Managing pulmonary embolism secondary to suppurative deep vein thrombophlebitis due to community-acquired *Staphylococcus aureus* in a resource-poor setting

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**ABSTRACT**

Deep vein thrombosis and pulmonary thromboembolism are rare and life threatening emergencies in children. We report an 11-year-old female who presented with acute complaints of high grade fever, pain in the left thigh and inability to walk and breathlessness since 6 days. On physical examination, there was a diffuse tender swelling of the left thigh, tachypnea, tachycardia with hyperdynamic precordium and bilateral basal crepitations. Ultrasonography and venous doppler of lower limbs showed mild effusion of left hip joint and thrombus in the left common femoral vein and left external iliac vein suggesting a diagnosis of septic arthritis with thrombophlebitis. The tachypnea and tachycardia which was out of proportion to fever and crepitations on auscultation prompted suspicion of an embolic phenomenon. Radiograph of the chest revealed multiple wedge shaped opacities in the right middle zone and lower zone suggestive of pulmonary embolism and left lower zone consolidation. For corroboration, computed tomography pulmonary angiography and computed tomography of abdomen was performed which showed pulmonary thromboembolism and deep venous thrombosis extending up to infrarenal inferior vena cava. On further workup, magnetic resonance imaging of hips showed left femoral osteomyelitis and multiple intramuscular abscesses in the muscles around the hip joint. Blood culture grew methicillin resistant *Staphylococcus aureus*. Antibiotics were changed according to culture sensitivity and there was a dramatic response. After four weeks of anticoagulation and antibiotics the child became asymptomatic and thrombus resolved. Thus, it is crucial to consider methicillin resistant *Staphylococcus aureus* infection as an important infection when we encounter such a clinical scenario. This case report highlights an unusual and potentially life threatening presentation of a virulent strain of a common pathogen, which when diagnosed was completely amenable to treatment.

**KEY WORDS:** Deep venous thrombosis, methicillin resistant *Staphylococcus aureus*, osteomyelitis, pulmonary thromboembolism, septic arthritis

**Case Details**

A previously healthy 11-year-old female child of Asian Indian origin born of a non-consanguineous marriage presented with acute onset of high-grade fever and progressively worsening pain in the left thigh since 6 days and breathlessness since 3 days. Routine activities were restricted due to painful ambulation. Parents had not noticed swelling or redness of the affected limb and joints. On enquiry, there was no history of previous hospital admissions, local trauma or injection, bleeding
Table 1: Differential diagnosis of unilateral limb pain in children

| Pathology                        | Etiology                                      |
|----------------------------------|-----------------------------------------------|
| Infection/infection-related      | Septic arthritis                              |
|                                  | Osteomyelitis                                 |
|                                  | Reactive arthritis                            |
|                                  | Toxic synovitis                               |
|                                  | Lyme disease                                 |
| Inflammatory                     | Rheumatic fever                               |
|                                  | Juvenile idiopathic arthritis                 |
|                                  | Systemic lupus erythematosus                  |
|                                  | Henoch–Schönlein purpura                     |
| Malignancy                       | Leukemia                                      |
|                                  | Neuroblastoma                                 |
|                                  | Bone tumors (osteosarcoma, Ewing sarcoma)     |
| Trauma/overuse                   | Fracture                                      |
|                                  | Soft tissue injury                            |
|                                  | Osgood–Schlatter disease                      |
|                                  | Hypermobility                                 |
| Hematological                    | Hemophilia                                    |
|                                  | Sickle cell anemia                            |
| Orthopedic/mechanical            | Slipped capital femoral epiphysis             |
|                                  | Legg–Calvé–Perthes disease                    |

diathesis, infective focus elsewhere in the body, underlying heart disease, diabetes mellitus, immunodeficiency, and tuberculosis or contact with a person affected by tuberculosis. There was no significant past or family history.

