Necrotising fasciitis in systemic lupus erythematosus: a case report and literature review

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ABSTRACT
Necrotising fasciitis (NF) is a rare infection of the subcutaneous tissue, known to be rapidly progressive and potentially fatal. Patients with systemic lupus erythematosus (SLE) may be predisposed to this condition, and early clinical recognition can be difficult. We report a case of necrotising fasciitis in a 26-year-old woman with SLE. She presented with painful swelling of her left leg, then developed clinical features of septic shock. Emergency debridement was performed. Intraoperative findings revealed NF and cultures grew Pseudomonas aeruginosa. The patient survived after a lengthy hospital admission, following several further debridements complicated by recurrent chest sepsis and multiorgan failure. We also review and discuss the published cases of NF in SLE patients.

INTRODUCTION
Necrotising fasciitis (NF) is a serious soft tissue and life threatening infection, primarily involving the skin and superficial fascia, characterised by a rapid and extensive necrosis of the subcutaneous tissue. Most patients have associated comorbidities, such as diabetes, HIV infection or treatment with immunosuppressive drugs, but it can also affect previously healthy individuals. Infection is one of the common causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). It is associated with immunosuppressive agents, renal failure, and increased disease activity. Despite the increased propensity of SLE patients to develop common and opportunistic infections, NF has rarely been reported. To our knowledge, only 31 cases are described in the literature to date (see table 1). NF has also been described in other rheumatic diseases including polymyositis, dermatomyositis, systemic sclerosis, rheumatoid arthritis and ankylosing spondylitis, but it appears that this association is more common in SLE.1 2

We describe the case of a NF caused by Pseudomonas aeruginosa, complicated by recurrent sepsis and multiorgan failure in a young patient with a history of SLE.

CASE REPORT
A 26-year-old Asian woman with a complex history of SLE, diagnosed at age 14 years when she presented with malar rash, arthralgia, mouth ulcers, pulmonary vasculitis, strongly positive anti-nuclear antibody and anti-dsDNA antibodies. Subsequently, she had idiopathic detrusor overactivity with repeated urinary tract infection. Linked to her corticosteroid treatment she developed avascular necrosis of her elbow (at that time, on prednisolone 6 mg daily). The patient was also treated with hydroxychloroquine (HCQ), azathioprine (AZA) (100 mg from 1999 to 2009) and had 14 courses of cyclophosphamide (CYC) (a cumulative dose of 14 g) and two of rituximab (RTX) (two 1 g intravenous infusions separated by 2 weeks), the last being given in March 2012 for a SLE flare manifested by severe vasculitic rash. Immediately prior to B-cell depletion, her C3 level was 0.33 g/L (normal: 0.65–1.65), cluster designation (CD) 19 count was 0.146/µL (0.11–0.69), and immunoglobulin G level was 23.4 g/L (7–16).

