CASE REPORT

Recurrent SDSE bacteraemia resulting in streptococcal toxic shock syndrome in a patient with Noonan syndrome

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SUMMARY

A 19-year-old man with chronic lymphoedema due to Noonan syndrome presented at our hospital with septic shock and pain in his lower leg. Blood cultures were positive for *Streptococcus dysgalactiae* subsp *equisimilis* (SDSE), resulting in a diagnosis of cellulitis with toxic involvement. He was treated with ampicillin for 3 weeks. Although he did well for 6 weeks, septic shock recurred. Blood culture again revealed SDSE, with the strain being identical to the first episode, suggesting that this infection had relapsed. He was treated with ampicillin for 6 weeks and prophylactically with trimethoprim-sulfamethoxazole for 12 months. Although SDSE bacteraemia occurs commonly in elderly patients, findings in this patient showed that it can also develop in younger persons with predisposing factors. This case also indicates that SDSE has the potential to recur, despite generally sufficient antibiotic administration, and that patients who experience recurrent episodes may require prolonged treatment with antibiotics, including prophylaxis.

BACKGROUND

Groups C and G streptococci are increasingly recognised as causes of a variety of human infections, especially in elderly patients and/or patients with comorbidities.^{1 2} Methods of classifying streptococci are complex and include colony size, haemolytic activity on blood-agar plates and the presence of Lancefield group antigens. Gene sequencing results have led to the re-evaluation of streptococcal taxonomy, resulting in the identification of a novel subspecies, *Streptococcus dysgalactiae* subsp *equisimilis* (SDSE).³ This microorganism possesses group C or G antigens (rarely, A antigen), and forms large, glossy colonies with strong β -haemolytic activity on blood-agar plates. SDSE is an important pathogen, as it causes invasive infections, and also recurrent infections in patients with predisposing factors.^{1 2} Although several case series have described patients with recurrent SDSE infections,⁴⁻⁶ appropriate treatment strategies have not yet been established. This report describes a patient with Noonan syndrome who developed recurrent SDSE bacteraemia and cellulitis, accompanied by streptococcal toxic shock syndrome (STSS).

CASE PRESENTATION

A 19-year-old man presented to a local hospital with a high fever. As a child, he was diagnosed with Noonan syndrome,⁷ which is characterised by

multiple congenital abnormalities, including congenital heart disease and lymphatic vessel dysplasia. At age 3 years, he underwent arterioplasty for a right ventricular outflow tract obstruction, with patch closure of an atrial septal defect, for congenital heart disease. At age 17 years, he underwent lymphaticovenular anastomosis earlier for lymphoedema. Except for prolonged bilateral lymphoedema, he had been well and was not taking any medications. At presentation, he had a fever (39.2°C), systolic heart murmur and bilateral lymphoedema; all other clinical findings were normal. Just before admission, he reported of pain in his right lower leg, accompanied by reddening and associated with flank pain. Since plain CT scan failed to show the origin of fever and flank pain, he was admitted to the local hospital with a diagnosis of cellulitis. After two sets of blood cultures were obtained, he was empirically treated with intravenous cefazolin. However, after 4 hours of treatment, he developed hypotension and reported of dyspnoea with severe right lower leg pain and was transferred to our hospital. On admission to our hospital, his oxygen saturation was 99% on 2 L/min oxygen inhalation via a nasal cannula, but he was tachypnoeic, with a respiratory rate of 38 breaths/min. Following intravenous administration of 1 L fluid, his blood pressure was 98/40 mm Hg and his heart rate was 121 bpm. His consciousness level on the Glasgow Coma Scale was E3V4M6 and his body temperature was 37.8°C. The reddening of his right lower leg rapidly expanded to close to the knee joint (figure 1A, B), and he reported of bilateral coxalgia and scrotal pain.

