate pathogenetic mechanisms and use of optimal and suitable anti-microbials with adjunctive therapies becomes of crucial significance in apposite management, to reduce and prevent the high rates of morbidity and mortality. Herein, an atypical presentation of an adolescent with multi-organ involvement is shown; rationalising the need for earlier recognition, appropriate use of anti-biotic and adjunctive therapies.**

INTRODUCTION

'My delight may be conceived when there were revealed to me beautiful tangles, tufts and chains of round organisms in great numbers, which stood out clear and distinct…'(1)

The role of staphylococci in sepsis and abscess formation stood highlighted in a series of studies published in the 1980s, human colonisation increasing risk of infection with these strains (2,3,4). The virulence of *Staphylococcal aureus*, (*S. aureus)*was underscored in a seven-year observational study in 1941(5). Today, decades later, the incidence of *S.aureus* bacteremia remains high, ranging from 10-30 per 100,000 person-years in the industrialised world, compared to 27 per 100,000 person-years among under-fives in Kilifi, Kenya, 48 per 100,000 person-years among <15 year olds in the Manhica District, Mozambique and 26 per 100,000 person-years among <13 year olds in Soweto, South Africa (6,7).

An intricatepathogenetic process associating a spectrum of virulence and genetic determinants to elude anti-microbial therapies, aids adaptability in micro-environments, blood-stream infections with metastatic infections being lethal causes of significant morbidity and mortality (8-10).Methicillin Resistant *Staphylococcus aureus*(MRSA), the resistant strains of *S. aureus*, is also a growing concern(11). Schaumburg *et al* identified 17-74% of the genes encoding the toxin Panton-Valentine leucocidin (PVL) in *S. aureus* isolates, methicillin susceptible, in the African region, branding *S. aureus* epidemiology in Africa different from Europe and North America (12). Opportune appraisal on the altering epidemiology and presentationis critical for better prevention and management of staphylococcal diseases (13). Herein,a case of a previously healthy adolescent with multi-organ failure is presented and to the best of our knowledge; this is the first report from Kenya of a fatal case due to methicillin sensitive *S. aureus*.

CASE REPORT

An eight-year-old African boy developed several episodes of Diarrhoea, post-prandial vomiting and fever associated with chills, one month after relocating to Kenya from the West. Diarrhoea remained non-mucoid, non-bloody; fever exhibited no diurnal variation. Empirical treatment with parenteral Ceftriaxone and Amikacin was discontinued after 72 hours exclusive of improvement, changed to Meropenem for ten days. Four episodes perceived over the following eight months displayed similar history of fever, Diarrhoea, vomiting and pancytopenia, amid normalcy in between episodes. Each episode was treated in various hospitals with parenteral Meropenem leading to subsidence of symptoms.Difficulty in breathing was an additional symptom during the fourth episode, with absence of cough, wheeze, chest pain or nasal discharge. General examination revealed pallor, sunken eyeballs, reduced skin turgor and generalised lymphadenopathy; absent jaundice and cyanosis. He was febrile, tachypnoiec and tachycardic. Intravenous (IV) rehydration, packed

red cell transfusion and anti-biotics, Meropenem and Amikacin were commenced together with other supportive care. With progressive deterioration, Teicoplanin and fluconazole were added to treatment. Ventilatory support with other supportive care was initiated in ICU due to impending respiratory failure and hypotension. Differential diagnosis of acute gastroenteritis with hypotension, myelodysplastic syndrome, sepsis and Acute Respiratory Distress Sydrome (ARDS) was entertained.

His past medical history was unremarkable with appropriate developmental milestones;up-to-date with vaccinations. He was the second born among five children, all others alive and well. Family history of chronic illnesses was nonexistent. A history of palpitations, headaches, leg or body pain and swelling were lacking; throat, ear pain and rashes were not reported, but a six-month history of easy fatigability and occasional dizziness was extant. Though ventilator-free within a week, fever and chills persisted with a new onset facial puffiness and bilateral pedal edema. A left sided tender submandibular swelling of size 3cm x 4cm and a pansystolic murmur, left sternal border was appreciated. Lower left first premolar dental caries with abscess was noted though parental consent was declined for incision, drainage and extraction under local anaesthesia.

Investigations (fourth admission):

Serum immunoglobulin levels: normal.
HIV 1 and 2 anti-body test: negative.

ESR: elevated at 62mm/hr.

ZN staining of pus aspirate: negative for acid-fast bacilli.