In May 2012, she presented to her local hospital with painful swelling of her left lower limb, she denied a history of trauma, and her inflammatory markers and ultrasonography were normal, and she was discharged. Within 12 h she was found at home with a Glasgow Coma Scale of 6, and was admitted to the intensive care unit (ICU). On examination, the patient was in septic shock with hypotension (systolic blood pressure 60 mm Hg), tachycardia (135/min), and respiratory failure (SaO2 70%). Poorly demarcated discolouration and blistering purpuric patches on her left lower limb were noted. Laboratory results showed erythrocyte sedimentation rate 96 mm/h (normal: 1–7),
| n | Race/age/sex | Organ involvement | Medications | Comorbidities | Reported anaemia | Alb (gr/dl) | WBC (×10³/mm³) (Lym) | Classification of NF | Isolated micro-organism | Presentation | Outcome | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | A, 26F | Lung and cutaneous vasculitis, myositis, Raynaud, thrombopenia, ART, hepatitis | CS, HCQ, CYC, RTX, Doxycycline | Detrusor overactivity, AVN of elbow, digital ischaemia. *Escherichia coli* urinary tract infections | Yes | 1.7 | 15.4 (1.9%) | 1 | *Pseudomonas* | Leg pain, purpuric patches | S | Current report |
| 2 | NA, 39F | N, ART, thrombopenia | CS, HCQ | DM | No | NA | 16.7 (NA) | 10.5 (9.5%) | 1 | *Aeromonas* | Leg pain, blisters | S | 1 |
| 3 | NA, 28F | Cerebral lupus, N, ART | CS | Mental retardation, AVN hips | No | NA | 3.3 | 7.0 (4.3%) | 2 | *Streptococcus, Serratia marcescens, Aeromonas, Morganella* | Thigh pain, fever | S | 1 |
| 4 | Aboriginal, 34F | N, APS | CS | Renal failure | No | 3.3 | 7.0 (4.3%) | 2 | *Streptococcus* | Thigh swelling, pain | S | 4 |
| 5 | H, 48F | Photosensitivity, oral ulcers, leucopenia, pleural effusion, haemolytic anaemia. | CS, anticoagulation. | PE, APS, DM. | Yes | NA | Normal | 1 | *SA* | Thigh swelling, pain | S | 5 |
| 6 | A, 58F | NA | CS | Hepatitis C, cirrhosis | No | NA | 21.6 (NA) | 17 (NA) | 1 | *SA, Serratia* | Swelling leg | D | 6 |
| 7 | A, 28F | Anaemia | None | None | Yes | NA | | 17 (NA) | 1 | *Pseudomonas* | Facial swelling, pain, fever | S | 8 |
| 8 | H, 34F | ART, seizures | CS | None | No | 3.3 | 15.6 (2.6%) | 2 | *Streptococcus* | Leg pain, swelling | S | 9 |
| 9 | H, 43F | ART, N | CS, CYC | None | No | 2.2 | 1.6 (23%) | 1 | *Escherichia* | Leg pain and oedema | D | 9 |
| 10 | AA, 53F | ART, N | CS | Hypertension | No | 1.9 | 1.3 (23%) | 1 | *Pseudomonas, Enterococcus* | Thigh ecchymosis, bullous lesion | S | 9 |
| 11 | AA, 12M | ART, N | CS | None | No | 2.9 | 4.3 (28%) | 1 | *Streptococcus pneumoniae, Streptococcus* | Neck pain, swelling | S | 9 |
| 12 | AA, 20F | ART, vasculitis, haemolytic anaemia, Vasculitis, neph | CS, AZA, HCQ, napro-xen | None | Yes | NA | 2 | *Streptococcus pneumoniae* | Streptococcus NA | S | 9 |
| 13 | H, 30F | Neph, ART, cerebritis | CS, AZA, HCQ | None | No | 3.3 | NA (0.5 ×10³/mm³) | NA | NA | NA | S | 9 |
| 14 | H, 38M | ART, rash | CS, ubupro-fen | None | No | 2.9 | 7.6 (9.2%) | — | Negative | NA | S | 9 |
| 15 | H, 57F | Neph, ART, cerebritis | CS | CAD, hypertension | No | 2.2 | 25.6 (9.2%) | 2 | *Streptococcus* | NA | D | 9 |
| 16 | Canadian, 30F | Serositis, purpura, ART, malignant hypertensio, N | CS, CYC | None | Yes | NA | NA (NA) | 1 | *Streptococcus pneumoniae* | Face and neck swelling, erythema | S | 10 |