INVESTIGATIONS

Laboratory examination revealed metabolic acidosis with respiratory compensation, an increase of lactic acid (3.0 mmol/L) and leucopenia with white cell count of 1840/ μ L. Other laboratory findings were as follows: haemoglobin, 14.1 g/dL; platelet count, $131 \times 10^3/\mu$ L; C reactive protein, 0.10 mg/dL; albumin, 3.7 g/dL; blood urea nitrogen, 15 mg/dL; creatinine, 0.90 mg/dL; lactate dehydrogenase, 150 IU/L; creatine kinase, 148 IU/L and procalcitonin, 25.33 ng/mL. Emergency CT scan with contrast of his lower extremities did not show gas or occlusive abnormalities in the lower blood vessels.

DIFFERENTIAL DIAGNOSIS

He was initially diagnosed with septic shock and a severe soft-tissue infection with toxic involvement.

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Figure 1 (A) Photograph showing bilateral lower extremities of the patient at admission to our hospital and (B) closeup photograph of his right foot. Although this patient previously had bilateral lymphoedema, his skin colour became red, rapidly extending to the knee region on his right side. Local heat and tenderness were also observed, suggesting severe inflammation.

He was started on multiple antibiotics, including meropenem (1 g every 8 hours), daptomycin (350 mg every 24 hours) and clindamycin (800 mg every 8 hours). His condition deteriorated over the next several hours and he developed thrombocytopenia (platelet count, $2.4 \times 10^4/\mu\text{L}$) due to disseminated intravenous coagulation. He was intubated because of acute respiratory distress syndrome and required high-dose catecholamine combined with hydrocortisone (300 mg/day) to achieve haemodynamic stability. With careful consideration of necrotising fasciitis, the need for surgical exploration was discussed with the patient every 4 hours, but his condition stabilised about 48 hours after admission. Blood culture on the second day was positive for a Gram-positive coccus, which was identified as SDSE. He was finally diagnosed with SDSE bacteraemia due to cellulitis accompanied by STSS.

TREATMENT

He was started on intravenous ampicillin (2 g every 6 hours), with the other antibiotics discontinued. His condition and inflammatory biological syndrome improved rapidly and follow-up blood culture was negative. He was extubated on his fourth day of admission. Since he had lymphatic vessel dysplasia, antibiotics were continued for another 3 weeks to prevent early recurrence.⁴

OUTCOME AND FOLLOW-UP

Following discharge from the hospital, he did well for 6 weeks, but subsequently developed the same symptoms and returned to the hospital in a state of shock. He was diagnosed with recurrent toxic shock syndrome, and was started on the same intravenous antibiotics (meropenem, daptomycin and clindamycin). A blood culture was positive for SDSE and semiautomated, repetitive, sequence-based PCR methods⁸ confirmed that this strain was identical to that isolated during the first episode (figure 2). This result suggested that this infection had relapsed, not only recurred. Antibiotics were de-escalated to intravenous ampicillin. Although we examined the reason of recurrent bacteraemia, a CT scan with contrast excluded the possibility of residual abscesses and transesophageal echocardiogram excluded the likelihood of infectious endocarditis. He was treated with 2 g ampicillin every 6 hours for prolonged duration (6 weeks), followed by prophylaxis with 1 g/day trimethoprim-sulfamethoxazole for 12 months, with no evidence of recurrence.

DISCUSSION

This report, describing a patient with recurrent SDSE bacteraemia with cellulitis, provides three crucial insights: (1) although SDSE bacteraemia occurs most commonly in elderly patients, it can also develop in younger individuals with predisposing factors, especially with lymphatic disorders. (2) Moreover, SDSE has the potential to relapse (not only recur) with the same

clinical symptoms, despite treatment with generally sufficient antibiotics. (3) Furthermore, patients with recurrent SDSE bacteraemia may require prolonged administration of antibiotics, including prophylaxis.

