CASE REPORT

Recurrent invasive group A streptococcal infection with four-limb amputation in an immunocompetent child

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Accepted 2 July 2018

SUMMARY

We report a previously well paediatric patient with two distinct presentations of invasive group A streptococcus (GAS) infection resulting in significant morbidity. The first episode, following GAS pharyngitis, involved multiorgan dysfunction syndrome. This included cardiorespiratory and acute hepatorenal failure and purpura fulminans that eventually necessitated four-limb amputation. The second episode occurred 12 months later, from undetermined aetiology, and resulted in septic shock. Molecular analysis of the emm gene and PCR for Serum Opacity Factor revealed that the initial isolate was M Type 4 and sof gene positive while the second isolate was M Type 1 and sof gene negative. Immunological investigations, including CH50, quantitative IgA, IgM and IgG, and flow cytometry measuring lymphocyte subsets, and vaccine response to measles, mumps, rubella and pneumococcus were normal. This is the first report of recurrent bacteraemia from different strains of *Streptococcus pyogenes* infection in an apparently immunocompetent child.

BACKGROUND

Streptococcus pyogenes (group A streptococcus, GAS) is a gram-positive extracellular bacterial pathogen. Invasive GAS (iGAS) is defined as laboratory isolation of GAS from a normally sterile site. Recurrent iGAS is exceedingly rare. We report the first previously well paediatric patient with two distinct presentations of different strains of iGAS infection. The potential for recurrent iGAS in a patient with apparently normal immune function underscores the importance of initial broad antibiotic coverage while awaiting antibiotic sensitivity profiles and of not assuming the same organism.

CASE PRESENTATION

A previously healthy 10-year-old girl presented to her local emergency department (ED) with a 3-day history of a sore throat followed by 1 day of fever and new, rapidly evolving purpuric skin lesions. In the ED, she developed circulatory failure requiring fluid resuscitation and inotropic support, including intubation and mechanical ventilation. Blood cultures were drawn and antibiotics (clindamycin, vancomycin and ceftriaxone) were initiated empirically. The patient was transported to the regional paediatric tertiary care centre.

Multiorgan dysfunction syndrome developed, including cardiorespiratory and acute hepatorenal failure, necessitating mechanical ventilation, continuous renal replacement therapy and ongoing inotropic support. She had one cardiac arrest requiring cardiopulmonary resuscitation for 6 min. She received 2 g/kg of intravenous immunoglobulin. All four limbs became ischaemic distal to elbows and knees including her buttock area. Her initial white blood cell (WBC) count was $15 \times 10^9/L$ with 76% neutrophils and 61% bands, and her peak WBC count 3 days later was $56 \times 10^9/L$ with 80% neutrophils.

Blood cultures grew gram-positive, bacitracin disc-susceptible, beta-haemolytic, catalase negative, Lancefield GAS and a throat swab was also positive for the organism, which was susceptible to penicillin, clindamycin and erythromycin. The patient had no sick contacts and none of her family complained of sore throat. She was living with both parents and a teenaged sister. Prophylaxis was provided to household contacts. Therapy for the initial GAS was continued with ceftriaxone, as the family reported penicillin sensitivity, for 14 days. The ischaemic areas developed gangrenous necrosis and antibiotic therapy was broadened to meropenem. The patient stabilised and remained in the paediatric intensive care unit (PICU) for weeks while the limits of viable limb tissue became delineated. A month after admission to PICU, she required multiple surgeries for four-limb amputation and diverting colostomy due to perianal necrosis.

The patient was discharged from the paediatric hospital after 5 months; her wounds were fully healed and skin intact. She was transferred to a rehabilitation centre in her home city for ongoing rehabilitation and prosthetic fittings.