**Question 1:** What are the causes of unilateral limb pain causing severe limitation of movements?

**Answer:** Causes of unilateral limb pain with limitation of movement in childhood are enumerated in Table 1.[1]

**Case Details (Continued)**

On examination, temperature was 40°C, pulse rate was 148/min, all peripheral pulses were well felt, respiratory rate was 44 breaths/min, and blood pressure was 108/70 mmHg. Personal hygiene was satisfactory. Respiratory distress was evident by subcostal and intercostal retractions. The weight and height were 38 kg and 146 cm, respectively, corresponding to the 50th centile (NCHS 2000 chart). There was pallor. Homan sign (deep pain in the calf muscle after dorsiflexion of ankle) and Moses sign (pain experienced by squeezing the calf muscle against tibia) were absent. On local examination, the left hip joint was flexed, abducted, and externally rotated. There was a diffuse, tender, circumferential swelling extending from the left hip joint to mid-thigh with erythema and edema of the overlying skin. A difference of 3 cm was noted in the limb girth at mid-thigh level (31 and 28 cm on left and right sides, respectively). Movements of the left hip and knee joint were painful but unrestricted. Examination of other joints was normal. Respiratory system examination revealed crepitations in bilateral infra-mammary areas. The only abnormality on cardiovascular system examination was a hyperdynamic precordium. Other systems were normal. On admission, arterial oxygen saturation by pulse oximetry on room air was 88%, which increased to 98% on supplementation of oxygen by face mask at 4 L/min.

**Question 2:** After examination, what was the likely differential diagnosis for the unilateral thigh swelling?

**Answer:** The likely differential diagnoses at this stage were cellulitis with septic arthritis or toxic synovitis of the left hip joint and osteomyelitis of the left femur.[1,2]

**Case Details (Continued)**

The preliminary investigations are summarized in Table 2. Since an infective etiology was suspected, intravenous ceftriaxone (100 mg/kg in two divided doses) and vancomycin (60 mg/kg in three divided doses) were started after sending blood culture within 1 h of admission.

**Question 3:** What is the explanation for respiratory involvement in this case? What would be the investigations of choice to determine the nature of respiratory involvement?
Answer: Our patient developed symptoms (breathlessness) and signs (tachypnea, crepitations, and hypoxia) suggestive of respiratory system involvement after the initial symptoms of fever and limb pain. This temporal association suggests that the respiratory system could be involved secondary to the original limb pathology. The usual etiology could be pneumonia due to hematogenous spread of infection from the limb or sepsis. Pulmonary embolism was another possibility, the source of emboli being vegetations from right side infective endocarditis (secondary to bacteremia from the infective focus in the limb). An exceptional occurrence is the development of pulmonary thromboembolism (PTE) secondary to suppurative deep vein thrombosis (DVT) following an infective process such as septic arthritis or osteomyelitis. Whereas association of septic PTE has been reported earlier with Lemierre’s syndrome and right side infective endocarditis due to intravenous drug use, vascular catheters, or implantable devices; recent papers have highlighted a change in the epidemiology of septic PTE. Septic PTE is now reported to occur secondary to septic thrombophlebitis as a result of deep soft tissue or bone infections of the extremities.

Further investigations planned were chest radiograph, lower limb venous Doppler examination, electrocardiogram (ECG), and two-dimensional echocardiography.

Case Details (Continued)

Chest radiograph showed wedge-shaped opacities in the right middle and lower zones suggestive of pulmonary embolism and left lower zone consolidation [Figure 1]. On Day 2 of admission, venous Doppler of both the lower limbs showed left common femoral vein and external iliac vein thrombosis. ECG and two-dimensional echocardiography were normal. Anticoagulation with subcutaneous administration of injection enoxaparin in a dose of 1 mg/kg in two divided doses was started. Computed tomography (CT) pulmonary angiography, which is the definitive diagnostic modality for PTE, showed multiple hemorrhagic infarcts in bilateral lung parenchyma involving the middle and lower zones in our patient [Figure 2]. CT abdomen was done to delineate the extent of thrombosis, which revealed that the thrombus was extending inferiorly from the infrarenal segment of the inferior vena cava to involve the left common femoral vein, external iliac vein, and common iliac vein. Thus, the diagnosis of extensive DVT with PTE was confirmed.

