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Short Report: Severe Myalgia of the Lower Extremities as the First Clinical Feature of Meningococcal Purpura Fulminans

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Abstract. In patients with meningococcal infection, devastating presentations, such as purpura fulminans, which can progress to extensive tissue necrosis of the limbs and digits, have a significant social impact. The case presented herein illustrates such a phenomenon in a patient who developed bilateral necrosis of the lower extremities as a result of infection with *Neisseria meningitis*. We emphasize that severe myalgia was the first clinical manifestation of meningococcal purpura fulminans in our case. However, myalgia has typically been overlooked and undervalued as an early clinical feature of meningococcal sepsis. Early recognition and prompt initial antibiotic therapy continue to be the cornerstones of the successful management of this dramatic disease, reducing morbidity and mortality.

Meningococcal disease continues to be a clinical and public health problem, presenting high rates of morbidity and mortality.[1–3] *Neisseria meningitidis*, a contagious pathogen found worldwide, causes a constellation of pathophysiologic phenomena, including meningitis, septic shock, myocardial dysfunction, coagulopathy, adrenal hemorrhage, pneumonia, pericarditis, and peritonitis. In patients with meningococcal infection, devastating presentations, such as purpura fulminans, which can progress to extensive tissue necrosis, have also been well documented.[4–7] The case presented herein illustrates such a phenomenon in a patient who developed bilateral necrosis of the lower extremities as a result of infection with *N. meningitis* serogroup C. A remarkable feature in this case was the severe myalgia as the first clinical manifestation of meningococcal sepsis.[1–3] We also discuss some aspects of the pathogenesis, as well as the diagnostic value of Gram staining and skin biopsy.

A previously healthy 20-year-old man presented with a 72-hour history of severe muscle tenderness in both legs. In the preceding 6 hours, he had developed petechiae on his arms, legs, trunk, and became febrile. On examination, a dramatic progression from petechiae to confluent ecchymoses was observed on his skin (Figure 1A), apparently fitting the clinical profile of disseminated intravascular coagulation (DIC). He had neck stiffness, and his Glasgow Coma Scale score was 13. His vital signs were as follows: axillary temperature, 38.4°C; pulse, 136 bpm; respiration, 24 breaths/min; blood pressure, 80/25 mm of Hg. The rest of the examination was unremarkable. The white blood cell (WBC) count was 9,900 leukocytes/mL, with a left shift (91% polymorphonuclear neutrophils, 35% of which were band cells). Hemoglobin was 14 g/dL, and the platelet count was 68,000 cells/mL. Coagulation studies revealed an international normalized ratio of 3.25 and an activated partial-thromboplastin time of 48.5 seconds. Abnormal laboratory values included the following serum levels: creatine kinase, 1,714 U/L; albumin, 2.6 g/dL; creatinine, 2.4 mg/dL. The acid-base response to this clinical profile was consistent with acidemia and metabolic acidosis (arterial pH, 7.22; bicarbonate, 16; base deficit, –8) accompanied by hyperlactatemia (lactates, 65 mg/dL). A computed tomography scan of the brain was normal, and a lumbar puncture was performed after transfusion of fresh-frozen plasma. The cerebrospinal fluid (CSF) was cloudy and contained 24,320 leukocytes/mL (87% polymorphonuclear neutrophils), 547 mg/dL of protein, and 3 mg/dL of glucose. A Gram stain of the CSF showed gram-negative diplococci, and *N. meningitidis* serogroup C was detected by latex agglutination (LA), counterimmunoelectrophoresis (CIE), and polymerase chain reaction (PCR). The CIE for *N. meningitidis* serogroup C in serum was also positive. In addition, gram-negative diplococci were detected in the hemorrhagic skin lesion sample (Figure 2A and B). The results of the Gram stain, culture, CIE, LA, and PCR analyses of body fluids and skin are shown in Table 1. The PCR amplification of *N. meningitidis* genes in the CSF was performed for two specific regions encoding for polysialyltransferases (siaD) for serogroup B (siaDB) and for serogroup C (siaDC). The pairs of primers used were as follows: forward siaD B, 5′-GGA TCA TTT CAG TGT TTT CCA CCA-3′; reverse siaD B, 5′-GCA TGC TGG AGG AAT AAG CAT TAA-3′; forward siaD C, 5′-TCA AAT GAG TTT GCG AAT AGA AGG T-3′; reverse siaD C, 5′-CAA TCA CGA TTT GCC CAA TTG AC-3′. PCR conditions and primers were based on those published by Taha.[4] The amplification was performed in a thermocycler Eppendorf (Mastercycler, Hamburg, Germany). Two whole cell suspensions of *N. meningitidis* clinical strains, with an optical density of 0.2 at 620 nm, in 0.02% phosphate-buffered saline (PBS) sodium azide (inactivated at 56°C/30 min and stored at 4°C), were used as positive controls, such as Nm573/03 for siaDB PCR, and Nm576/03 for siaDC PCR. The PCR products were electrophoresed on an agarose gel, containing 22 μg ethidium bromide/50 mL of gel (15 minutes at 40 V/cm and 30 minutes at 80 V/cm) and sized with a 100-bp DNA ladder (Invitrogen, Carlsbad, CA). A single product of 450-bp siaDB or 250-bp siaDC was interpreted as a positive result. Only siaDC PCR was positive for the CSF sample evaluated in this study.

