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Human Recombinant Activated Protein C in Meningococcal Sepsis

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(on each hospital readmission); the findings of both were normal. However, on retracting the bronchoscope on his last examination, a mucosal lesion was seen in the oropharynx at the root of the tongue. A subsequent examination under anesthesia of the pharynx and larynx demonstrated a normal postnasal space and larynx. Valleculae varicosities were seen bilaterally at the base of the tongue, and diathermy was performed successfully. Since this time, there have been no further episodes of hemoptysis. His lavage cultures identified *Mycobacterium avium-intracellulare* resistant to all initiated agents, and his antituberculous chemotherapy was discontinued. He remains well with resolution of the right upper lobe consolidation and no CT evidence on follow-up of bronchiectasis.

Discussion

Hemoptysis is one of the most alarming symptoms frequently heralding the recognition of serious disease. It generally relates to blood originating distal to the vocal cords, but in some instances hemorrhage arising from the pharynx will cause diagnostic confusion. Most cases can be identified by a combination of bronchoscopy and CT scanning of the thorax.[1] In a retrospective analysis of 208 patients presenting with hemoptysis over a 15-year period, bronchiectasis (20%), lung cancer (19%), bronchitis (18%), and pneumonia (16%) were responsible for the majority of episodes of hemoptysis.[1] The severity of hemoptysis in our patient was not in keeping with an infectious etiology and evidence of an underlying structural abnormality was lacking. Only one specimen of *M avium-intracellulare* was cultured. Subsequent successive negative culture findings (despite resistance to all drugs used) suggest environmental contamination and clinical irrelevance. No fresh blood was seen in the region of the valleculae during endoscopic examination, though this was usually performed 2 to 3 days following the cessation of bleeding. The extensive negative search for a bleeding source coupled with its cessation following diathermy is suggestive that the origin of bleeding was from these varicosities.

The valleculae are a little known, but definite, anatomic entity of the oropharynx, representing pockets lying bilaterally between the epiglottis and tongue and formally referred to as the *valleculae epiglottica*. To our knowledge, there is only one previous report[2] in the literature of spontaneous hemorrhage from the root of the tongue; reports of massive hemorrhage from the valleculae have so far been secondary to surgical trauma.[3] Wetherill and Ganghi,[2] as in this case, reported abnormal and tortuous vessels in a patient with an infective exacerbation of bronchitis.

The published literature provides sparse insight into the etiology of oropharyngeal varicosities. Increasing age is regarded as an important factor and most are commonly sublingual; varicosities of the lip and buccal mucosa are seen less frequently.[4] Vallecular anomalies are not listed as a prominent area for oropharyngeal abnormality, although one may speculate that this relates to the inaccessibility of the region to easy inspection.

The venous drainage of the pharynx and larynx may explain the origins of oropharyngeal varicosities, particularly in patients with chronic chest disease. A venous plexus eventually tributary to either the internal jugular or brachiocephalic veins drains the pharyngeal and laryngeal structures. Chronic elevations of right-heart pressure may predispose to variceal formation. Factors influencing variceal size and wall tension may be responsible for episodes of acute hemorrhage, perhaps hypoxia. It is well recognized, in esophageal varices, that portal pressure reflects intravariceal pressure,[5] and that the likelihood of hemorrhage relates to four factors: (1) pressure within the varix, (2) tension on the variceal wall, (3) variceal size, and (4) severity of liver disease.[6]

It is evident that the origin of large-volume hemoptysis is not always readily apparent even after extensive investigations. In this patient, no gross structural lung damage existed, confirmed by high-resolution CT scanning and repeated direct visualization of the endobronchial anatomy with a flexible fiberoptic scope. Consequently, and with the aid of time, we are confident that the varices seen within the oropharynx represent the sole reason for his hemoptysis, perhaps supported by its cessation following variceal diathermy. We highlight the valleculae as a region worthy of thorough inspection in order that considerable morbidity can be avoided.

