The Pivotal Role of Deep Vein Thrombophlebitis in the Development of Acute Disseminated Staphylococcal Disease in Children

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ABSTRACT. Deep vein thrombophlebitis (DVT) and septic pulmonary emboli (PE) are rare in children. The association of DVT and acute disseminated staphylococcal disease (DSD) during childhood has not been previously reported. We report 3 children who developed a triad of DVT, septic PE, and acute osteomyelitis with *Staphylococcus aureus* cultured from blood and bone. One child succumbed, while 2 survived following prolonged, morbid hospitalizations. The rapid clinical deterioration observed in these patients might be caused by the aggressiveness of staphylococcal infection combined with an ongoing showering of septic emboli from the ileo-femoral DVT. We suggest that infected DVT with septic PE had a pivotal role in the development of DSD in these children. The presence of this triad should prompt aggressive treatment with the appropriate antibiotics, anticoagulation, surgical drainage, and assisted ventilation when indicated. *Pediatrics* 2000;106(6). URL: http://www.pediatrics.org/cgi/content/full/106/6/87; deep vein thrombophlebitis, disseminated staphylococcal disease, osteomyelitis, pediatric, septic pulmonary emboli.

CASE REPORTS

Patient 1

An 11-year-old previously healthy boy presented with left hip pain, fever (approaching 39.7°C), recurrent vomiting, and a generalized erythematous rash of 2 days duration. Physical examination showed an alert child: temperature, 39°C; heart rate, 188 beats/minute; respiratory rate, 32 breaths/minute; and blood pressure, 75/50 mm Hg. A diffuse erythematous rash was present over the extremities. Chest examination revealed crepitations over the left side. The left hip joint was tender with no evidence of local infection.

Initial laboratory results included: hemoglobin, 12.6 g/dL; white blood cell count (WBC) 28 287/mm3; platelet count, 168 000/mm3; prothrombin time, 24% (international normalized ratio: 2.2); and partial thromboplastin time, 42.8 seconds. The chest radiograph showed bilateral diffuse infiltrates (Fig 1). Ultrasonography of the left hip joint demonstrated intraarticular fluid and thickening of the joint capsule. A bone scan was consistent with osteomyelitis of the left proximal femur. Doppler ultrasound revealed thrombosis with partial occlusion of the left femoral vein (Fig 2). Blood cultures were drawn and intravenous administration of vancomycin and gentamicin was begun. The child was taken to the operating room for surgical exploration. The left hip and femur were involved in an extensive inflammatory process, and foul-smelling pus was drained from the hip joint and the upper femur. Both blood and pus cultures grew *Staphylococcus aureus*. Amikacin, vancomycin, and rifampicin were given based on culture sensitivities. Anticoagulation was started with intravenous heparin, maintaining partial thromboplastin time at 50 to 70 seconds.

The patient’s clinical condition deteriorated requiring various modes of ventilatory support, including high-frequency ventilation. Repeated chest radiographs showed multiple pneumatoceles and bilateral pneumothoraces, which were drained. Despite adequate anticoagulation and adjusted antibiotic treatment, the child died on the sixth day of admission because of refractory respiratory and multiorgan failure.

Patient 2

A 10-year-old boy was referred to our facility after 3 weeks of hospitalization elsewhere, where he had been admitted for pain and swelling of the left thigh after trauma. During his initial hospitalization, he underwent a negative exploratory laparotomy for unexplained abdominal dissection. Fever, bilateral pneumonia, and a left pneumothorax complicated the postoperative course. He was referred to our department for further treatment. On physical examination, he had a temperature of 38.6°C, heart rate of 124 beats/minute, respiratory rate of 30 breaths/minute, and blood pressure of 100/60 mm Hg.

Chest examination revealed bilateral bronchial breathing. The abdomen was mildly distended. The left lower extremity was edematous with increased venous marking over the upper thigh and lower abdomen. Laboratory results included: hemoglobin, 11.8 g/dL and WBC, 21 000/mm3. A chest radiograph showed an infiltrate over the right lung and a left pneumothorax. A thoracostomy tube was inserted and 100 mL of purulent fluid was drained. The patient was admitted to the pediatric intensive care unit. Intravenous administration of methylcellulose and amikacin was initiated. Bone scan demonstrated osteomyelitis of the left femoral head. Venography showed complete obstruction of the left femo-
ral vein with collaterals. Anticoagulation with heparin was begun. Cultures taken from the left chest, hip joint, and an abdominal incision were all positive for \textit{S aureus}. The antibiotic treatment was changed to nafcillin, according to the culture sensitivities. The patient had a prolonged hospitalization, complicated by high-grade fever, recurrent episodes of pneumothoraces, dehiscence of the abdominal wound, and persistent drainage from the left femur. The patient was discharged from the hospital after 6 weeks in satisfactory condition, afebrile, and on oral antibiotics.

Patient 3

A 10-year-old boy presented to the emergency department limping, with fever and pain in the left ischial tuberosity of 3 days duration. On admission, his temperature was 38.7°C, the lungs were clear, and there was slight tenderness over the left ischial area.