Seven months later (12 months from the first presentation), the patient re-presented to her local ED from home in septic shock with inflammation noted in the left thigh and tibial stump, but no sites of skin breakdown. Blood cultures were drawn and empiric intravenous antibiotics (ceftriaxone and meropenem) given. She was transported again to the tertiary care paediatric centre and readmitted to PICU. Initial and peak WBC count was $22.4 \times 10^9/L$ with 93% neutrophils and 65% bands. The overlap in antibiotic spectrum was noted and ceftriaxone was discontinued. Initial blood cultures were again positive for GAS that was susceptible to penicillin,

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To cite: Gazzaz N, Mailman T, Foster JR. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225292

Table 1 Markers of sepsis and organ failure, values at presentation and peak values

	Episode 1: initial value	Episode 1: peak value	Episode 2: initial value	Episode 2: peak value
CRP, mg/L	317	317	214	241
Lactate, mmol/L	7	44.9	3.6	3.6
Blood urea nitrogen, mmol/L	21.5	45.9 (pre-dialysis)	8.4	8.4
Creatinine, mmol/L	335	335	63	63
ALT, mmol/L	52	3801	66	66
AST, mmol/L	70	13 553	68	68
WBC count (absolute neutrophil count), $\times 10^9/L$	9.9 (4.7)	56.9 (45.5)	22.4 (20.8)	22.4 (20.8)
INR	2.19	10.0	—	—

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C reactive protein; INR, international normalised ratio; WBC, white blood cell.

clindamycin, and erythromycin. We assumed that she had been reinfecting from a latent source of her initial GAS isolate, likely from her tibial stump.

INVESTIGATIONS

Typing results

Matrix-assisted laser desorption/ionisation/time of flight (Vitek MS system) spectra performed after her second infection on frozen samples of both bloodborne bacteria confirmed *Streptococcus pyogenes*. Both isolates were typed at the Canadian National Microbiology Laboratory in Winnipeg. M typing was based on molecular analysis of the *emm* gene. Presence of the serum opacity factor (*sof*) gene was assessed by PCR. The initial isolate was M Type 4 and *sof* gene positive while the second isolate was M Type 1 and *sof* gene negative.

Markers of sepsis and organ dysfunction are presented in table 1.

Immunological investigation

The patient had no history of other recurrent infections or other symptoms suggestive of immunodeficiency. She had normal-appearing tonsils on both presentations, and her spleen appeared normal sonographically. Vaccine response to measles, mumps, rubella and pneumococcus were normal. Results of other immunological testing are provided in table 2.

OUTCOME AND FOLLOW-UP

Her clinical condition improved rapidly. Bone scan and MRI were negative for osteomyelitis or abscesses that could have sequestered the initial organism. No clear portal of entry was identified with this episode, though it was suspected that she had developed cellulitis of the left tibial stump. There were no known sick contacts; the patient had been attending school.

She completed a 10-day course of intravenous cefazolin and was discharged home in good clinical condition to complete a 3-week antibiotic course with amoxicillin. Household contacts

received prophylaxis again and there were no secondary cases. Given the patient's remote home location, long-term antimicrobial prophylaxis was implemented with penicillin V after a successful penicillin challenge with amoxicillin.

DISCUSSION

Host invasion by GAS is enabled by a variety of virulence factors. Several proteins on the extracellular bacterial surface including M proteins, the major streptococcal virulence factor, may promote GAS survival through antiphagocytic properties.¹ Further, some species of GAS produce extracellular enzymes that act as superantigens, such as streptococcal pyrogenic exotoxins (Spe). They degrade host serum proteins and may contribute to severe disease by stimulating T and mononuclear cell pro-inflammatory cytokine production, resulting in endothelial injury and haemodynamic compromise.¹ The Spe superantigen profiles are considered an important predictor of GAS invasiveness.² We did not have data on this profile for our patient.

Although macrophages are an important component of the initial innate immune response to iGAS, the organism can survive intracellularly and has been shown to replicate within human macrophages,³ forming a reservoir of bacteria with the potential to cause reinfections.