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Human Recombinant Activated Protein C in Meningococcal Sepsis*

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A 19-year-old woman presented with purpura fulminans and septic shock; subsequently, progressive coagulopathy, widespread purpura fulminans associated with meningococcemia, severe shock, respiratory, and renal failure developed. This clinical course was associated with depletion of functional protein C levels to < 5%. We describe her clinical

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course and therapy with human recombinant activated protein C. ***(CHEST 2002; 121:292–295)***

Key words: human recombinant activated protein C; purpura fulminans; renal failure; respiratory failure; septic shock

Abbreviations: DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; NESI = Neisseria sepsis index; PTT = partial thromboplastin time

Sepsis is a complex syndrome caused by the response of the organism to infection. The precise pathogenesis of sepsis remains only partly defined, but many of its characteristics can be reproduced by the injection of cytokines into experimental animals. However, while some proinflammatory cytokines mimic some of the physiologic syndrome, it has become evident that the entire syndrome represents a complex balance of proinflammatory and anti-inflammatory cytokines, and that some of the participants are, almost certainly, yet undiscovered.[1–3]

While the precise pathogenesis of the entire sepsis paradigm is uncertain, portions of it are better understood. Endothelial intimal surfaces are affected by cytokines, with activation of ineffective clotting, which evolves into disseminated intravascular coagulation (DIC).[4] Purpura fulminans, which is most often associated with meningococcemia, is a flagrant expression of sepsis-induced DIC, and is usually associated with profound shock, organ dysfunction, and high mortality. It presents clinically as retiform purpura, which histologically is a bland thrombosis of capillaries filled with fibrin. Prior reports[5,6] of purpura fulminans in conjunction with meningococcemia have documented depletion of protein C, an important suppressor of thrombosis. Purpura fulminans also develops in patients with congenital protein C deficiency, and this disease responds to protein C supplementation.[7] Smith et al[8] extended the logic of this intervention, and successfully treated patients with meningococcus-induced purpura fulminans with protein C concentrate. In this article, we report the first case of purpura fulminans associated with meningococcemia treated with a human recombinant activated protein C.

Materials and Methods

Routine laboratory and coagulation studies were done in the clinical pathology laboratories of the University of Iowa Hospital. Recombinant human activated protein C was provided through a compassionate use protocol, LY203638, by Eli Lilly and Co. (Indianapolis, IN). This protocol was evaluated and approved by the University of Iowa Hospital Human Use Committee. Appropriate patient consent was obtained.

Case Presentation

A 19-year-old female college student without a significant medical history presented with 2 weeks of sore throat, diarrhea, and intermittent fevers. Four days prior to hospital admission, she had a frontal headache with vomiting. The day prior to hospital admission, her symptoms had improved enough for her to attend classes. On the day of hospital admission, she awoke with diffuse myalgias and arthralgias and she noted "blotchy brown spots" on her legs. Her sexual history was noncontributory. She had no history of tobacco, alcohol, or drug abuse. Her temperature was 36.7°C, BP was 50/37 mm Hg, heart rate was 135 beats/min and regular, and respirations were 20 breaths/min with an O_2 saturation of 98% on room air. She was alert but appeared acutely ill. Examination of her skin revealed a blotchy retiform purpuric rash on the lower extremities, trunk, and face. Some of the lesions on her lower extremities were > 2 cm in diameter. There was no meningismus, and she denied photophobia. The lungs were clear to auscultation, and heart sounds were normal. Pelvic and abdominal examination findings were unremarkable. Neurologic examination findings were normal, except for diffuse weakness.

The WBC count was 8,700/μL, hemoglobin was 11.5 g/dL, and platelet count was 101,000/μL. The creatinine level was 2.4 mg/dL (212 μM). The prothrombin time was 14 s, and the partial thromboplastin time (PTT) was 45 s. Fibrin degradation products were > 80. Functional protein C was 23%. Results of a portable chest radiograph were normal. A lumbar puncture was performed, and the cerebrospinal fluid contained 1 WBC and 18 RBCs. The cerebrospinal fluid protein level was 26 mg/dL, and the glucose level was 60 mg/dL (1,080 mM). No organisms were seen on Gram's stain.

She received 2 g of ceftriaxone, 130 mg of gentamicin, and 1 g of vancomycin, and was admitted to the ICU. She also received 5.5 L of saline solution, 4 L of fresh frozen plasma (FFP), dopamine, and norepinephrine over the first 12 h to maintain a target mean arterial BP of 60 mmHg. Five hours after ICU admission, her oxygenation was worse, with a Pao_2 of 49 mm Hg while receiving 85% oxygen by face mask. She was intubated, and mechanical ventilation was initiated. Her Pao_2/fraction of inspired oxygen ratio was 52. A chest radiograph showed diffuse bilateral alveolar infiltrates. Her coagulation profile had also deteriorated. Her prothrombin time was 25 s, PTT was 73 s, and platelet count was 31,000/μL (Fig 1). Functional protein C was 5%. She received 4 U of FFP, and protein C increased to 15%. Ten hours after ICU admission, blood culture findings were positive for Gram-negative diplococci. Her APACHE (acute physiology and chronic health evaluation) II score during the first 24 h was 28.

