Case Series

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Received 16 January 2014
Accepted 20 May 2014

Severe infection with encapsulated bacteria as the initial presentation of systemic lupus erythematosus: two case reports and a review of the literature.

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Introduction: Severe bacterial infection is an unusual initial presentation of systemic lupus erythematosus (SLE).

Case presentation: We describe two cases of severe encapsulated bacterial infection in women with previously undiagnosed SLE.

Conclusion: Hypocomplementaemia associated with SLE is an important infection risk and should be considered in the evaluation of patients who present with unusual and severe infection with encapsulated bacteria.

Keywords: encapsulated bacteria; *Haemophilus influenzae*; hypocomplementemia; systemic lupus erythematosus; *Streptococcus pneumoniae*.

Background

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease that presents in a myriad of ways, leading to difficulty and delays in diagnosis. The recently updated classification criteria include acute and chronic cutaneous findings, oral ulcers, alopecia, synovitis, serositis, renal, neurological, haematological (haemolytic anaemia, leukopenia or lymphopenia, or thrombocytopenia) and immunological criteria [anti-nuclear antibody (ANA), anti-dsDNA or anti-Smith; evidence of anti-phospholipid antibody or circulating anti-coagulant; positive direct Coombs'; and hypocomplementaemia] (Petri *et al.*, 2012).

Infection is a leading cause of death in SLE (Petri, 1998) but is a rare initial presentation of the disease. Therefore, here we present two women in whom the diagnosis of SLE was only suspected after they presented with severe and unusual encapsulated bacterial infection. Despite minimal preceding symptoms of SLE prior to the onset of severe infection, both had profound hypocomplementaemia, which was both a significant risk factor that led to their infection and an important clue to the diagnosis of SLE.

Case reports

Patient 1

A 20-year-old female college student, without significant past medical history, presented to urgent care with several days of fever, malaise and left hip pain. Examination found erythema surrounding her left hip and thigh. She was hypotensive and tachycardic, and was admitted to the hospital. Her medications prior to admission included dextroamphetamine/amphetamine for attention deficit disorder. Laboratory evaluation was notable for a white blood cell (WBC) count $1.5 \times 10^3 \mu\text{l}$ (differential not obtained), haemoglobin 9 g dl^{-1} , platelet count $66 \times 10^3 \mu\text{l}$, creatinine 1.9 mg dl^{-1} , international normalized ratio (INR) 1.6 and lactate 3.8 mmol l^{-1} . Other laboratory tests were unremarkable, including urinalysis and renal and liver function studies. Antibiotics were started (piperacillin/tazobactam, vancomycin and clindamycin). She remained hypotensive despite aggressive intravenous fluids, requiring pressor administration. Computed tomography scans of her head/chest/abdomen/pelvis were significant for inflammatory changes in her left hip without gas formation, abscess or bone abnormalities. She was taken to the operating room for possible necrotizing fasciitis involving the hip and thigh; no necrosis or purulence was found intra-operatively but hip/thigh tissue was sent for culture. Blood and intra-operative hip/thigh tissue cultures ultimately grew *Streptococcus*

Abbreviations: INR, international normalized ratio; IU, international units; SLE, systemic lupus erythematosus; WBC, white blood cell

pneumoniae (pan-sensitive). She required intubation and ventilation for 6 days, indicated for hypoxia and metabolic acidosis. She remained hypotensive for several days despite multiple pressors, leading to acute kidney and liver injury, which resolved without sequelae. She developed digital ischaemia involving multiple digits and ultimately required amputation of the distal phalanx of the right index finger.