Despite 5 days of empirical antibiotic therapy (ceftriaxone + vancomycin), fever and local signs of inflammation persisted, along with worsening of the respiratory status requiring bilevel positive airway pressure (BiPAP) ventilation. Magnetic resonance imaging (MRI) of the hip joint along with diagnostic and therapeutic aspiration of the joint fluid was planned. The critical condition of the child did not permit immediate imaging and aspiration. Meanwhile, the blood culture report was available and it revealed growth of methicillin-resistant *Staphylococcus aureus* (MRSA). Initial antibiotics were substituted by intravenous linezolid (30 mg/kg in three divided doses) according to the sensitivity pattern showing minimum inhibitory concentration of 0.4–3 µg/mL for linezolid. Vancomycin discs for sensitivity testing were not available in our institute while our patient was being treated. Within 48 h of commencing linezolid, there was a dramatic clinical response with resolution of fever, reduction of limb swelling and pain, and gradual reduction in oxygen requirement. BiPAP ventilation was discontinued after 2 days and oxygen support could be withdrawn after 5 days. Limb MRI could be performed after 16 days of admission (22 days after onset of symptoms). Abnormal hyperintense signals were noted on the MRI involving the left femoral proximal metaphysis and epiphysis, lesser trochanter and greater trochanter, and effusion of left hip joint [Figure 3]. In addition, there were multiple abscesses in the left vastus medialis, vastus lateralis, iliacus, and quadrates lumborum muscles (the largest abscess measured 3 × 1.5 cm) and mild effusion of the right hip joint. Thus, our patient had an unusual complication of septic PTE due to suppurative deep vein thrombophlebitis with primary infective focus being left femoral osteomyelitis, septic arthritis, pyomyositis, and cellulitis [Figure 3]. The effusion of the right hip joint could be an early stage of infective arthritis as a part of the disseminated *Staphylococcus* infection.

Question 4: What could be the reason for multifocal infection with CA-MRSA in a previously healthy girl?

Answer: Our patient was previously healthy, had no prior hospitalization, and the parents did not recall any obvious trauma. The infection was most likely due to community-acquired MRSA (CA-MRSA) causing septicemia and complications due to widespread local infection. The spectrum of infections due to CA-MRSA includes severe multifocal disease manifesting as necrotic skin lesions, abscesses, arthritis, and osteomyelitis complicated by deep vein thrombosis and severe necrotising pneumonia.[9,10] High virulence of *S. aureus*, including CA-MRSA has been attributed to Panton–Valentine leukocidin (PVL), which is a cytotoxin causing leukocyte destruction and tissue necrosis.[11] A polymerase chain reaction (PCR) test for PVL genes (*lukS-PV* and *lukF-PV*) and simultaneous discrimination of MRSA from methicillin-sensitive strains of *S. aureus* has recently been developed.[12] Detection of PVL carrying...
S. aureus has been performed in India for research purposes.\(^{11}\) However currently, PCR for PVL and identification of MRSA genes and immunological tests for PVL are neither available commercially nor for research basis locally or at other centers in India. Therefore, these tests, although indicated, could not be performed in our patient.

**Question 5:** What is the antibiotic of choice for treatment of severe CA-MRSA infection?

Vancomycin is the antibiotic of choice for treatment of bone and joint infection and/or severe sepsis due to CA-MRSA infection in children.\(^{14}\) However, it is critical to recognize and treat persistent methicillin-resistant S. aureus bacteremia (MRSAB) as it is both limb and life-threatening.\(^{15}\) Alternative approaches to treat MRSAB should be considered within 3–4 days of persistent MRSAB.\(^{16}\) As our patient was clinically deteriorating despite 5 days of therapy with vancomycin, we substituted vancomycin + ceftriaxone with intravenous linezolid according to published recommendations.\(^{16}\) Linezolid is considered appropriate for the treatment of complicated MRSA skin and soft tissue infections, including the treatment of lower extremity infections as it achieves high penetration into skin and soft tissues.\(^{17}\)

**Question 6:** Since DVT in our patient is a known complication of osteomyelitis and arthritis caused by MRSA, are additional investigations required to determine other risk factors predisposing to DVT?

