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Pneumococcal Sepsis–induced Purpura Fulminans in an Asplenic Adult Patient Without Disseminated Intravascular Coagulation

Christine Saraceni, DO and Daniel Schwed-Lustgarten, MD

Abstract: Acute perturbations in the hemostatic balance of anticoagulation and procoagulation antecede the manifestation of purpura fulminans, a rare syndrome of intravascular thrombosis and hemorrhagic infarction of the skin. Hallmarks include small vessel thrombosis, tissue necrosis and disseminated intravascular thrombosis. The course may be rapidly fulminant resulting in multiorgan failure with thrombotic occlusion of the vasculature, leading to distal extremity ischemia and necrosis. Depletion of protein C (PC) has been emphasized in the pathogenesis. Early intravenous antibiotic administration and hemodynamic support are cornerstones in management. Herein, we report a case of pneumococcal sepsis-induced purpura fulminans limited to the skin in an asplenic adult patient without the development disseminated intravascular coagulation.

Key Indexing Terms: Purpura fulminans; *Streptococcus pneumoniae*; Adult; Sepsis. **[Am J Med Sci 2013;346(6):514–516.]**

Purpura fulminans is a rare limb-threatening syndrome characterized by hemorrhagic infarction of the skin and small vessel microthrombi that is commonly associated with disseminated intravascular coagulation (DIC).[1] The clinical spectrum of disease includes 3 distinct subtypes, namely (1) inherited or acquired coagulopathies of the protein C or protein S (PS) anticoagulant pathway that often manifest in the neonatal period; (2) idiopathic PF which is typically a postinfectious phenomena and (3) acute infectious PF in cases of severe bacterial infections and foremost reported in meningococcal disease[2,3] followed by pneumococcal sepsis in adults.[4] Sepsis-induced purpura fulminans has been reported with various causative microorganisms[4–7] and can lead to multiorgan failure and significant long-term morbidity with a high case fatality rate.[1,4,8] Overwhelming postsplenectomy sepsis is a well-documented sequela of *Streptococcus pneumoniae* septicemia and other encapsulated bacterial infections with pneumococcal purpura fulminans reported with increased frequency.[4,9] There is a lifelong risk of occurrence in patients with asplenia.[5] It is unclear whether vaccination averts the likelihood of severe complications of pneumococcal sepsis in splenectomized individuals.[10] The mainstay of our insight into the pathophysiology of this syndrome has been derived from the experience in childhood cases gathered from single case reports, case series and limited reviews and have focused on the effects of endotoxin and its role in the inflammatory cascade of gram-negative sepsis.[2–4,6–12]

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CASE PRESENTATION

A 46-year-old woman with a history of idiopathic thrombocytopenic purpura with subsequent splenectomy 1 year before presentation and unknown vaccination status presents to the emergency department with productive cough, fever, rigors and chest discomfort found to be in septic shock, adult respiratory distress syndrome and respiratory failure. She required iatrogenic support, including intubation and vasopressors (norepinephrine, dobutamine and vasopressin) and stress dose steroids. She was found to have *Streptococcus pneumoniae* necrotizing pneumonia and bacteremia with positive blood and sputum cultures and was treated with intravenous ceftriaxone (2 g q24 hours) for a 14-day course. Within 24 hours of admission, she developed generalized purpura fulminans of the extremities, trunk, chest, face and neck and was transferred from the referral facility on hospital day 4 after development of extensive bullae formation and skin sloughing. She arrived off all vasopressors with resolution of septic shock. There was no history of hypercoagulable state, heparin or warfarin (Coumadin) exposure or prone ventilation.

Pertinent laboratory findings at the initial presentation to the outside facility included: leukocytosis 91,000/mm^3, platelets 29,000/mm^3, hemoglobin 9.7 g/dL, blood urea nitrogen 42 mg/dL and creatinine 0.84 mg/dL. Upon transfer, coagulation studies showed prothrombin time of 15.1 seconds, partial thromboplastin time of 30.6 seconds, D-dimer 18.47 μg/mL and fibrinogen 600 mg/dL. Manual review of the peripheral smear indicated no evidence of microangiopathic hemolytic anemia. There was questionable history of remote systemic lupus erythematous. However, serologies indicated no active connective tissue disease. Markers for autoimmune thrombosis including B2-glycoprotein antibodies, anti-cardiolipin antibodies and lupus anticoagulant were negative. Venous duplex ultrasounds of the upper and lower extremities were negative for deep or superficial venous thrombosis. Echocardiogram was negative for vegetations. Skin biopsy of purpuric abdominal lesions revealed thrombotic vasculopathy and associated ischemic epidermal necrosis without evidence of vasculitis consistent with the clinical picture of pneumococcal-induced purpura fulminans without DIC and limited to the skin.