Blood and urine and stool culture:no growth obtained.

Bone marrow aspirate:overall low cellularity with dysplasia, reactive changes, no evidence of hematological disorder.

Gene-expert study with tracheal aspirate and gastric lavage specimens: mycobacteria undetected.

Chest-X ray: bilateral heterogenous opacification

ECHO: right ventricular hypertrophy, mild-moderate mitral regurgitation, mildly thickened mitral valve leaflet, no features of infective endocarditis.

Peripheral blood flow cytometry: negative myeloid markers, T-lineage markers, HLA-DR and other immaturity markers like Tdt, CD10 and CD117.
T-lineage markers (CD2, CD7 and Cyt CD3) and immaturity marker, CD34, were positive.

Culture tracheal and pus aspirate from submandibular swelling: grew *Staphylococcus aureus* sensitive to Vancomycin, Cloxacillin, Augmentin and Cefotaxime.

Table 1
Full Blood Count (FBC)

WBC ($x10^9/l$)	1.49	0.604	2.63	3.81	6.2	7.36
Neutrophils ($x10^9/l$)	0.049	0.003	1.17	1.22	2.4	3.21
Lymphocytes ($x10^9/l$)	1.16	0.34	1.01	1.86	3.52	2.46
RBC ($x10^{12}/l$)	0.883	2.51	4.27	3.3	3.03	3.21
HB (g/dl)	2.63	6.87	11.5	10.6	8.12	9.84
MCV (Fl)	85.7	80.3	83.5	84	82.9	86
Platelets ($x10^9/l$)	151	84.3	37	203	715	602

Red cells exhibited a normocytic picture. A very low white blood cell count with a normal morphology was prominent.

Table 2
Renal and Liver Function Tests (RFT & LFT)

Urea (mmol/L)	27.8	32.5		14.1	2.2
Creatinine (mmol/L)	225	165	149	26	37
Na (mmol/L)		151.4		161	
K (mmol/L)		4.07		4.36	
AST (U/L)	57	50	99	39	24
ALT (U/L)	45	28	29	22	14
ALP (U/L)	64	76	59	81	65
GGT (U/L)	26		41	41	24
T protein (g/L)	49	52	40	48	52
Albumin (g/L)	32	29	22	23	23

Anti-biotics were de-escalated to IV Coamoxiclav and patient discharged to wards. An erythematous rash extending from the neck to abdomen with desquamation was noted on Day 3 of anti-biotic change, penicillin allergy was suspected and Coamoxiclav was stopped. IV Meropenem and Teicoplanin were restarted. Gradually, condition further deteriorated and attempts at resuscitation were unsuccessful.

Post-mortem findings exposed heavy, firm lungs with diffuse alveolar damage, micro abscessesin spleen, liver and heart, histology displayed infection with Gram-positive cocci.

Final Anatomic Diagnosis (Including ICD 10 codes): Diffuse alveolar damage (J80) due to Staphylococcal sepsis(CMA41) due to pancytopenia (D61.9) due to Acquired Myelodysplasia (AMD)

DISCUSSION

Our case is a child who died at our institution after progressive clinical deterioration from *S. aureus* infection with pancytopenia, acute respiratory distress syndrome and hypotension. *S. aureus* strains were isolated from a dental abscess focus and from liver, spleen and heart through postmortem examination. Of particular note was the dearth of defining risk factors for infection of such severity; history of prolonged anti-biotic course or immunosuppressive therapy. HIV anti-bodies were negative and serum immunoglobulin levels were normal, though other immunodeficiency conditions could not be tested. No similar case was recorded among adults or children during that period. The patient was clinically septic and very toxic with evidence of metastatic infection. It is not clear whether an extraordinarily virulent strain of *S. aureus* with genes encoding toxins like the PVL was involved in the dissemination of infection or the occurrence was a consequence of some undefined defect in host resistance. Our limited phage typing data was insufficient to draw conclusion regarding virulence of the infecting strain. Delayed surgical drainage of the foci of infection may also have contributed to blood stream seeding withdissemination of infection.