**Answer:** Our previously healthy patient did not have risk factors for thromboembolism at the time of initial presentation. Knowing that DVT with PTE is a well-documented complication of bone and joint infection and severe sepsis caused by MRSA, investigations for thrombophilia in such a patient can be avoided in a resource-limited setting. Though we could not test for PVL, it seemed prudent to rule out an underlying thrombophilia in presence of extensive DVT and PTE as coexisting inherited thrombophilia would determine requirement for long-term anticoagulation therapy.\(^{18}\)

**Case Details (Continued)**

Laboratory work-up for thrombophilia [serum homocysteine, factor V Leiden mutation (G1691A mutation of F5 gene), prothrombin G20210 A mutation, and measuring levels of protein C, protein S, and antithrombin III] was sent before starting enoxaparin on day 2 of admission which showed low protein C value of 32%, suggestive of protein C deficiency (normal range of 60%–150% for age and sex).\(^{18,19}\) The results of investigations for thrombophilia are shown in Table 3.

**Question 7:** What is the interpretation for low protein C activity in our patient?

**Answer:** Protein C deficiency is tested by measuring protein C antigen level (quantitative) via enzyme-linked immunosorbent assay (ELISA). Protein C deficiency is a rare inherited autosomal recessive disorder.\(^{19}\) Patients with homozygous deficiency manifest symptoms in early life in the form of purpura fulminans, cerebral thrombosis, ophthalmic thrombosis, disseminated intravascular coagulation, and large vessel thrombosis.\(^{18}\) Heterozygous deficiency occurs in 0.2% of the population, and among these, 3% present with venous thromboembolism.\(^{19}\) In our patient, the presentation was late, without any past

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**Table 3: Results of investigations for thrombophilia**

| Tests                        | Patients’ value | Normal range |
|------------------------------|----------------|--------------|
| Antithrombin III             | 86%            | 70%-140%     |
| Factor V leiden mutation     | Not detected   |              |
| Prothrombin gene (20210 A) mutation | Not detected |              |
| Serum homocysteine           | 1.9 μmol/L     | <2.5 μmol/L  |
| Protein C level              | 32%            | 60%-150%     |
| Protein S level              | 80%            | 60%-150%     |
history or family history of thromboembolism, and therefore, homozygous protein C deficiency would be less likely.

Low values of protein C are also encountered as an acute phase reaction or secondary to acute thrombosis, infection, inflammation, hepatic dysfunction, and vitamin K antagonist (protamine sulfate) use.[19] Therefore, in our patient, the low protein C activity was attributable to an acute thrombotic state secondary to infection.

Case Details (Continued)

After 4 weeks of treatment with anticoagulants, repeat lower limb venous Doppler revealed complete recanalization of left common femoral vein, external iliac vein, common iliac vein, and infrarenal inferior venous cava with no residual thrombus.

Question 8: What was the long-term monitoring plan for this patient?

Answer: Antibiotic therapy is recommended for 4–6 weeks in such cases.[20] Our patient received intravenous linezolid for 3 weeks, after which the patient improved clinically and was transitioned to oral linezolid (10 mg/kg/dose thrice a day) for 3 weeks (total duration of 6 weeks). Enoxaparin was continued for 3 months and then stopped.[19] Documentation of normal protein C level by repeat testing after resolution of the acute thrombotic episode and discontinuation of anticoagulation therapy ruled out primary inherited protein C deficiency. Due to the dynamic state of growth in children, sequelae of skeletal infections might not become apparent for months or years, and therefore long-term follow-up is necessary with close attention to range of motions and bone length in the affected limb.[20]

Conclusion

Multifocal, deep-seated, fulminant infection complicated by severe sepsis and/or DVT in a previously healthy immunocompetent child should arouse suspicion of infection due to an organism like highly virulent CA-MRSA. Early, aggressive, and pragmatic treatment is necessary to successfully treat a child who is critically ill due to CA-MRSA infection. Vancomycin is the drug of first choice in the treatment of CA-MRSA. However, in the absence of sensitivity testing for vancomycin and especially when there is persistent MRSAB beyond 3–4 days, it is prudent to consider alternative approaches to treating this life-threatening infection. The present case amply demonstrates that in a resource-poor setting wherein optimal antibiotic sensitivity testing facility may not be available, a prudent and pragmatic decision has to be taken in deciding not only the first-line antibiotics (vancomycin + ceftriaxone) but also knowing when to change the antibiotics (to linezolid) while treating persistent CA-MRSAB (CA-MRSA bacteremia).

Declaration of patient consent
The authors certify that appropriate patient consent was obtained.