The patient developed progressive ischemia and necrotic gangrene of 24% of total body surface area and ultimately required multiple areas of debridement and skin grafting and after full demarcation, underwent bilateral below-the-knee amputations, left hand amputation and partial amputations of digits 2 and 3 at the distal interphalangeal joint level of the right hand. With supportive care and antibiotics, she improved clinically. Her graft and donor sites healed remarkably, and the patient was discharged from the intensive care unit at day 48 for aggressive rehabilitation.

DISCUSSION

Cardinal features of acute infectious PF include dermal vascular thrombosis, secondary hemorrhagic necrosis and systemic consumptive coagulopathy, including DIC in the setting of

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septic shock.[2,6] Classically, acute infectious PF cultivates in the setting of gram-negative sepsis and endotoxemia resulting in hemostasis disruption. Development of systemic consumptive coagulopathy is a hallmark of PF.[2] This cascade typically involves DIC (reported in >90% of cases), particularly in adult patients with severe sepsis, PF has become a cutaneous stigmata for DIC.[4] Our case is an unusual variant in an adult patient with this procoagulant state without overt DIC and represents the minority of cases without clinical signs of bleeding or thrombosis in the setting of severe septic shock.[9] The exact prevalence of severe complications of pneumococcal sepsis in the community is unknown.[13] Adult cases of pneumococcal PF without the development of DIC are uncommon. An extensive Medline literature search of adult cases of pneumococcal PF was performed, and to our knowledge, there have only been 4 other reported cases of pneumococcal PF in adult patients without the development of DIC.[9,10]

DIC is a clinicopathologic syndrome marked by a derangement of the fibrinolytic system, resulting in a severe consumptive coagulopathy with acute perturbation in compensatory hemostatic mechanisms leaving to hemorrhage and thrombosis. Systemic fibrin deposition in small- and medium-sized vessels compromises blood supply to multiple organs with consequent organ failure. The diagnosis is primarily clinical. However, laboratory abnormalities of coagulation can support the diagnosis. Although no single laboratory value definitively establishes the diagnosis, common laboratory findings include prolongation of prothrombin time and/or activated partial thromboplastin time, platelet counts $\leq$100,000/mm^3, the presence of schistocytes in the peripheral blood smear, elevated levels of fibrin degradation products and low fibrinogen. [9,14]

Our patient did not develop widespread coagulation activation leading to systemic bleeding and thrombosis as seen in DIC nor did she have evidence of microangiopathic hemolytic anemia. Purpura fulminans was the primary manifestation in this case, which was isolated to the skin. Hemorrhagic infarction of other tissues with subsequent multisystem organ failure did not occur as usually seen in DIC.

There may be an inherent difference in the pathophysiology of DIC in purpura fulminans caused by pneumococcal sepsis compared with gram-negative sepsis.[9] Overwhelming sepsis with circulatory collapse and tissue ischemia directly damages endothelial cells and kindles the development of microthrombic vasculopathy. The systemic inflammatory response in severe sepsis activates the coagulation and complement pathways, causing a disturbance in the anticoagulant and procoagulant activities of endothelial cells.[2] This is mediated by endotoxin in gram-negative and exotoxin in gram-positive sepsis through the actions of cytokines (mainly tumor necrosis factor–α, interferon-γ and interleukin-1) and the consumption of proteins C and S and antithrombin III.[3] In unrecognized cases of a partial heritable defect in the protein C anticoagulation pathway, acute sepsis may be the trigger to incite the development of PF.[11]

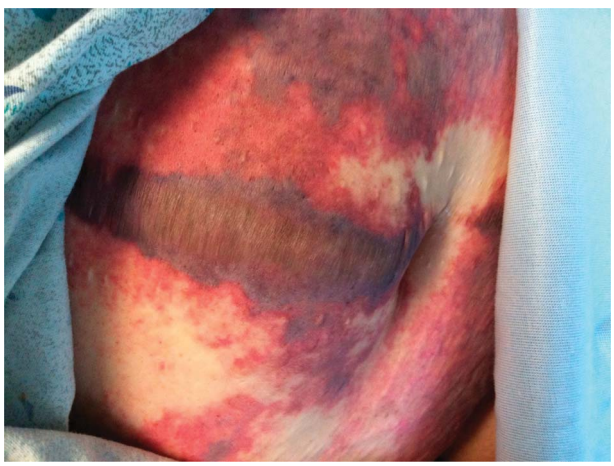

FIGURE 1. Patchy, confluent ecchymosis of the abdomen in early presentation of pneumococcal-induced purpura fulminans.