The initial diagnosis was meningococcal septic shock accompanied by meningitis, rhabdomyolysis, acute renal failure, and purpura fulminans. Therefore, antibiotic treatment was initiated with ceftriaxone (total daily dose of 4 g for 7 days) and dexamethasone (10 mg every 6 hours for 4 days). In

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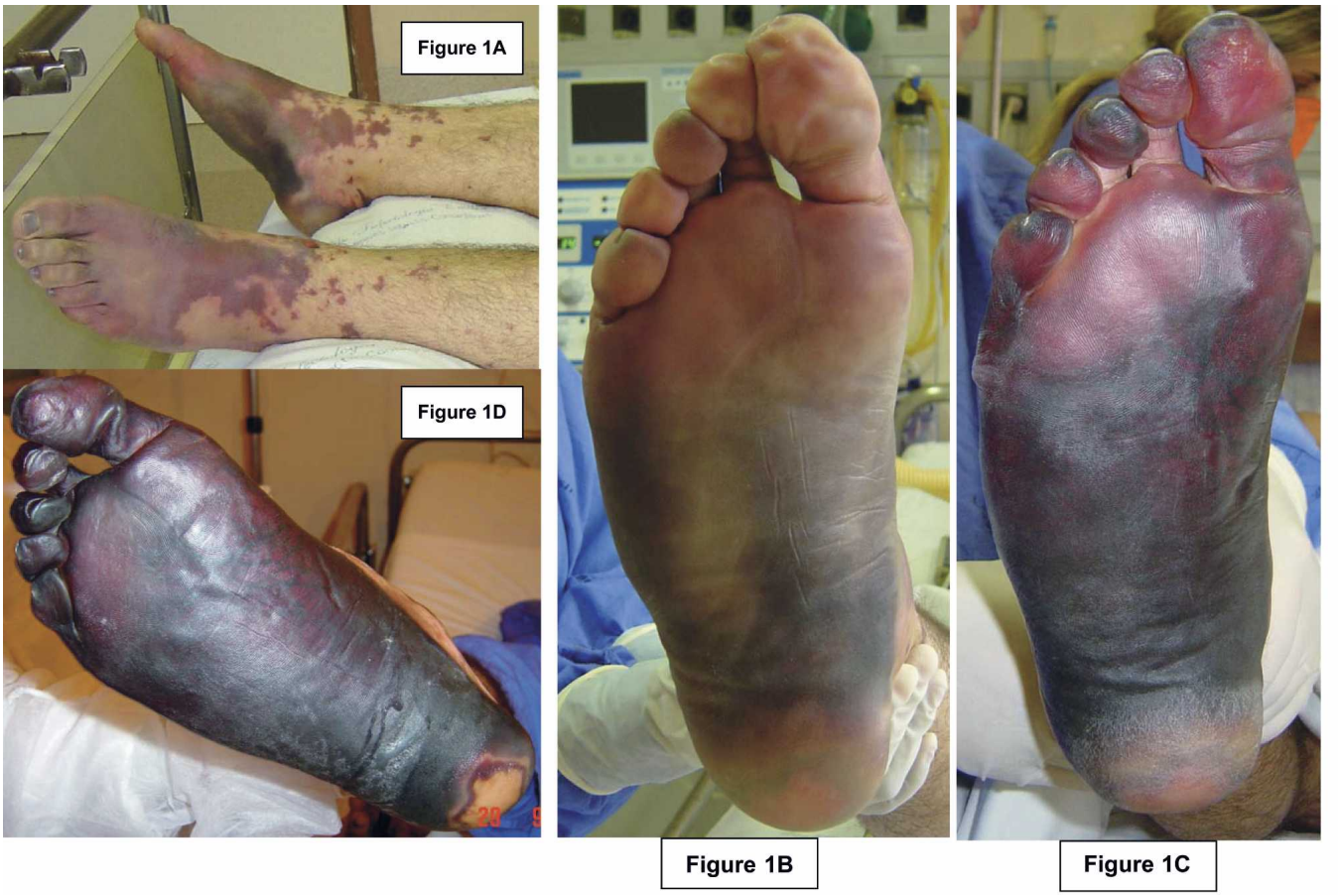