On the second day, the retiform purpura progressed and coalesced, involving more than half of her skin surface. A biopsy of the skin lesions showed thrombosis of superficial and deep vessels, mild inflammatory cell infiltrate, and focal extravasation of erythrocytes. Four more units of FFP were administered. Continuous venovenous hemofiltration was started for oliguric (urine output < 15 mL/h) renal failure (creatinine level, 4.4 mg/dL [389 μM]). While the cortisol level at ICU admission was 71 μg/dL (1,960 nM), the cortisol level on day 2 was 7.8 μg/dL (215 nM) and the response to synthetic adrenocorticotropic hormone was blunted. Treatment with dexamethasone was started.

Thirty-four hours after presentation, an infusion of recombinant activated protein C was started at 18 μg/kg/h and increased to 24 μg/kg/h after 30 min. This infusion was continued for 96 h. Figure 1 outlines the time course of her coagulopathy.

On the third day, the Gram-negative cocci in the blood cultures were identified as *Neisseria meningitidis*, group C, sensitive to penicillin, and antibiotics were changed to penicillin G. By the fourth day, oxygenation began to improve, and positive end-expiratory pressure was reduced to 10 cm H_2O with a Pao_2/fraction of inspired oxygen ratio of 237. On the fifth day, urine

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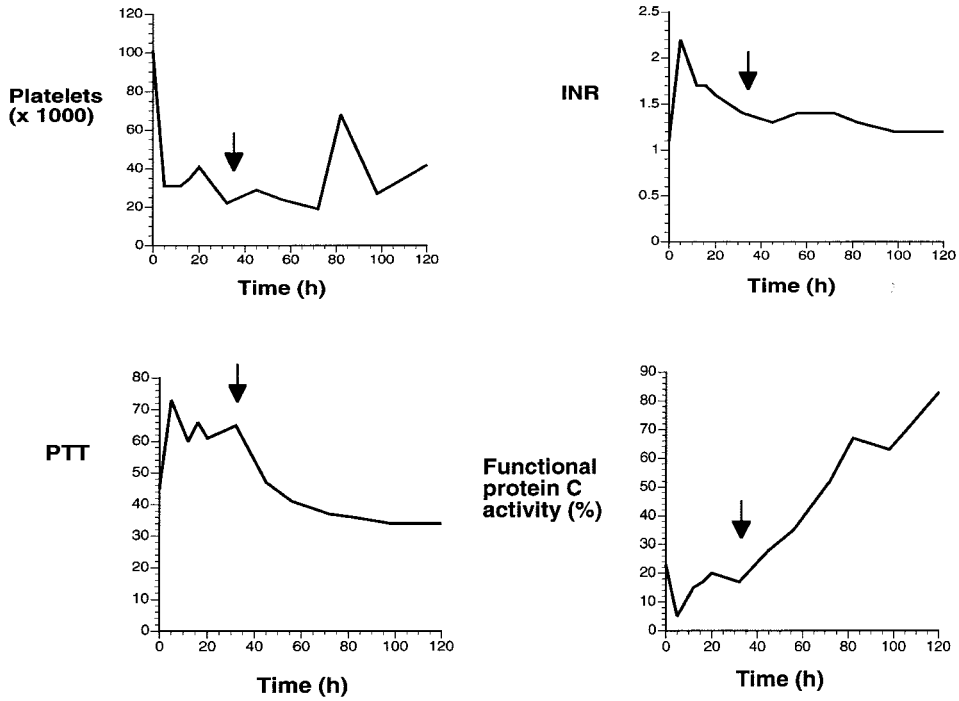

FIGURE 1. Sequence of changes in platelets, international normalized ratio (INR), PTT, and functional protein C activity in the patient over the first 120 h. She received 2 U of FFP at 6 h and 8 h, and 4 U at 23 h. Infusion of recombinant activated protein C was started at 34 h (arrows) and continued for 96 h.

output increased to 30 mL/h and continuous venovenous hemofiltration was stopped. Her chest radiograph cleared, and she was extubated on the sixth day. She required dialysis for renal failure on days 6, 8, and 14, after which she regained adequate renal function. Subsequently, she developed acalculous cholecystitis that responded to drainage, and a severe postinfectious arthritis developed that responded to treatment with corticosteroids. Her skin lesions healed, and she required no grafts. She was transferred from the ICU to the ward on day 23, and she left the hospital alive on day 46.