SDSE causes severe soft-tissue infections, and severe systemic infections, including STSS.^{1–4 9} The overall incidence of invasive SDSE infection is higher among men than women and increases with age. Almost all (90–96%) patients with SDSE bacteraemia have an underlying disease, such as immunosuppression, malignancy, diabetes mellitus or rheumatoid arthritis, which may predispose to infection.^{1–3} Breakdown of the skin and lymphatic system is a frequent predisposing factor for bacteraemia.⁴ Although patients with Noonan syndrome are usually immunocompetent,⁷ lymphoedema related to Noonan syndrome played a significant role in the development of SDSE bacteraemia in this patient.

The rate of recurrence of group G *Streptococcus* bacteraemia has been reported to be 5–10%, higher than that of *Streptococcus pyogenes* (group A *Streptococcus* (GAS)) bacteraemia.^{4–6} As in our patient, recurrence of the identical strain has been reported, providing evidence for relapse. Although our patient relapsed within a relatively short period, we confirmed the clearance of his cellulitis and bacteraemia following antibiotic administration for the first episode. In addition, we ruled out of the possibility of infective endocarditis and remote abscess. Thus, the course of disease in this patient was simply not due to treatment failure. Bacteraemia tends to recur within 1 year.^{4–6} The virulence properties of *S. pyogenes* and SDSE overlap, due primarily to horizontal gene transfer from the former to the latter.^{1 10} SDSE is now regarded as being a topical microorganism causing non-group GAS STSS.¹¹ Clinical manifestations may recur, especially in patients with severe disease. Unlike *S. pyogenes*, SDSE may persist in tissues despite antibiotic treatment, contributing to recurrence.¹² The median age of patients with recurrent infection was 10 years less than that of patients with primary infection. Younger patients may be at higher risk of recurrence,¹² with chronic lymphatic abnormality at the infection site strongly predisposing to future episodes.⁴ Various general and local risk factors may play a role in recurrences. Further studies, including assessments of molecular characteristics, are required to determine whether recurrences are specifically associated with certain strains.

Bacteraemia being a life-threatening condition, the rapid initiation of effective intravenous empirical antibiotic therapy is essential. However, the relatively high recurrence rate^{4–6} suggests a reconsideration of the appropriate duration of antibiotics administration. Findings after the first episode in our patient suggests that antibiotic treatment for 3 weeks was insufficient for controlling infection in patients with strongly predisposing factors. Studies on the potential role of prophylactic antibiotics in reducing recurrence are ongoing.¹³ Of course, it is hard to generalise the appropriateness of antibiotic prophylaxis from

Figure 2 The result of semiautomated, repetitive, sequence-based PCR (rep-PCR) performed on a DiversiLab microbial typing system (bioMérieux, Marcy l'Etoile, France). The use of defined primers for PCR amplification of interspersed repetitive DNA elements present at distinct locations in prokaryotic genomes is referred to as repetitive element rep-PCR. The amplified DNA fragments, when separated by electrophoresis, constitute a genomic fingerprint that can be employed for subspecies discrimination and strain delineation of bacteria. This result confirmed that the isolates from both episodes belonged to the same strain.

only one case. As selection pressure may enhance the growth of resistant microorganisms, antibiotic prophylaxis may be indicated in patients with a previous severe SDSE infection predisposed to recurrence. In addition, vaccination trials against GAS infection are now underway,^{2 14} suggesting that vaccination against SDSE infection may be warranted.

Since the number of elderly individuals and immunodeficient patients with comorbidities will continue to increase, invasive SDSE infection may also increase. We should indicate vigorous intention to continue discussion on the management of this an emerging infection.

Learning points

- ▶ Although *Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE) bacteraemia occurs most commonly in elderly patients, it can also develop in younger individuals with predisposing factors, especially with lymphatic disorders.
- ▶ SDSE has the potential to recur with the same clinical symptoms, despite treatment with generally sufficient antibiotics.
- ▶ Patients with recurrent SDSE bacteraemia may require prolonged administration of antibiotics, including prophylaxis.

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Contributors KS collected the data and drafted the manuscript. KS, KI and HI were involved in the treatment of the patient. AN made the molecular biological diagnosis. HI revised and edited the manuscript. All authors have read and approved the final version of the manuscript.

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