FIGURE 1. **A,** The patient developed purpura fulminans during meningococcal septic shock. **B–D,** The patient developed deep, extensive skin necrosis in the lower extremities. This figure appears in color at www.ajtmh.org.

addition, supportive measures to maintain homeostasis were adopted, as necessary, in a timely fashion. Such measures included fluid resuscitation, electrolyte replacement, vitamin K administration, transfusion of fresh-frozen plasma, catheterization, monitoring of central venous oxygen saturation, enteral nutrition, cardiovascular support, and mechanical ventilation. The close contacts received rifampin as chemoprophylaxis.

Despite the poor prognosis, general health status and kidney function improved by Day 7, and the patient was moved to the infirmary. However, during his stay in the intensive care unit (Figure 1B and C) and infirmary (Figure 1D), he developed a deep, extensive skin necrosis in the lower extremities and in one finger of the left hand. Therefore, he received care from a multidisciplinary rehabilitation team that included physical therapists, psychologists, plastic surgeons, orthopedic surgeons, and a group of highly skilled nurses. It became necessary to amputate both lower extremities and the one finger of the left hand.

Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure cytokine levels in the CSF and blood collected on admission. The results are shown in Table 2. The results of the immunologic tests for rheumatoid factor, antinuclear antibody, and antiphospholipid antibody were negative. After the acute phase, we also screened for anticoagulant factors such as protein C, protein S, and antithrombin III, all of which were found to be within normal limits. Cultures obtained at the time of admission showed no growth.

Based on all of the available clinical and laboratory evidence, the patient was diagnosed with purpura fulminans secondary to infection with *N. meningitidis* serogroup C, complicated by bilateral necrosis of the lower extremities and necrosis of one digit of the left hand. After discharge, appropriate rehabilitation was maintained. The evolution was favorable in the postoperative period and over the long term.

Cutaneous manifestations can be a feature of infections caused by a variety of pathogens such as *N. meningitidis*, which is the organism most often responsible for purpura fulminans.[5,6] However, similar lesions can be seen in sepsis caused by *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* Group A streptococci, rickettsial infections, and viral infections, as well as by other, noninfectious diseases.[5–8]

We emphasize that severe myalgia was the first clinical manifestation of meningococcal sepsis as shown in our patient. However, myalgia has typically been overlooked and undervalue as early clinical feature of meningococcal sepsis.[1–3] Classic clinical features of meningococcal disease as purpuric skin lesions and impaired consciousness appear late in the illness.[1–3] Thus, recognizing early symptoms of meningococcal sepsis could increase the number of patients identified by primary care clinicians and shorten the time to hospital admission.[1]

