Neisseria meningitidis Serogroup 29E (Z') Septicemia in a Patient with Far Advanced Multiple Myeloma (Plasma Cell Leukemia)

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A case of septicemia caused by *Neisseria meningitidis* serogroup 29E (Z') in a patient with plasma cell leukemia is described. The patient developed disseminated intravascular coagulation, had a cardiopulmonary arrest, and died. The effects of altered immune function leading to a predisposition to meningococcal infections are discussed.

Since the original four serotypes of *Neisseria meningitidis*, A, B, C, and D, were described in 1953 (3), nine additional groups have been identified. The three Slaters groups, X, Y, and Z, were named in 1961 (18), groups 29E (Z') and W135 were identified in 1968 (8), and recently, groups H, I, and K (6) and group L (1) have been described. During the last two decades, shifts have occurred among the serogroups most responsible for disease in civilian and military populations. Observations of these changes were summarized in 1980 (4). Two extensive epidemiological studies, one at Walter Reed Army Institute, Washington, D.C., where 648 meningococci were serotyped (8), and the other in New York City, N.Y., where 843 strains were serotyped (9), indicated that serogroups B, C, and Y predominated. The isolation of serogroup 29E (Z') from clinical specimens has been reported infrequently, and thus, its pathogenicity has been uncertain. Among the 1,491 meningococci serotyped in the two epidemiological studies (8, 9), there were 51 isolates of serogroup 29E (Z'), and most were from asymptomatic carriers. One isolate was recovered from cerebrospinal fluid, and two isolates were recovered from systemic infections for which no clinical details were noted. We report here a case of *N. meningitidis* 29E (Z') septicemia in a patient with plasma cell leukemia.

A 59-year-old male receiving prednisone (20 mg per day) for thalassemia minor was diagnosed in September 1982 as having kappa light-chain immunoglobulin G (IgG) plasma cell leukemia and was started on the M2 protocol, a regimen of melphalan (Alkeran; Burroughs Wellcome Co., Research Triangle Park, N.C.), cyclophosphamide (Cytosan; Mead Johnson & Co., Evansville, Ind.), prednisone, vincristine, and 1,3-bis-(2-chloroethyl)-1-nitrosourea (10). He promptly entered a partial remission, with elimination of plasma cells from his peripheral blood and reduction of plasma cells from 95 to 40% in his bone marrow. The paraprotein decreased by 30%. Three days before admission, he started therapy on his fourth M2 cycle. On 26 December 1982, he was admitted to Memorial Sloan-Kettering Cancer Center with fever, extreme shortness of breath, weakness, productive cough, anemia, and neutropenia.

On physical examination, the patient had a temperature of 39.6°C, a pulse rate of 120 beats per min, a respiratory rate of 40/min, and a blood pressure of 100/60 mm Hg. His weight

at admission was 96.3 kg. Rales were heard in both lungs. Examination of the heart revealed sinus tachycardia, with frequent premature atrial and ventricular contractions. On neurological examination, he was found to be irritable and agitated. Bilateral infiltrates were seen in the chest roentgenogram taken at admission. A complete blood count revealed the following: leukocytes, 2,600/mm³, (absolute neutrophil count, 364); erythrocytes, 2.17 × 10⁶/mm³; hemoglobin, 6.4 g/dl; hematocrit, 18.4%; and platelets, 1.26 × 10⁵/mm³. Coagulation studies revealed a prothrombin time of 13.6 s (control, 13.0 s) and a partial thromboplastin time of 27.2 s (control, 42.0 s). Electrolyte levels were as follows: Na⁺, 134 meq/liter; K⁺, 3.9 meq/liter; CO₂, 21 meq/liter; Cl⁻, 104 meq/liter; blood urea nitrogen, 15 meq/liter; and creatinine, 1.6 mg/dl.

Examination of cerebrospinal fluid obtained by lumbar puncture revealed clear fluid, with an opening pressure of 290 mm H₂O, a glucose concentration of 185 mg/dl, and a protein concentration of 72 mg/dl. Serum protein electrophoresis revealed the following protein levels: albumin, 2.04 g/dl; alpha₁, 0.45 g/dl; alpha₂, 0.87 g/dl; beta, 0.53 g/dl; gamma, 5.70 g/dl; and total protein, 9.6 g/dl. Immunoelectrophoresis revealed the following immunoglobulin levels: IgG, 6.6 g/dl (N, 0.8 to 1.8); IgA, 0.05 g/dl (N, 0.09 to 0.45); and IgM, 0.07 g/dl (N, 0.06 to 0.25).