Blood cultures remained negative, though bacteremia could not be ruled out in our toxic febrile child. Inadequate submissions and insufficient amounts of samples and prior anti-biotic use could have resulted in a negative blood culture (14-16). Bone marrow examination disclosed a hypo-cellular marrow with dysplastic features, explicating a persistent pancytopenic picture. Bone marrow dysplasia and pancytopenia, with recurrent and insistent infection could have deteriorated our patient's immunological status (17). Acute myelodysplasia (AMD) is associated with risk of severe infections, bacterial infections being the most common (18). Myelodysplasia in children shadow a variety of causes like unremitting infection, drug therapy and chronic diseases, but could not be categorised as myelodysplastic syndrome (MDS) in our patient, as the minimum criteria for the diagnosis of MDS were missing (19,20). An underlying genetic defect or a viral infection like Epstein-Barr virus (EBV), could have predisposed to AMD at an early age (21,22). Significantly elevated EBV loads were found in children aged 1-4 years living in malaria holo-

endemic regions in Kenya (23), though a diagnostic serology was absent to establish the same.

Our patient showed clinical improvement on Meropenem, a broad-spectrum carbapenem amid good activity against methicillin sensitive *Staphylococcus aureus* (MSSA) (24). Suboptimal treatment duration may have steered persistent metastatic infection, inadequate abscess site penetration and symptom resurgence. A systematic review on management of *S. aureus* bacteremia with metastatic infections highlights a prolonged anti-biotic course with b-lactams of 4-6 weeks as optimal treatment (25). Though a possibility of penicillin group allergy as etiology of the erythematous desquamative rash was regaled, a feature of sepsis syndrome was entertained after post-mortem findings, as sudden fatal deterioration three days after discontinuation of Coamoxiclav could not be explained (26).

Despite better knowledge and improved standards of patient care, high case fatalities from these strains persist (27). Shulman and Ayoubhad used the term 'staphylococcal sepsis' on previously healthy children who presented with manifestations of severe life-threatening septicemia during a three-year period, beginning in early 1972 (28). Mongkol tattanothai *et al* used the term 'sepsis syndrome' to describe the multi-system clinical manifestations on Paediatric patients with *staphylococcus* infection in 2000 (29). This syndrome, which was similar to toxic shock syndrome (TSS), did not fulfill all the clinical criteria for that syndrome as defined by the Centers for Disease Control and Prevention (30). Adem PV *et al* defined 'sepsis syndrome' as isolation of *S. aureus* from a clinically important site, hypotension, respiratory distress syndrome or respiratory failure, plus involvement of liver, kidneys, muscles or skin or hemostasis or the presence of leukopenia or thrombocytopenia (30).Toxins released by toxin producing strains of *Staphylococcus aureus* can act as super-antigens causing inexplicably exuberant immune response leading to rapidly progressive multi-organ failure virtually indistinguishable from septic shock (31).Our patient exhibited all features under the classification of 'sepsis syndrome.'

Adalat *et al* highlighted the difficulties in recognising and identifying cases of TSS(32). Though relatively rare, is comparatively more common in children due to lack of protective anti-bodies against toxins, leading to uncontrolled pro-inflammatory cascade, endothelial damage and capillary leak, resulting in hypotension and multi-organ failure, though noteworthy that some cases may be deemed 'sepsis' without appreciating the role of super-antigen toxins in the illness (33), as noted in our patient. Adjunctive therapies to counter effects of super-antigen toxins were not initiated, though laboratory and animal studies support the role of both Clindamycin and IV immunoglobulin (IVIG) in TSS (33,34). With an ability to interrupt ongoing stimulation of pro-inflammatory cascade by inhibiting the bacterial toxin production, Clindamycin potentiates phagocytosis, has enhanced tissue penetration and longer post-anti-biotic effect compared to ß-lactams (33). Though observational studies support a beneficial role for IVIG in TSS, evidence from clinical trials is lacking, (35). Though IVIG contains neutralising anti-bodies to staphylococcal super-antigen toxins and inhibits T-cell proliferation and cytokine production, uncertainties in the use of IVIG exists as relates to patient selection, role of host genetic factors, optimal time and dose. Our patient was not treated appropriately because of late recognition and paucity of knowledge on adjunctive therapies.

Recognising and eliminating infective focus, use of anti-biotics, fluid resuscitation and supportive care remain of critical importance and should not be replaced by adjunctive therapy, though an earlier initiation of adjunctive therapy interrupts inflammatory cascades more effectively (33). Various traits of *S.aureus* identified in urban and rural populations of sub-Saharan Africa, with a high prevalence of PVL-positive strains, anti-microbial multi-susceptibility and genetic diversity imply that these strains could act as a pool for materialisation of PVL-positive clones (12,13). Hence, better phage typing and research efforts and sustained surveillance should be emphasised so that the medical burden caused by *Staphylococcus aureus* is not neglected.

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