Given her severe presentation, work-up for an underlying immunodeficiency was initiated. She had no personal or family history of recurrent infections. Evaluation for human immunodeficiency virus infection was negative. Her immunoglobulin levels were normal (IgA 201 mg dl⁻¹, IgG 1491 mg dl⁻¹, IgM 86 mg dl⁻¹), although she had received an intravenous immunoglobulin dose early in her illness. Her spleen appeared normal on her multiple abdominal imaging studies and her peripheral blood smear showed no evidence of Howell–Jolly bodies. The results of her rheumatological work-up are shown in Table 1, showing profound hypocomplementaemia, strongly positive ANA, positive direct Coombs', and positive lupus anti-coagulant, anti-cardiolipin, anti-dsDNA, anti-Smith and anti-ro (SSA). When questioned specifically, the patient and her family endorsed a history of migratory joint pain, fatigue and pain in the hands upon exposure to cold. The patient had not sought medical attention for these symptoms and had instead attributed them to stress associated with her college studies. She was given a new diagnosis of SLE based on history of arthralgia, thrombocytopenia and immunological criteria (ANA, low complement, anti-phospholipid

antibody, positive direct Coombs', anti-dsDNA and anti-Smith).

She was started on hydroxychloroquine during her hospitalization. At her most recent outpatient visit 19 months after her acute illness, she remains on hydroxychloroquine 200 mg daily and prednisone 3 mg daily. Her most recent laboratory work showed a normal platelet count ($230 \times 10^3 \mu\text{l}$) and normal creatinine (0.9 mg dl⁻¹) but persistent leukopenia (WBC count, $3.5 \times 10^3 \mu\text{l}$) and lymphopenia (absolute lymphocyte count, $0.5 \times 10^3 \mu\text{l}$). Her complement levels have improved but not normalized (C3 53 mg dl⁻¹, C4 6 mg dl⁻¹). She has had no further infections.

Patient 2

A 50-year-old female with a past medical history of hypertension presented to the emergency department with several days of worsening shortness of breath, neck pain, difficulty swallowing and vomiting. On examination, she was tachycardic and tachypneic, with audible stridor. During intubation, a red, swollen epiglottis was seen, consistent with epiglottitis. She had immigrated to the USA from Mexico 10 years earlier; her immunization status was unknown. Her only medication was lisinopril. Laboratory evaluation showed blood urea nitrogen 64 mg dl⁻¹, creatinine 2.3 mg dl⁻¹, WBC $11.7 \times 10^3 \mu\text{l}$ (absolute neutrophil count $11 \times 10^3 \mu\text{l}$, absolute lymphocyte count $0.5 \times 10^3 \mu\text{l}$), haemoglobin 8 g dl⁻¹, platelets $59 \times 10^3 \mu\text{l}$,

Table 1. Rheumatological evaluation of two case patients with severe encapsulated bacterial infection

Laboratory test (units), reference range	Case patient 1	Case patient 2
Haemoglobin (g dl ⁻¹), 11.5–15.7*	9	8
White blood cells ($\times 10^3 \mu\text{l}$), 4–10*	1.5	11.7
Absolute lymphocytes ($\times 10^3 \mu\text{l}$), 0.8–4*	Not available	0.5
Platelets ($\times 10^3 \mu\text{l}$), 150–400*	66	59
C3 (mg dl ⁻¹), 76–197	<9	25
C4 (mg dl ⁻¹), 14–46	<2	7
CH ₅₀ (U ml ⁻¹), 22–66	<11	Not available
Rheumatoid factor (IU ml ⁻¹), 0–10	14	Not available
Lupus anti-coagulant		
Silica clotting time, 0–1.16	1.91	1.25
Dilute Russell's viper venom time, 0–1.2	2.23	1.15
Anti-cardiolipin		
IgA (APL units), 0–11.9	13.4	20.3
IgG (GPL units), 0–14.9	15.8	19.3
IgM (MPL units), 0–12.4	5.6	21
Direct Coombs'	Positive	Positive
ANA	1:320, 4+ speckle	1:320, 2+ homogenous
Anti-dsDNA (units), 0–30	>300	>300
Anti-Smith	Positive	Negative
Anti-ribonucleoprotein	Undetermined	Negative
Anti-ro (SSA)	Positive	Negative
Anti-la (SSB)	Negative	Negative

*Values were upon initial presentation to a health care facility.