Within several hours of admission, the patient required emergency endotracheal intubation and placement of a Swan-Ganz catheter. Gentamicin (80 mg intravenously [i.v.] every day), ticarcillin (3 g i.v. every 12 h), and cefazolin (1 g i.v. every 12 h) were started for presumed sepsis with septic shock. Doses were adjusted for renal failure. The patient also received methylprednisolone (20 mg i.v. every 6 h). He developed disseminated intravascular coagulation and renal failure, and peritoneal dialysis was started with 500 U of heparin and 8 mg of gentamicin. Although his neutrophil counts recovered temporarily, a low-grade fever persisted. A progressively worsening right pleural effusion and right lower lung collapse became apparent on subsequent chest roentgenograms, and the patient experienced atrial fibrillation, which persisted despite treatment with digitalis and procainamide.

On hospital day 3, gram-negative diplococci were recovered from the blood culture bottles, and the cerebrospinal fluid cultures were negative. Gentamicin therapy was dis-

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continued, and aqueous penicillin G (2.5×10^6 U i.v. every 4 h) was started.

The organism grew in two blood culture bottles, each containing 50 ml of Columbia broth supplemented with cysteine (1 g/liter) (BBL Microbiology Systems, Cockeysville, Md.). One bottle of the set was transiently vented. The bottles were incubated at 35°C and, when the broth was turbid, subcultures were made onto chocolate agar. Smooth, raised colonies were observed on agar plates at 48 h.

The organism was an oxidase-positive, gram-negative diplococcus which grew well on Columbia blood agar and modified Thayer-Martin agar in 10% CO₂ at 35°C but not at 25°C. It fermented glucose and maltose but not sucrose or lactose. It agglutinated in antiserum to *N. meningitidis* type 29E (Z') but not in antisera to groups A, B, C, D, X, Y, Z, or W-135 (serotyping was performed by both Sam Schaeffer, New York City Health Department, New York City, N.Y., and Richard Roberts, New York Hospital, New York City, N.Y., using Centers for Disease Control, Atlanta, Ga., antisera). Susceptibility to penicillin, chloramphenicol, and sulfisoxazole was determined by the standard disk diffusion method (2); all zones of inhibition were >30 mm. The rapid chromogenic cephalosporin test for beta-lactamase production was negative (14).

On hospital day 9, the patient developed conjunctivitis of the right eye, bleeding lip sores, and a mixed Herpes simplex and *Staphylococcus epidermidis* infection on his face. This infection was characterized by bilateral erythematous and vesicular plaques, diffuse crusting, and oozing blood. His temperature rose to 39.8°C the next day. Sputum cultures were positive for *Candida parapsilosis* and *Enterobacter aerogenes*; blood cultures were negative. Penicillin was discontinued, and oxacillin (1,500 mg i.v. every 4 h) and gentamicin (80 mg i.v. every day) were started. He defervesced but became progressively nonresponsive. The patient had a cardiopulmonary arrest and died on 8 January 1983. Permission for autopsy was denied.

The clinical course of *N. meningitidis* infection in this patient was that of meningococcemia with disseminated intravascular coagulation presumably caused by the meningococcal endotoxin. Meningococcal septicemia is characterized clinically by shock, cyanosis, cutaneous hemorrhages, and severe consumption coagulopathy. Cor pulmonale is also a possible sequela of septic shock (5).

Findings from retrospective studies suggest that infections in patients with multiple myeloma often occur in those with uncontrolled disease and follow a biphasic microbial pattern. *Streptococcus pneumoniae* and *Haemophilus influenzae* infections are seen at diagnosis and in the early months of treatment, whereas infections caused by *S. aureus* and gram-negative pathogens predominate in later months. Infections caused by the latter are, in particular, associated with refractory advancing disease and neutropenia (12, 13, 17, 19). Norden reported that life-threatening infections with pneumonia or septicemia or both are most often caused by *S. aureus* or polysaccharide-encapsulated organisms (13).

Serum bactericidal activity against gram-negative organisms, specifically *N. meningitidis*, involves both complement and IgM (13). Thus, a generalized depression in serum immunoglobulin levels, a deficit in immunoglobulins directed specifically against the meningococci, or abnormalities in serum complement levels (especially components C6 through C8) all may enhance susceptibility to bacteremia (11, 15, 16). In this patient, IgM levels were barely normal, and IgA levels were low; complement testing was not done. A previous report of a meningococcal infection in a patient

with multiple myeloma revealed no detectable C1q or C4 (the source of infection, serotype, and immunoglobulin levels were not given) (7). Low serum immunoglobulin levels may facilitate bloodstream invasion, as infecting meningococci are usually only found in carriers (16). There are no data on the frequency of *N. meningitidis* serotypes causing disease in cancer patients.

We have reported a case of meningococcemia that was caused by the infrequently reported serogroup 29E (Z') in a patient with plasma cell leukemia. Because such isolates can only be identified by serological testing, reference laboratories specializing in such methods will continue to be needed to distinguish among the serogroups. As we see additional unusual infections in immunosuppressed patients, it will be important for clinical microbiology laboratories and reference laboratories to work together to identify these isolates as completely as possible. We will then be better able to assess the frequency and clinical nature of these unusual infections.

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