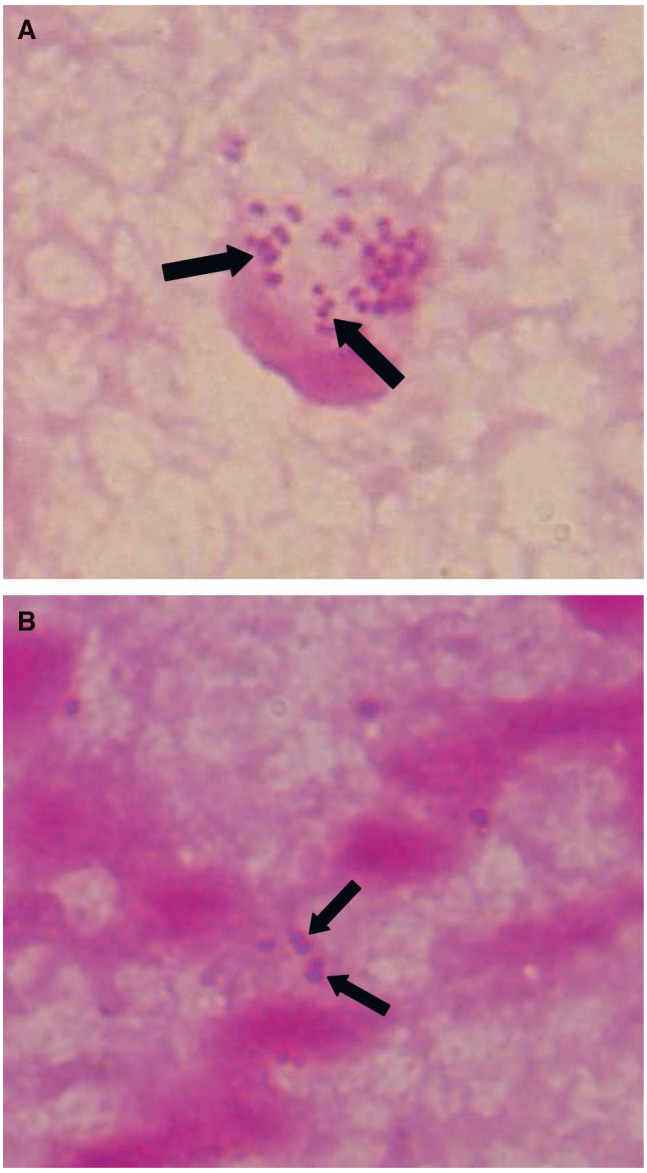

FIGURE 2. **A** and **B,** Gram-negative diplococci were detected in the hemorrhagic skin lesion sample (arrow). This figure appears in color at www.ajtmh.org.

Meningococcal purpura fulminans is a syndrome characterized by widespread purpuric skin lesions, DIC, and multiorgan dysfunction.[6] In fact, the presence of such skin lesions has been shown to correlate with the degree of thrombocytopenia and can be used as a prognostic factor.[7] In addition, coagulopathy in meningococcal disease is characterized by longer than normal prothrombin and activated partial-thromboplastin times, as well as by greater concentrations of fibrin degradation products, depletion of coagulation factors, and thrombocytopenia.[9]

TABLE 1

Analyses of blood, cerebrospinal fluid, and skin samples by Gram stain, culture, counterimmunoelectrophoresis, latex agglutination, and PCR

Specimen	Gram stain	Culture	LA	CIE	PCR
Blood	NP	–	–	+	NP
CSF	+	–	+	+	+
Skin	+	NP	–	NP	NP

NP, not performed.

TABLE 2

Concentrations of cytokines in our meningococcal septic shock patient on admission, as assessed through ELISA of the serum and cerebrospinal fluid

Cytokine	Serum (pg/mL)	CSF (pg/mL)
IL-4	27	121
IL-6	578	145
IL-10	395	676
IFN-γ	631	37

None of these cytokines could be detected in sera and cerebrospinal fluid of control persons.