Laboratory results included: hemoglobin, 14.6 g/dL; WBC, 10,900/mm$^3$ with 86% neutrophils; and the erythrocyte sedimentation rate, 115 mm. Chest and pelvic radiographs were normal. Blood cultures, drawn on admission, were positive 24 hours later for \textit{S aureus}, and the patient was treated with intravenous cloxacillin. A bone scan was inconclusive, and the possibility of osteomyelitis of the left femur was raised.

A chest radiograph performed 5 days later showed bilateral multiple well-circumscribed round infiltrates. On the same day, edema of the left leg with increased venous marking was noticed. An abdominal computer-assisted tomography showed hepatosplenomegaly and left iliac vein thrombosis, confirmed by Doppler sonogram. Anticoagulation with heparin was initiated. After a 3-week course of intravenous antibiotics and heparin, the lung lesions resolved. The patient was discharged from the hospital on oral antibiotics and anticoagulant therapy. Six months later, he was readmitted because of pain in the left hip joint and a limp. A bone scan and hip joint radiograph were consistent with chronic osteomyelitis of the left femoral neck. The patient was treated with oral fucidic acid for 3 months and recovered.

DISCUSSION

Staphylococcal infection may cause a varied spectrum of diseases in children. The most severe form is acute DSD, first described by Hieber et al\textsuperscript{1} in 1977. The disease occurs primarily in previously healthy children 5 to 15 years of age, progresses rapidly, and carries mortality rates of 13% to 27%\textsuperscript{2,3} The diagnostic criteria of DSD are infection at 2 or more anatomic sites and the isolation of a coagulase-positive \textit{S aureus} from the blood or from a site of infection. Lungs, bones, and joints are the most common organs involved in DSD, followed by skin and muscles, kidneys, liver, central nervous system, and heart.\textsuperscript{3} To the best of our knowledge, infected DVT has not been described in the literature as part of DSD. \textit{S aureus} is the most common cause of osteomyelitis and septic arthritis in children, accounting for 40% to 80% of cases.\textsuperscript{4} There are few reports associating acute osteomyelitis with DVT in children.\textsuperscript{5,6} Horvath et al\textsuperscript{5} discuss the differential diagnosis of osteomyelitis and DVT.

Many strains of \textit{S aureus} release various exotoxins. \textit{α}-toxins act on cell membranes and may produce aggregation of platelets and spasm of smooth muscle. A variety of enzymes are released by staphylococci; among them coagulase, which specifically interacts with fibrinogen and causes plasma to clot.\textsuperscript{4} These factors may predispose to the development of DVT adjacent to osteomyelitis caused by \textit{S aureus}.
The present series of patients had *S. aureus* induced osteomyelitis of the left hip or femur and DVT of the ipsilateral extremity. Noniatrogenic DVT of the pelvis and the lower extremities are related to localized or widespread inflammatory processes such as peritonitis, sepsis, or osteomyelitis. Cockett et al. note that thrombosis occurs more frequently in the left than in the right leg. It has been shown by phlebography that normal iliac veins are more often slightly compressed at the point where the left common iliac vein is crossed by the right common iliac artery; therefore, he has coined the term “iliac compression syndrome.” Horvath et al and Jupiter et al emphasize the association between septic thrombophlebitis and osteomyelitis but do not relate to the radiologic findings encountered in their patients’ chest radiographs. Felman and Shulman report on 10 patients with staphylococcal osteomyelitis suffering from sepsis and PE or pulmonary disease but do not mention deep vein thrombosis as the source of septic emboli. They noticed that early pulmonary radiograph findings in the majority of their patients consist of multiple scattered bilateral densities situated predominantly in the peripheral and inferior segments of the lung, as was seen in case 1. These densities generally coalesced rapidly to form segmental and lobar aggregates.

Septic emboli from staphylococcal thrombophlebitis may cause necrotizing pneumonitis, emphysema, pneumatocele, pneumothorax, and broncho-pleural fistula. The rapid clinical deterioration observed in our patients might be caused by the aggressiveness of staphylococcal infection combined with an ongoing showering of septic emboli from the ileo-femoral DVT. These emboli may cause pulmonary infarction, a sudden increase in pulmonary vascular resistance, and a decrease in cardiac output.

We suggest that infected DVT with septic PE has a pivotal role in the morbidity and frequent poor outcome in DSD in childhood. The combination of acute osteomyelitis, septic deep thrombophlebitis, and PE is a life-threatening syndrome. Although noniatrogenic DVT is rare in children, it should be actively sought in every child presenting with local tenderness, swelling, edema, or positive Homans’ sign, especially when the left lower extremity is involved.

The diagnosis of acute osteomyelitis does not rule out the coexistence of underlying DVT. The combination of acute osteomyelitis and patchy or localized pulmonary lesions should prompt the physician to search for DVT as a source for septic emboli using any of the diagnostic modes that are currently available. Ultrasound doppler is sensitive in detecting DVT in the thigh and popliteal areas. Phlebography can detect both distal and proximal thrombi in the femoral and iliac veins. Computer-assisted tomography can detect thrombosed veins in the abdomen and pelvis and is considered superior to conventional phlebography in visualizing thrombi in the great veins.

A high index of suspicion for this triad, prompt diagnosis, and aggressive treatment with appropriate antibiotics, anticoagulation, surgical drainage, and assisted ventilation when indicated are the cornerstones for potential cure in this life-threatening syndrome.

REFERENCES
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