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Conflict of interest
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References

1. Tse SM, Laxer RM. Approach to acute limb pain in childhood. Pediatr Rev 2006;27:170-9.
2. Belthur MV, Birchnsby SB, Verdugo AA, Mason EO Jr, Hulten KG, Kaplan SL, et al. Pathologic fractures in children with acute Staphylococcus aureus osteomyelitis. J Bone Joint Surg Am 2012;94:34-42.
3. Lepeage AA, Hess EP, Scheers RM. Septic thrombophlebitis with acute osteomyelitis in adolescent children: A report of two cases and review of the literature. Int J Emerg Med 2008;1:155-9.
4. Kaplan SL. Osteomyelitis in children. Infect Dis Clin North Am 2005;19:787-97.
5. Shaikh N. Emergency management of fat embolism syndrome. J Emerg Trauma Shock 2009;2:29-33.
6. Goswami U, Brenes JA, Punjabi GV, Le Claire MM, Williams DN. Associations and outcomes of septic pulmonary embolism. Open Respir Med J 2014;8:28-33.
7. Ye R, Zhao L, Wang C, Wu X, Yan H. Clinical characteristics of septic pulmonary embolism in adults: A systematic review. Respir Med 2014;108:1-8.
8. Crawford T, Yoon C, Wolfson K, Beller M, Emerick A, Goldin JG, et al. The effect of imaging modality on patient management in the evaluation of pulmonary thromboembolism. J Thorac Imaging 2001;16:163-9.
9. David MZ, Daum RS: Community-associated methicillin-resistant Staphylococcus aureus: Epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev 2010;23:616-67.
10. Lin MY, Rezai K, Schwartz DN. Septic pulmonary emboli and bacteremia associated with deep tissue infections caused by community-acquired methicillin-resistant Staphylococcus aureus. J Clin Microbiol 2008;46:1553-5.
11. Health Protection Agency. Guidance on the diagnosis and management of PVL-associated Staphylococcus aureus infections (PVL-SA) in England. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/322857/Guidance_on_the_diagnosis_and_management_of_PVL_associated_SA_infections_in_England_2_Ed.pdf. [Last accessed 2017 July 10].
12. Liassine N, Auckenthaler R, Descombes MC, Bes M, Vandenbroucke F, Etienne J. Community-acquired methicillin-resistant Staphylococcus aureus isolated in Switzerland contains the Panton-Valentine leukocidin or exfoliative toxin genes. J Clin Microbiol 2004;42:825-8.
13. Eshwara VK, Munim F, Tellapragada C, Kamath A, Varma M, Lewis LE, et al. Staphylococcus aureus bacteremia in an Indian tertiary care hospital: Observational study on clinical epidemiology, characteristics, and carriage of the Panton-Valentine leukocidin gene. Int J Infect Dis 2013;17:1051-5.
14. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:e18-55.
15. Vander Have KL, Karmazyn B, Verma M, Caird MS, Hensinger RN, Farley FA, et al. Community-associated methicillin-resistant Staphylococcus aureus in acute musculoskeletal infection in children: A game changer. J Pediatr Orthop 2009;29:927-31.
16. Kullar R, McKinnell JA, Sakoulas G. Avoiding the perfect storm: The biologic and clinical case for reevaluating the 7-day expectation
for methicillin-resistant Staphylococcus aureus bacteremia before switching therapy. Clin Infect Dis 2014;58:1455-61.

17. Bassetti M, Baguneid M, Bouza E, Dryden M, Nathwani D, Wilcox M. European perspective and update on the management of complicated skin and soft tissue infections due to methicillin-resistant Staphylococcus aureus after more than 10 years of experience with linezolid. Clin Microbiol Infect 2014;20(Suppl 4):3-18.

18. Raffini LJ, Scott JP. Thrombotic disorders in children. In: Kliegman RM, Stanton BF, St Gerne JW, Schor NF, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2016. p. 2394-7.

19. Raffini LJ, Scott JP. Hereditary predisposition to thrombosis. In: Kliegman RM, Stanton BF, St Gerne JW, Schor NF, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2016. p. 2392-3.

20. Kaplan SL. Osteomyelitis. In: Kliegman RM, Stanton BF, St Gerne JW, Schor NF, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2016. p. 3322-27.