*Continued*
| n  | Race/age/sex | Organ involvement | Medications | Comorbidities | Reported anaemia | Alb (gr/dl) | WBC (x103/mm³) (Lym) | Classification of NF | Isolated micro-organism | Presentation | Outcome | Reference |
|----|--------------|-------------------|-------------|---------------|------------------|------------|----------------------|----------------------|------------------------|-------------|---------|-----------|
| 16 | NA 17F       | NA                | NA          | NA            | No               | NA (NA)    | 1                    |                         | Streptococcus pneumoniae | Dyspnoea, dysphagia, neck stiffness | S           | 11      |
| 17 | NA 18F       | NA                | NA          | NA            | No               | NA (NA)    | 4 (8%)               | 1                     | Salmonella              | Fever, lumbar pain | D        | 12       |
| 19 | NA 19F       | NA                | NA          | NA            | Yes              | NA (NA)    | 3.7 (NA)             | 1                     | Streptococcus pneumoniae | Thigh swelling, tenderness, pain | D           | 13       |
| 20 | A 20F        | N, thrombopenia   | CS          | NA            | Yes              | NA (NA)    | 15 (3%)              | 1                     | Salmonella              | Fever, thigh pain, swelling and haemorrhagic bleb | S           | 14       |
| 21 | French 66F   | Anaemia           | AZA         | DM            | Yes              | NA (NA)    | 1.8 (NA)             | 2                     | Streptococcus           | Abdominal pain, leg swelling, haemorrhagic bleb | D           | 15       |
| 22 | NA 40M       | N                 | CS          | NA            | No               | NA (NA)    | 2.1 (20%)            | 1–2                   | Serratia                | Leg cellulitis          | S           | 16       |
| 23 | NA 46F       | Pleuritis, ART    | CS          | None          | Yes              | NA (NA)    | 16 (40%)             | 1                     | Bacteroides, Morganella | Thigh ecchymosis, oedema, bullae, Bartholin abscess | S           | 17       |
| 24 | A 21F        | N                 | CS          | Chronic renal failure | No | 2.3 | 16 (40%) | 1 | Bacteroides, Morganella | Arm pain, swelling | S           | 18       |
| 25 | A 31F        | N, thrombopenia   | CS, CYC     | DM, chronic watery diarrhoea | Yes | 1.9 | 6.1 (9%) | 1 | Salmonella | Dysphagia, dyspnorea, trismus neck pain, oedema | S           | 19       |
| 26 | H 23F        | NA                | CS          | Deeply carious tooth | No | NA | 16.5 (NA) | 2 | Streptococcus, Staphylococcus | Flank and thigh pain | S           | 20       |
| 27 | NA 21F       | N                 | CS, RTX, plasma-pheresis | TTP, mesenteric vasculitis, C. difficile-associated colitis | No | NA | NA | 1 | Acinetobacter | Back, abdominal pain, fever | D           | 21       |
| 28 | NA 36F       | Raynaud, APS, heart block, aseptic meningitis | CS, HCQ     | Hip AVN | No | NA | 8.2 (8.5%) | 2 | Streptococcus | Back, abdominal pain, fever | S           | 22       |
| 29 | NA 14F       | NA                | CS, AZA     | NA            | No               | NA (NA)    | 2.3 (NA)             | 1                     | Streptococcus pneumoniae | Fever, pain on ischial areas | S           | 23       |
| 30 | A 40F        | Photosensitivity, Raynaud, oral ulcer | CS, HCQ, AZA | Systemic sclerosis, cutaneous ulcers | Yes | NA | NA | 1 | Enterobacter, Enterococcus | Fever, pain on ischial areas | S           | 24       |
c-reactive protein 281 mg/dL (0–5), white blood cells 15 400/µL (3000–10 000) (97% neutrophils; 1.9% lymphocytes), haemoglobin 9.6 g/dL (11.5–15.5), platelet 50 000/µL (150 000–400 000), Na 138 mmol/L (135–145), creatine kinase 474 IU/L (26–140), urea 16.8 mmol/L (1.7–8.3), alanine transaminase 384 IU/L (10–35), total bilirubin 11 mg/dL (0.3–1.9), albumin 17 g/L (34–50), creatinine 290 µmol/L (49–92) and proteinuria 2.30 g/L (0–0.10). Anticardiolipin antibodies were negative. Her C3 level was 1.0 g/L (0.65–1.65), CD19 count was 0.001/µL (0.11–0.69), and immunoglobulin G level was 9.32 g/L (7–16).