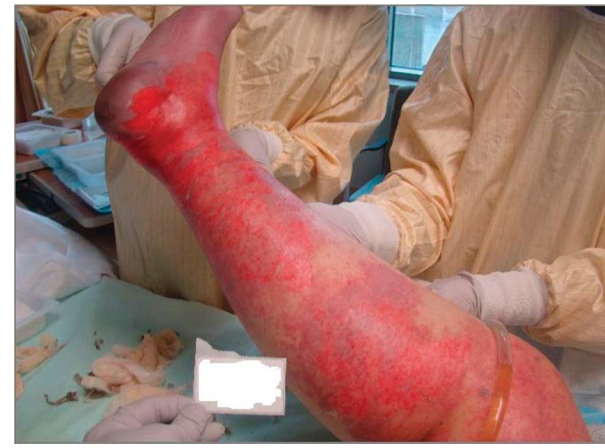

FIGURE 2. Ecchymotic nonblanching macular lesions of the lower extremity in the early course of pneumococcal purpura fulminans.

Cutaneous lesions initially appear as nonblanchable well-demarcated erythematous macules that rapidly evolve into painful, indurated plaques of blue-black hemorrhagic necrosis. Hemorrhage into the necrotic dermis promotes vesicle and bullae formation that often progresses within 24 to 48 hours into full-thickness skin necrosis that ultimately forms a sloughing eschar.[2,6,11,15] The distal extremity vascular beds (venules and capillaries) are least tolerant to dermal vascular microthrombosis with resultant symmetric distal ischemia that may progress proximally in a patchy distribution and may affect large confluent areas of the entire body surface[2,11] (Figure 1). Gangrenous necrosis may often extend into soft tissue compartments necessitating surgical debridement, skin grafting, fasciotomies or amputation,[11,12] services that are readily available at our institutional burn center[8] (Figures 2 and 3). Although initially sterile, gangrenous tissue is

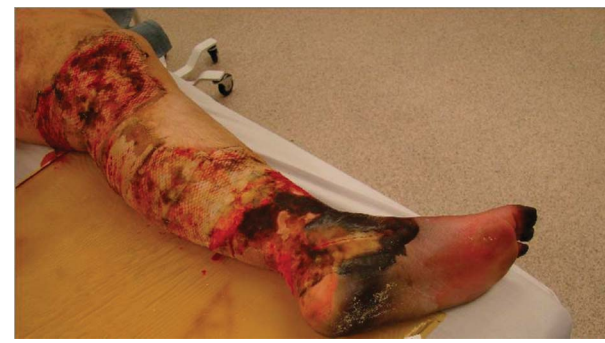

FIGURE 3. Multiple areas of gangrenous necrosis of the distal extremity. Operative course included excision with allografting and split thickness skin graft closure. Patient required below-the-knee amputation.

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a conduit for secondary infection.[4] Our case is atypical as the lesions were generalized and erupted concomitantly with extremity lesions at sites including the face, neck, chest and torso that defy the typical pattern of proximal progression. Interestingly, the posterior cutaneous surfaces of the back and buttocks were completely sparred.

Early antibiotic therapy and hemodynamic support in the intensive care setting are paramount life-sustaining measures. Initial empiric antibiotic treatment should include a third-generation cephalosporin for *Neisseria* and *Streptococcus* coverage and consideration of methicillin-resistant *Staphylococcus aureus* coverage until the causative agent is identified.[4,7] In instances of full-thickness skin loss, aggressive debridement of necrotic tissues and skin grafting are often necessary. If feasible, limb preservation strategies include allowing dry gangrenous areas of tissue necrosis to fully demarcate before amputation.[4,8,12] In cases of DIC, fresh frozen plasma provides exogenous PC and PS replacement and volume replacement and vitamin K corrects vitamin K–dependent coagulation factors.[2,11] Newer adjuvant therapies aimed at amelioration of the procoagulant complications in sepsis have been promising in severe systemic consumptive coagulopathy and include recombinant activated protein C (APC) concentrate and plasma-derived protein C concentrate but should not supersede standard sepsis management.[3,7,8,13,16] However, prospective randomized controlled trials are lacking and treatments have been empirical. The role of recombinant tissue plasminogen activator in sepsis-induced purpura fulminans has not been fully elucidated, likewise because of lack of randomized trials. The use of unfractionated or low-molecular-weight heparin anticoagulation is controversial and should be reserved for carefully selected cases, particularly in large vessel thrombosis.[3] In all these treatments, the risk of hemorrhagic diathesis should be weighed against the potential benefits before initiation of therapy. A multidisciplinary approach to treatment affords the greatest therapeutic benefit to survivors in PF, and treatment regimens should be tailored to individual cases until further validated.

CONCLUSIONS

Pneumococcal sepsis with purpura fulminans is a rare but important sequelae of asplenia. Successful management includes aggressive resuscitation, early antibiotic therapy and debridement of necrotic tissue. As the development of purpura fulminans is a rapidly progressive inflammatory cascade leading to appreciable morbidity with a significant number of cases resulting in partial or complete extremity loss, it is important that the clinician be aware of this syndrome.

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