INR 1.4, aspartate aminotransferase 578 international units (IU) l^{-1} , alanine transaminase 100 IU l^{-1} , alkaline phosphatase 652 IU l^{-1} , total bilirubin 4.3 mg dl^{-1} (direct 3.9 mg dl^{-1}), which increased to 11.4 mg dl^{-1} , albumin <1 g dl^{-1} , lipase 385 IU l^{-1} , which increased to 2500 IU l^{-1} , and urinalysis showing 2+ protein and blood. Abdominal imaging by computed tomography scan and ultrasound showed biliary sludge, acute pancreatitis and a normal-appearing spleen. Her peripheral blood smears showed no evidence of Howell–Jolly bodies. Tests for human immunodeficiency virus and hepatitis A (IgM), B and C infection were negative. Blood culture grew *Haemophilus influenzae* (pan-sensitive), which was not typed. Her hospital course was complicated by septic shock leading to multi-organ failure, including acute liver failure, cholangitis and pancreatitis requiring biliary tract drainage, acute renal failure requiring continuous renal replacement therapy, acute respiratory distress syndrome, disseminated intravascular coagulation, intra-abdominal haemorrhage leading to abdominal compartment syndrome, diffuse pulmonary alveolar haemorrhage and anoxic brain injury.

A review of her chart yielded laboratory evaluation 6 months prior with urinalysis showing 2+ proteinuria and moderate blood, creatinine 0.9 mg dl^{-1} (glomerular filtration rate 71, creatinine clearance 83) and thrombocytopenia ($94 \times 10^3 \mu\text{l}$), obtained due to symptoms of a urinary tract infection. Given these previous laboratory abnormalities and her low albumin on admission, chronic nephrotic range proteinuria was suspected, and SLE was considered in the differential. Renal biopsy was not performed due to her unstable condition. Her ANA was elevated at 1:320 homogeneous 2+. This led to further evaluation, as shown in Table 1, demonstrating profound hypocomplementaemia, positive lupus anti-coagulant (by silica clotting time) and positive anti-cardiolipin and anti-dsDNA. Her family was questioned in detail and reported a 1 year history of fatigue, and intermittent pain in her wrists and knees. SLE was diagnosed based on renal disease, thrombocytopenia and immunological criteria (ANA, low complement, anti-phospholipid antibody, positive direct Coombs' and anti-dsDNA).

She was treated with methylprednisolone 1 g daily for 3 days followed by 1 mg kg^{-1} daily, and then slowly tapered during her hospitalization. Thrombocytopenia requiring daily platelet transfusions persisted despite apparent resolution of disseminated intravascular coagulation. Bone marrow biopsy and aspirate was consistent with an autoimmune thrombocytopenia. Her thrombocytopenia was refractory to intravenous immunoglobulin, plasmapheresis and rituximab. She remained ventilator and dialysis dependent throughout her prolonged hospital course. Despite extensive effort, she died 7 weeks after admission. Pertinent findings on autopsy included diffuse lupus nephritis with subendothelial immune deposits, an aortic valve vegetation concerning for Libman–Sacks endocarditis, and serositis (pericarditis, pleuritis and

peritonitis). Cause of death was multisystem organ failure caused by sepsis in the setting of severe SLE.

Discussion

Although, in retrospect, both women had evidence of mild SLE symptoms prior to hospitalization (fatigue and joint pain), neither individual sought medical attention for their symptoms and SLE was suspected only after they presented with severe encapsulated bacterial infections. In both cases, SLE was confirmed by detailed questioning of family members and additional immunological criteria, including hypocomplementaemia.

There are rare reports of severe bacterial infection as a new SLE presentation in prior literature, including fatal pneumococcal bacteraemia in an 18-year-old female (Petros & West, 1998) and *H. influenzae* epiglottitis and bacteraemia in a 5-year-old (Charuvani & Houghton, 2009). There are no published reports of an adult patient diagnosed with lupus after presenting with epiglottitis. Similar to our case patients, both of these patients were found to have hypocomplementaemia during their initial presentation. The female with fatal pneumococcal bacteraemia also had mild preceding symptoms of malaise and arthritis for which she did not seek care; no mention is made of any preceding SLE symptoms in the 5-year-old.

