Infection with uncommon subgroup Y Neisseria meningitidis in patients with systemic lupus erythematosus

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ABSTRACT
The association of Neisseria meningitidis infection and systemic lupus erythematosus (SLE) is uncommon. We describe here three patients with SLE who developed disseminated meningococcal disease. Each patient had long-standing SLE and was receiving treatment with prednisone. Furthermore, each patient showed serum hypocomplementemia at the time of the infection. N. meningitidis Group Y, considered to be an organism of relatively low virulence, was isolated from the blood or cerebrospinal fluid in each case. The patients presented with diverse clinical manifestations of meningococcal disease. The relationship of disseminated meningococcal infections to hypocomplementemia in patients with SLE is discussed in light of a review of the literature.

Introduction
In patients with systemic lupus erythematosus (SLE), infections are a leading cause of morbidity and mortality. Anti-microbial host defense mechanisms are compromised in these patients. Furthermore, therapy with corticosteroids significantly increases the risk of infection (1, 2).

Meningococcal infection spans a wide spectrum of clinical presentations, ranging from transient fever and bacteremia to disseminated intravascular coagulation and shock (3). Involvement of the respiratory and genitourinary tracts, cranial and lumbosacral nerves, pericardium and joints have all been described (3).

The complement system plays a pivotal role in defense from meningococcal infections (4-7). Despite the frequent finding of complement abnormalities in SLE, however, only a handful of cases of meningococcal infections associated with SLE have been reported (8-15).

We now describe 3 patients with SLE who presented with meningococcal disease which was due to the relatively uncommon meningococcus serogroup Y.

Case reports
The pertinent clinical and laboratory features of the three patients are summarized in Table 1.

Case 1
An 18-year-old woman presented with a four-day history of shoulder and ankle pain. She had SLE for 5 years, presenting primarily with thrombocytopenia, skin rash and polyarthritis. She was being treated with prednisone (15 mg/day). One month prior to admission, she complained of worsening skin rash, and the dose of prednisone was increased to 25 mg/day.

On admission to the hospital, she was afebrile. Her neck was supple, and physical examination was remarkable only for evidence of ankle tenosynovitis. Laboratory studies showed a white blood cell count (WBC) of 24,500/mm³ (37% bands and 62% neutrophils), and a platelet count of 176,000/mm³. Urinalysis revealed proteinuria and red blood cells. Serum levels of complements (C3 and C4) were moderately reduced, whereas late complements were normal. Blood cultures grew N. meningitidis subgroup Y.

The patient was treated with intravenous penicillin (18 million U/day) for 10 days with good response. A kidney biopsy revealed diffuse proliferative glomerulonephritis, subsequently treated with high dose prednisone and cyclophosphamide.

Case 2
A 46-year-old woman was found unresponsive at home. She had SLE for 14 years. One month prior to admission, her disease appeared relatively quiescent. Medications included prednisone (7.5 mg/day for 12 years) and hydroxychloroquine (400 mg/day).

On admission to the hospital, she was responsive only to painful stimuli, with a blood pressure of 155/100 mm/Hg, respiratory rate of 30/min, pulse of 120/min and temperature of 102°F. Physical examination revealed a supple neck and spontaneous movements of all extremities. Babinski signs were negative. No synovitis or rash was noted. Laboratory investigations showed WBC 5,400/mm³ (22% bands and 68% neutrophils), and a platelet count of 143,000/mm³. Urinalysis showed trace proteinuria. Cerebrospinal fluid (CSF) analysis showed WBC 3280/mm³ with 100% neutrophils. Gram stain of the CSF revealed gram-
negative diplococci, and cultures grew *N. meningitidis* Group Y. Blood cultures were negative.

The patient was treated with intravenous Ceftriaxone. She had a complicated hospital course necessitating ventilatory support and treatment for nosocomial pneumonia. She had a residual right sixth nerve palsy and right sided hemiparesis on discharge three weeks later. Her subsequent course was unremarkable.

**Case 3**

A 24-year-old woman presented with two days’ cough, chills, vomiting and diarrhea. She had SLE for 8 years, complicated by avascular necrosis of the hips, treated with bilateral arthroplasty. She had been on prednisone since the initial diagnosis, and hydroxychloroquine for several years. Two months previously, she experienced worsening skin rash, arthralgia, and her serum complement levels were found to be low. The dose of prednisone was increased to 20 mg/day, and azathioprine (50 mg/day) was started.

On admission to the hospital, she was lethargic. She had a systolic blood pressure of 60 mm/Hg, and a temperature of 102°F. Physical examination revealed a supple neck. There were no skin lesions, or focal abnormalities on neurologic or joint examination. Laboratory tests revealed WBC 1,300/mm³, and a platelet count of 22,000/mm³. Urinalysis showed trace proteinuria. Within 24 hours after admission, she developed severe ischemic changes with bullae on her fingers, toes and forearms. Petechiae were noted on the abdomen and lower extremities. Blood cultures grew *N. meningitidis* Group Y.