DISCUSSION

Our patient's clinical course was fortunate. By many criteria, she had an expected mortality of > 90%. She met four of the five criteria of Stiehm and Damrosch,[9] and three of five criteria were predictive up 90% mortality in their series. She had a Glascow meningococcal septicemia prognostic score of at least 9, which is predictive of mortality with a specificity of 95%.[10] The level of protein C depletion is also a strong predictor of outcome in meningococcemia with purpura fulminans. Depletion of protein C to levels ≤ 5% has been associated with mortalities > 90%.[8,11,12]

Other more recent reports would also indicate that our patient had a high expected mortality. Nurnberger et al[13] reported on the potential efficacy of hemostatic therapy (heparin, antithrombin, protein C concentrate, or FFP) in children with meningococcemia. They used the Neisseria sepsis index (NESI) to stratify the severity of illness in their patients. Of patients with NESI scores of 3 to 5, 90% of patients receiving hemostatic therapy survived while only 55% of patients not receiving hemostatic therapy survived. All of their patients with NESI scores of 6 to 8 died (five patients, four of whom received hemostatic therapy). They concluded that this therapy was probably not efficacious in this most seriously ill group. Our patient had a NESI of 7 to 8.

In another recent report, White et al[14] compared children treated with protein C concentrate with historical control subjects. They also used the Glasgow meningococcal scoring system as an estimate of mortality, and observed a mortality of 8% in a cohort with a predicted mortality of 50%. This is similar to that observed by Nurnberger et al[13] in the NESI 3 to 5 group. The Barcelona experience is another study[15] that is a rich epidemiologic base for meningococcemia. Of the Barcelona patients with a hemorrhagic diathesis, the odds ratio for death was 63 (confidence interval, 20.7 to 194), and the observed mortality rate in this group was 60%.

Our patient's functional protein C levels were rapidly depleted within a few hours of hospital admission, and she had a severe coagulopathy (Fig 1). The coagulopathy responded partially to treatment with FFP, but functional protein C never was > 20% prior to initiating infusion of recombinant, activated protein C. This may reflect the amount of protein C available in the FFP, or it may reflect the effects of sepsis on activation of inactive protein C found in FFP.

Protein C is a serine protease and natural anticoagulant that binds endothelial surface thrombomodulin in the presence of excess thrombin to produce activated protein

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C.[16] Activated protein C then interacts with protein S to inhibit factors Va and VIIIa and thereby limits thrombosis.[17] *In vitro*, activated protein C also binds to a receptor on macrophages and inhibits tumor necrosis factor production.[18] During sepsis-induced DIC, much of the protein C is complexed with inhibitors and cannot be activated.[19,20] Sepsis may also inhibit the activity of thrombomodulin, which is necessary to activate protein C.[21]

Consumption of protein C in meningococcal purpura fulminans and other types of Gram-negative sepsis is well documented.[11,12,20,22] Hereditary protein C deficiency manifests as purpura fulminans and responds to protein C concentrate.[7] This is part of the rationale for using protein C concentrate in patients with purpura fulminans associated with meningococcemia. While there have not been large controlled trials of the efficacy of protein C in meningococcal purpura fulminans, the efficacy of protein C concentrate in those series[8,11,13,14] in which it has been used is impressive when compared to historical control subjects.

Protein C concentrate contains inactive protein C that must be activated by the recipient's microvasculature, and, as discussed above, this activation may be impaired in sepsis. The recombinant activated protein C we administered to our patient is activated when it is administered, and sepsis-derived inhibitors and decreased thrombomodulin activity do not affect its efficacy. The recombinant protein has also been reported[22] to be more resistant to proteolysis by neutrophil elastase than native protein C. Hence, the recombinant activated protein C could potentially have more potency in meningococcal purpura fulminans than protein C concentrate, and it avoids the potential problems of blood product transmission of other diseases inherent in the concentrate preparations.

After this article was initially submitted, Bernard et al[23] published a report of the efficacy of recombinant activated protein C in patients with severe sepsis. The observed efficacy (reduction of mortality from 31 to 25%) was not dependent on depletion of protein C, indicating that activated protein C affects the physiology of sepsis by mechanisms other than just restoring normal functional levels of an endogenous anticoagulant. However, the extreme depletion of protein C and the extensive microvascular thrombosis that is the essence of meningococcal purpura fulminans makes it very possible that repletion with activated protein C will have even greater efficacy in this setting than in sepsis from other causes. The efficacy of protein C concentrate in meningococcal purpura fulminans is consistent with this hypothesis.

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