Individuals with abnormalities (deficiency or dysfunction) of protein C or protein S are more susceptible to developing purpura fulminans, and infectious disease is a common cause of acquired deficiency of protein C or protein S.[10] However, in our patient, the post-acute phase levels of these physiologic anticoagulants factors were within normal limits.

The cellular and molecular mechanisms of meningococcal-induced purpura fulminans are not fully understood. The pathways leading to purpura fulminans during meningococcal sepsis can involve up-regulation of proinflammatory cytokines, as reflected by elevated interleukin-6 (IL-6) plus interferon gamma (INFγ) concentrations in serum (Table 2), accompanied by downregulation of coagulation inhibitors (such as protein C), which can result in a hypercoagulable state.[9–13] These two pathways have common underlying mechanisms and interact with each other. *N. meningitidis* and its products, such as lipo-oligosaccharide and DNA, can trigger a powerful host inflammatory response by activating immunologic and endothelial cells[14] through the intricate interaction among the transmembrane toll-like receptor 4, receptor CD14, MD-2, and lipooligosaccharide,[11,14] which in turn stimulates the intracellular signaling network to release cytokines in serum,[11,14] as shown in our patient (Table 2). High levels of cytokines have been implicated in the breakdown of the endothelium and coagulation homeostasis, leading to overexpression of adhesion molecules on the surface of the endothelium, together with fibrin precipitation in vessels.[9,11,12] These prothrombotic disorders can progress to intravascular microthrombus formation and subsequent ischemic events.[9,11–13] In addition, *N. meningitidis* causes overproduction of NO in the endothelium, potentially compromising endothelial function and viability.[15] This complex chain of events is mirrored by the histopathologic findings in cutaneous lesions caused by meningococcal disease. Such findings include neutrophils and mononuclear cells surrounding the vessels and infiltrating the connective and adipose tissue, together with occlusive thrombi consisting of platelets, red blood cells, and fibrin.[16] Necrosis and swelling of endothelial and muscle cells in the vascular wall are also seen in such lesions.[16]

Meningococcal disease is frequently accompanied by skin lesions that present extensive colonization by *N. meningitidis.*[16] Therefore, we emphasize the diagnostic value of Gram staining skin lesion samples obtained from patients with meningococcal disease. Although Gram staining is a rapid, inexpensive technique that facilitates diagnostic evaluation, it has been evaluated in only a few studies.[7] Hoyne and Brown[8,17]

identified meningococci in 69.8% of the petechial smears examined. In addition, van Deuren and others[7] reported that, in meningococcemia, Gram staining of skin lesion samples presented greater sensitivity than did Gram staining of CSF. After the administration of antibiotics, recovery of *N. meningitidis* from cultures of CSF and blood is difficult, although, interestingly, this is not the case for skin biopsy samples.[18] We have also had success with these methods at our facility in recent years and therefore recommend the use of these forgotten diagnostic tools, principally after the administration of antibiotics. In addition, molecular techniques are powerful tools for the diagnostic evaluation and clarification of meningococcal septic phenomena[19] and could give us more information in relation to microbiological exploration of a skin biopsy or tissue samples[20] in patients that are supposed to have meningococcal disease. However, it is not known what percentage of skin lesions is positive by the PCR method, because the application of PCR directly on skin biopsies has not been studied in meningococcal disease.[20] We did not perform the molecular techniques on skin lesions, because the application of these techniques for meningococcal disease is limited to CSF in our facilities. In fact, a predilection for either Gram staining or PCR on skin lesions cannot be given, because laboratory facilities decide which of these assays will be most workable.[21]

In conclusion, meningococcal purpura fulminans is a complex catastrophic phenomenon that can converge rapidly to irreparable ischemia of the limbs and digits. Muscle tenderness of the lower extremities is under-recognized as an early clinical feature of this overwhelming disease.[1–3] Early recognition and prompt initial antibiotic therapy continue to be the cornerstones of the successful management of this dramatic disease, reducing morbidity and mortality. The treatment can require immediate admission to an intensive care unit and a multi-disciplinary approach. In addition, although there are a variety of diagnostic techniques that can facilitate the detection of *N. meningitis,* they have typically been overlooked.

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