Intravenous Ceftriaxone was administered for 10 days. She required intravenous vasopressors, temporary ventilatory support due to acute respiratory distress syndrome, and hemodialysis for acute renal failure. Within several days, she developed gangrene of all her fingers, necessitating digital amputations. She was discharged from the hospital after two and a half months. Her renal function slowly recovered and subsequently she has done well.

**Discussion**

Meningococcal infections are strongly correlated with deficiencies in C3, properdin and late complement components (4-7). Although disseminated meningococcal infections have been described in patients with SLE, they appear to be relatively uncommon (8-15). Nevertheless, patients with SLE may be more susceptible to infections with such organisms than healthy people by virtue of the generalized hypocomplementemic state that characterizes SLE. The complement cascade is activated in SLE patients, as evidenced by increased serum levels of the complement breakdown products C3a and C5a (16). Activation of the membrane attack complex has been reported in patients with SLE (17). Concentrations of Factor B and properdin in the serum are also decreased, suggesting that activation of the alternative complement pathways also occurs in SLE (18). The complement profile of patients with SLE therefore may closely mimic that of patients with inherited complement deficiencies known to be associated with meningococcal infections. Immunoglobulin deficiency and defects in chemotaxis and phagocytic activity may also play a role in the increased susceptibility of SLE patients to infection.

We describe 3 patients with SLE and meningococcal infection. The duration of SLE prior to meningococcal disease was 5 - 14 years. The average duration of prednisone use was 8 years, with a mean prednisone dose of 16 mg/day (range, 7.5-25 mg/day). The patients had various clinical presentations, ranging from meningococcal meningitis to fulminant meningococcemia. Each had abnormally low serum levels of complements. Of note, serogroup Y *N. meningitidis* was found to be the causative agent in all 3 cases. Levels of terminal components (C5-C9), factor B and properdin were normal in all three patients, ruling out inherited complement deficiencies.

A review of the English language literature (published between 1966 and 1996) using the Medline database revealed 8 previously published reports of meningococcal disease in patients with SLE (8-15). Due to a paucity of information provided in the reports, only 11 of 17 cases are included in our analysis (Table II).

Except for one case, all the patients were young females (mean age 21 years), and at the time of infection 8 of 11 were being treated with corticosteroids (mean dose 16 mg/day).

### Table I. Clinical and laboratory data of patients with SLE and meningococcal disease.

<table>
<thead>
<tr>
<th>Case</th>
<th>Dur.* (yrs.)</th>
<th>Age (yrs.)</th>
<th>Medications</th>
<th>Dur. prednisone use</th>
<th>Prednisone use levels</th>
<th>Presentation</th>
<th>Clinical presentation</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>18</td>
<td>Prednisone (25 mg/d)</td>
<td>5 yrs</td>
<td>Sm 551 U/ml (&lt; 90) dsDNA 52 IU/ml (&lt; 40) ssDNA 600 U/ml (&lt; 99) RNP 1970 U/ml (&lt; 83)</td>
<td>CH50 = 66 U/ml (130 - 410 U/ml)</td>
<td>Tenosynovitis</td>
<td><em>N. meningitidis</em> group Y</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>46</td>
<td>Prednisone (7.5 mg/d) Plaquenil (400 mg/d)</td>
<td>12 yrs</td>
<td>ssDNA 866 U/ml SSA 280 U/ml</td>
<td>C3 = 52 mg/dl (83 - 177 mg/dl) C4 = 19 mg/dl (15 - 45 mg/dl)</td>
<td>Meningitis</td>
<td><em>N. meningitidis</em> group Y</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>24</td>
<td>Prednisone (15 mg/d) Plaquenil (400 mg/d) Azathioprine (50 mg/d)</td>
<td>8 yrs</td>
<td>Sm 179 U/ml dsDNA 46 IU/ml ssDNA 577 U/ml RNP 6700 U/ml</td>
<td>C3 = 45 mg/dl C4 &lt; 10 mg/dl</td>
<td>Fulminant meningococcemia</td>
<td><em>N. meningitidis</em> group Y</td>
</tr>
</tbody>
</table>

*Duration of SLE prior to meningococcal disease; † Determined by ELISA; values in parentheses indicate normal values.*
CASE REPORT

N. meningitidis infection in SLE / R. Feliciano et al.

The mean duration of SLE prior to the onset of meningococcal disease was three years. Four of six patients had low serum levels of complements. The majority were bacteremic at presentation. The varied manifestations of meningococcal infection in these patients were difficult to differentiate clinically from an SLE flare.

