
The Value of Looking

Multiple Myeloma Discovered by an Unusual Finding in Gram-Stained Spinal Fluid

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Multiple myeloma is a disease of immature and mature plasma cells. These cells, which accumulate in the bone marrow and other tissues, often overproduce monoclonal immunoglobulins. Many of the clinical features of this disease result from the accompanying disordered immune response, which increases susceptibility to infection.

Blood levels of normal immunoglobulin often are decreased in patients with multiple myeloma. They may also have quantitative and functional deficits in complement activity. The net result is a sluggish primary immune response, manifested by a slow rise in immunoglobulin M (IgM) titers, and a reduced capacity to synthesize other immunoglobulin classes needed for secondary immune response. There may be impaired synthesis of antibodies that bind to invading bacteria and thereby make them susceptible to ingestion by phagocytes (a process called opsonization). This puts patients with multiple myeloma at high risk of infection by encapsulated bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenzae*. In general, the infections seen in patients with multiple myeloma are the same as those seen in patients with sickle cell anemia, agammaglobulinemia, and other conditions that disorder bacterial opsonization.

Our Patient

A 65-year-old black man came to the Emergency Department complaining of a single episode of rigor during the preceding night; he was feverish thereafter. Two weeks earlier he had had a cough productive of yellow sputum which persisted for 4-5 days, but had cleared 6 days before

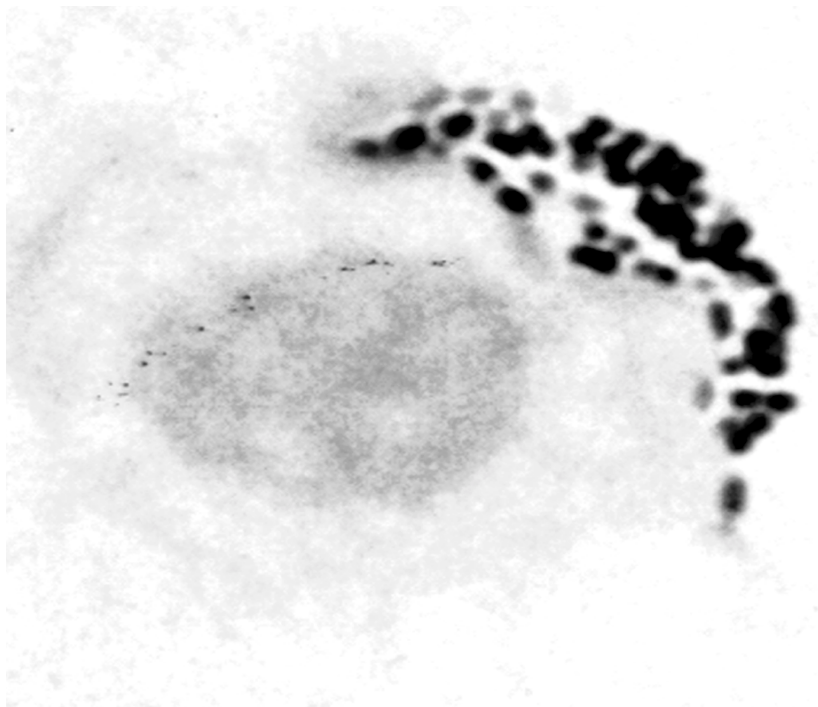
the onset of fever. The day after his episode of rigor, he awoke with soreness in his left neck and a mild headache, but no photophobia or diplopia. Aside from known hypertension his history was unremarkable.

Physical examination revealed an elderly man who appeared acutely ill. His blood pressure was 160/95; temperature, 38.2° C; heart rate, 125 beats/min; and respiratory rate, 26 breaths/min. The patient was able to flex and extend his head and neck normally, but unable to turn his head to the left. The left sternocleidomastoid muscle was tense, and palpation of the lateral border of the medial belly of the muscle caused significant pain. The neurological examination was normal, and neither Brudzinski's nor Kernig's signs could be elicited. The remainder of the physical examination was unremarkable. The white blood cell count was $21 \times 10^9/L$; hemoglobin, 13.3 g/dL; creatinine, 1.5 mg/dL; and blood urea nitrogen, 24 mg/dL. A chest X-ray was normal, and the electrocardiogram revealed only sinus tachycardia.

The patient was admitted for further evaluation of his acute febrile illness. A computed tomographic scan of the neck showed no soft tissue mass or retropharyngeal abscess. A lumbar puncture was performed, and the cerebrospinal fluid (CSF) was grossly purulent. The CSF contained 843×10^6 nucleated cells/L and 48×10^6 red blood cells/L; protein concentration was 247 mg/dL, and glucose, 42 mg/dL. The Gram's stain showed 4+ gram-positive cocci in pairs and chains, and multiple gram-positive diplococci clumped in a capped appearance on the outside of neutrophils. (Figure 1). Of particular note, there were *no* intracellular diplococci.

The patient was treated empirically with ceftriaxone and vancomycin. Culture of the CSF grew pan-sensitive *S. pneumoniae*, as did two sets of blood cultures obtained before beginning antibiotic therapy. Once the CSF and blood culture results were available, vancomycin was discontinued and the patient treated with ceftriaxone alone for two weeks. The failure of the patient's phagocytes to ingest the infecting bacteria suggested a disorder of immune function. Serum protein electrophoresis and immunofixation identified a

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Note the Gram-positive diplococci clumped on the outside of white cells in CSF fluid.

monoclonal IgG kappa paraprotein in high concentration (2.27g/dL) and an elevated beta-2 microglobulin, but urine protein electrophoresis revealed only a trivial amount of protein. The bone marrow contained 30% plasma cells.

Skeletal radiographs showed no lytic lesions; renal function and serum calcium levels were normal. The patient was considered to have multiple myeloma and scheduled for therapy after completing treatment for *S. pneumoniae* bacteremia and meningitis.

Comment

Robert Austrian's classic 1957 review identified the clinical triad of pneumococcal infection: pneumococcal pneumonia, pneumococcal endocarditis, and pneumococcal meningitis ("Austrian's Triad").¹ *S. pneumoniae* is a leading cause of meningitis in adults, but pneumococcal meningitis as the sole presenting manifestation of multiple myeloma, without pneumonia or endocarditis, has not previously been described.

The initial manifestation of multiple myeloma can be pneumococcal bacteremia, pneumonia, or septic arthritis.^{3,4} We suspected that our patient had an underlying immune deficiency because the CSF showed clumped diplococci on the surface of, but not within, white cells. This suggested a

defect in opsonization. Posner et al had described a patient with an IgG kappa myeloma who presented in coma and was found to have clumped diplococci on the surface of neutrophils in the peripheral blood.⁵ Many patients with multiple myeloma have decreased serum complement levels; defects in the complement system, specifically the C3 component, may play a crucial role in making myeloma patients susceptible to bacterial infections.^{6,7}

In our patient, pneumococcal meningitis was the initial manifestation of multiple myeloma. We suspected an underlying immunodeficiency because the stained smear of CSF disclosed multiple extracellular—but not intracellular—Gram-positive diplococci. The literature suggests that these CSF findings reflect defective complement activation; when such findings are noted, it is important to undertake a careful search for disorders causing defects in the immune response.

Our patient's case highlights how important it is for doctors to look carefully and personally at the actual Gram's stained slide.

References

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