She had aggressive debridement and a diagnosis of NF was made. Cultures of muscle tissue only grew P aeruginosa, resistant to piperazillin-tazobactam; therefore, she was treated with meropenem, teicoplanin and clindamycin. As her clinical condition gradually improved, the antimicrobial therapy was stopped by the 2nd week. However, 1 week later, she deteriorated, with thick yellowish sputum, fever, respiratory distress and the chest X-ray showed right consolidation. Ciprofl oxacin and teicoplanin were empirically started, and the patient’s clinical condition gradually improved. A week after this treatment had finished, the patient became worse with a new left lower lobe consolidation, so the antibiotic therapy was changed to ceftazidime. Her lupus flared with a marked malar rash over both cheeks, so her steroids (prednisolone) were increased to 20 mg per day and HCQ was restarted.

She was in the ICU from May to August 2012, but made a remarkable recovery and was discharged home with a steroid-tapering regimen and HCQ. Later, she developed two more SLE flares, which were treated again with CYC and RTX, achieving good response. At 18 months follow-up, there is no evidence of new recurrent or severe ongoing infections.

DISCUSSION

Since 1883, more than 500 cases of NF have been reported. Most patients with NF ranged from 38 years to 44 years, with a male to female ratio of 2–3:1, and apparently an increased incidence in African and Asian countries. The true incidence is not known (it is estimated to be approximately 0.4 cases per 100 000), with a reported mortality from 20% to as high as 80%. The causative agents of NF vary and include two main categories, polymicrobial (type 1) and infection of group A streptococcal (type 2).

Patients with SLE have an increased risk of infections, due to immunological dysfunction and the use of steroids and immunosuppressive agents. Other factors, such as the presence of a variant form of the Fc receptor are also believed to contribute to the risk of pneumococcal infection.

NF due to Pseudomonas has very rarely been reported. The clinical presentation of patients with NF may be deceptively benign at onset, and it may not be possible to
distinguish it clearly from minor soft tissue infections. Our patient was discharged from the original hospital before being admitted subsequently severely ill to University College Hospital. The lesion was rapidly progressive, probably due to her SLE, and the prolonged steroid treatment and recent administration of CYC and RTX might have increased the risk of infection. During the initial period, exploration of the wound may be necessary even before the diagnosis is clear, particularly in a patient who is clearly toxic.

In addition to the present case, the other 31 cases of NF in SLE patients that have been reported are summarised in Table 1. The ages ranged from 12 years to 66 years, and 27 (84%) were female. Most of the patients reported were Asian (33%, 7 patients), 33% (7 patients) Hispanic and 19% (4 patients) African–American. The sites of infection included the upper or lower limb (60%, 17 patients), the face, neck or tongue (18%, 5 patients), the genital area (11%, 3 patients) and the abdomen (11%, 3 patients). NF Type 1 was identified in 22 patients (71%) and Type 2 in 7 patients (23%), and when reported, the most common isolation was Streptococcus (50%, 16 patients). Most of the patients presented with intense pain, poorly demarcated erythematous, swollen lesions over the limbs and systemic inflammatory response; 28 patients (88%) were receiving corticosteroids and 7 HCQ (22%). Additionally, use of other immunosuppressive drugs has been reported (5 CYC, 5 AZA, 2 RTX, 1 mycophenolate, 1 methotrexate, 1 fludarabine) before or at the time of infection. Other associated conditions have been identified, including nephritis (54%; 15 patients of 28 reported), either during the current presentation or in the past, 13 (42%) had nephritis (54%; 15 patients of 28 reported), either during the current presentation or in the past, 13 (42%) had a history of complications (such as sepsis or pulmonary embolism).

The case presented here and the literature reviewed suggests that acute disease, nephropathy, lymphopenia, anaemia, low serum albumin levels, immunosuppressive therapy and significant infections in the past, may constitute risk factors for the development of NF in patients with SLE. A high index of suspicion for the diagnosis is required, and surgical exploration should not be delayed, especially during the early stages, to improve the prognosis of this devastating complication.

Contributors All authors have contributed equally to this work.

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