In 6 of 7 patients, relatively uncommon meningococcal serogroups (Groups Y and W-135) were found. Serogroups B and C are implicated in the majority of N. meningitidis infections, accounting for 55% and 20% of clinical disease, respectively (20). Disease due to the less common X, Y and W-135 meningococcal serogroups suggests underlying complement deficiency, particularly of C3, properdin, and late complement components (21). In one study, 44% of the infections with Group Y meningococcus occurred in individuals who had late complement component deficiencies (5). Similarly, in properdin-deficient individuals meningococcal Groups Y and W-135 infections predominate (7, 22). The high incidence of Group Y meningococcal infections in individuals with deficiencies of late complement component could be due to ineffective phagocytic killing of this serotype compared to Group B (23). Phagocytosis is believed to play an important role in the defense against meningococci in patients with terminal complement deficiencies, wherein there is an absence of serum bactericidal activity in these organisms (23). The explanation for the Group Y predominance in properdin-deficient patients is less clear (7, 24). Defects in chemotaxis and phagocytic activity, as well as immunoglobulin and complement deficiency, may render patients with SLE more susceptible to Group Y infections.

Initial clinical distinction between an infectious process and flare of disease may be difficult in patients with SLE. This is well illustrated in meningococcal infections whose diverse clinical presentations may closely resemble the features of an SLE flare. Being alert to

Table II. Characteristics of reported cases of meningococcal infections in patients with SLE.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yrs.)</th>
<th>Dur.* (yrs.)</th>
<th>Medications at onset of infection</th>
<th>Levels of serum complement components</th>
<th>Presentation of meningococcal infection</th>
<th>Organism/culture</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>2</td>
<td>Methylprednisolone (4 mg qod)</td>
<td>C3 = 76 mg/dl (&gt; 84 mg/dl) C4 = 9 mg/dl (&gt; 15 mg/dl)</td>
<td>Headache, somnolence</td>
<td>N. meningitidis (not serotyped) Blood+, CSF+</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>5</td>
<td>Prednisone (20 mg/day) Plaquenil</td>
<td>CH50 = &lt; 20% of control</td>
<td>Fever, rash, headache, pharyngitis</td>
<td>N. meningitidis (not serotyped) Blood+, CSF+</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>—</td>
<td>Imuran (100 mg/day)</td>
<td></td>
<td>Fever, disorientation</td>
<td>N. meningitidis Group, Y</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>—</td>
<td>Decadron (11.5 mg/3 mg on alternate days) Imuran (100 mg/day)</td>
<td>Normal</td>
<td>Cough, chest pain, headache</td>
<td>N. meningitidis Group Y CSF+</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>—</td>
<td>None</td>
<td>C3 = 54 mg/dl C4 = 8 mg/dl</td>
<td>Headache, rash, arthritis</td>
<td>N. meningitidis Group Y Blood+, CSF+</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>9 mos</td>
<td>Prednisone (dose unknown)</td>
<td></td>
<td>Arthralgias</td>
<td>N. meningitidis Group W-135 Synovial fluid+</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>4</td>
<td>Prednisone (dose unknown)</td>
<td></td>
<td>Arthralgias</td>
<td>N. meningitidis (not serotyped) Blood+, synovial fluid+</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>1</td>
<td>None</td>
<td>C3 = 35 mg/dl C4 = 4 mg/dl</td>
<td>Fever, rash, arthralgias</td>
<td>N. meningitidis Group B Blood+, synovial fluid+</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>5</td>
<td>None</td>
<td>Normal</td>
<td>Abdominal pain, dyspnea, edema</td>
<td>N. meningitidis (not serotyped) Blood+, pericardial effus.+</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>5</td>
<td>Prednisone (20 mg qod)</td>
<td></td>
<td>Fever, pleuritic chest pain, cough</td>
<td>N. meningitidis Group W-135 Sputum+, Blood+</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>3</td>
<td>Prednisone (30 mg qod)</td>
<td></td>
<td>Fever, abdominal pain, diarrhea</td>
<td>N. meningitidis Group W-135 Blood+</td>
<td>13</td>
</tr>
</tbody>
</table>

* Duration of SLE prior to onset of meningococcal disease. CSF = cerebrospinal fluid
this possibility is important, since the early recognition of meningococcal infection may be life-saving. The three patients described in the present report shared a long history of SLE, chronic prednisone use, and hypocomplementemia at the onset of infection. Two patients had experienced recent SLE flares. Neisseria meningitidis Group Y was identified as the infectious agents in each case. These findings indicate the importance of this serogroup in SLE, in addition to its established association with deficiencies of properdin and late complement components. Group Y meningococcus, generally considered to be a microorganism of relatively low virulence, is capable of causing potentially life-threatening disease in patients with SLE.

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References