Encapsulated bacterial infections are reported more frequently in patients with longer-standing severe SLE. *S. pneumoniae* skin and soft-tissue infections are frequently documented, and are postulated to be a 'distinct clinical syndrome' given the propensity for upper body involvement (Hill & Karsh, 1997). *S. pneumoniae* has been documented to cause necrotizing fasciitis in SLE patients as well (Kamran *et al.*, 2008). *H. influenza* infection has been reported less frequently, including septic arthritis (Borenstein & Simon, 1986) and soft-tissue infections (necrotizing fasciitis) (Robinson *et al.*, 2010).

Infections are a main cause of morbidity and mortality in SLE, not only from immunosuppression caused by SLE treatment but also due to immune system defects caused by SLE itself (Petri, 1998). SLE affects the immune system in a variety of ways, including defects in neutrophil chemotaxis, circulating autoantibodies interfering with opsonization, defective phagocytosis due to immune complex binding on neutrophil Fc receptors, macrophage dysfunction, deficiencies in immunoglobulin and mannose-binding lectin, neutropenia, lymphopenia, splenic dysfunction and hypocomplementaemia (Petri, 1998; Cuchacovich & Gedalia, 2009). Factors predisposing to infection in SLE patients found in multiple studies include active rheumatological disease, renal involvement and hypocomplementaemia (Petri, 1998; Cuchacovich & Gedalia, 2009). The most frequent cause of infections are common bacterial pathogens (e.g. *Staphylococcus aureus*, *Escherichia coli*), and SLE patients are frequently bacteraemic (Petri, 1998; Cuchacovich & Gedalia, 2009). Other

encapsulated organisms (particularly *S. pneumoniae*) are also frequently seen, reflecting potential chemotaxis and opsonization defects, splenic dysfunction and hypocomplementaemia (Petri, 1998). Splenic dysfunction has been reported to occur in 5 % of SLE patients, and may be due to a variety of aetiologies including circulating immune complexes, and impairment of splenic circulation due to vasculitis or thrombotic events (Santilli *et al.*, 2003). SLE patients without functioning spleens are at especially high risk for severe infection, most commonly due to *S. pneumoniae* (Santilli *et al.*, 2003). While no formal splenic function testing was performed on our case patients to confirm that they had fully functioning spleens, both had normal-appearing spleens on imaging and no Howell–Jolly bodies were seen on blood smears.

Hypocomplementaemia was a major risk factor for infection in our patients and other case reports in the literature (Hill & Karsh, 1997; Petros & West, 1998; Charuvani & Houghton, 2009). Hypocomplementaemia in SLE patients can be a cause or a consequence of SLE. Inherited complement deficiencies are rare but do lead to increased risk of infection and development of SLE, particularly deficiencies in C1q, C4 and C2 (incidence of SLE 90, 75, and 15 %, respectively) (Unsworth, 2008). Inherited C3 deficiency has also rarely been seen in SLE, and predisposes to encapsulated bacterial infection (Petri, 1998). More commonly, patients with SLE have hypocomplementaemia due to complement consumption from immune complex generation (C3 or C4) or autoantibodies (C1q) (Truedsson *et al.*, 2007; Unsworth, 2008). Initial testing for complement deficiency should include total haemolytic complement activity (CH₅₀), which would be low with any deficiency in the classical or terminal pathway (Ross & Densen, 1984). Testing of specific complement components can then be undertaken, with low values for multiple components, as seen in our case patients, generally suggestive of an acquired defect (Ross & Densen, 1984). The most common acquired complement deficiency in SLE is C4, but C1q, C3 and C9 also show variable reductions (Petri, 1998).

The cases reported here are notable because in our patients the first clue to the diagnosis of SLE was overwhelming sepsis caused by encapsulated bacteria and hypocomplementaemia. The diagnosis of SLE had not been made prior to their hospitalizations because the patients did not seek medical attention for their mild preceding symptoms.

Clinicians should consider the possibility of complement deficiencies in adult patients with severe and unusual infection due to encapsulated organisms, and the presence of hypocomplementaemia should suggest the possibility of SLE, even in patients with no prior history of SLE.

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