Despite this potential reservoir, recurrent iGAS is rare. The majority of published recurrences report infection with the same organism, supporting recurrence hypotheses involving incomplete antimicrobial treatment or an inaccessible bacterial reservoir. In 1994, Santos *et al* reported recurrent iGAS infection in a patient with immunodeficiency and illicit intravenous drug use, though the GAS was not further classified.⁴ In the report of a Danish outbreak of GAS postpartum sepsis, one patient had two episodes of GAS endometritis caused by the same serotype (T3-13-B3264).⁵ Infections occurred 12 weeks apart and the second was after oral penicillin treatment. Rasmussen reported recurrent infection with *emm*87 type in an elderly man with several risk factors for severe infection including a mechanical aortic valve, type 2 diabetes mellitus and severe arteriovascular disease.⁶ This patient lacked a specific subset of antibodies, though his complement and immunoglobulin levels were normal. Finally, an outbreak of GAS among nursing home residents in the USA included recurrent iGAS infections from type *emm*11, where contributing factors to recurrence may have included open wounds and sustained transmission of the progenitor strain for at least 19 months.⁷

Exposure to another strain of GAS is common and was not unexpected in our patient. The nasopharyngeal mucosa acts as a reservoir for GAS colonisation, and patients may acquire a different GAS strain of a different serotype following successful treatment of GAS pharyngitis.⁸ However, to our knowledge, there is only

Table 2 Results of immunological work-up

Test	Results
Multicolour flow cytometry analysis with extended panels (1 and 2) for immunodeficiency studies	Interpretation: normal
CH50 alternate (normal $\geq 40\%$ control)	$>122\%$ of control
MBL activity (normal 30%–200% control)	137% of control
IgG (normal 7.7–16.4), g/L	9.3
IgA (normal 0.52–2.56), g/L	1.2
IgM (normal 0.41–2.47), g/L	2.28

All tests performed after second episode of sepsis, when patient was healthy.

MBL, mannose binding lectin.

one other report in the medical literature of recurrent iGAS with different, genetically distinct strains. Hattori *et al* reported the case of a 4-year-old child with immunodeficiency (abnormal CD4/CD8 ratio and low lymphocyte blast transformation) who was infected first with *emm* type 1 and then *emm* type 12 thirteen months later.² With a functioning immune system, repeated infection should be rare. As postulated previously,⁶ although type-specific immunity relies on antibodies towards the hypervariable amino-terminal component of M proteins,⁹ iGAS infections should generally result in production of specific opsonising antibodies against M-protein, providing broader protection against repeat invasive disease. It is possible that our patient has an unrecognised lacunar defect in GAS immunity.

Learning points

- Management of severe invasive group A streptococcus (iGAS) disease involves supportive treatment with fluids and vasoactive agents as needed, specific therapy with antimicrobials and the use of measures to minimise or neutralise the effects of toxin production.
- Recurrent iGAS, particularly with different strains of the organism, is rare but possible and underscores the importance of broad initial antibiotic coverage.
- While recurrence should prompt investigation for a latent source of undertreated infection, molecular serotyping may be important.
- Immunological assessment and initial broad antibiotic coverage while awaiting antibiotic sensitivity profiles is advised.

Contributors All authors contributed significantly to this manuscript. NG wrote the initial draft. JRF provided edits and critically altered the discussion. TM provided input on immunological and infection-related topics. All authors have seen and approved the manuscript as submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Hamada S, Kawabata S, Nakagawa I. Molecular and genomic characterization of pathogenic traits of group A *Streptococcus pyogenes*. *Proc Jpn Acad Ser B Phys Biol Sci* 2015;91:539–59.
- 2 Hattori T, Minami M, Narita K, *et al*. Recurrent bacteremia with different strains of *Streptococcus pyogenes* in an immunocompromised child. *J Infect Chemother* 2016;22:421–3.
- 3 O'Neill AM, Thurston TL, Holden DW. Cytosolic replication of group A streptococcus in human macrophages. *MBio* 2016;7:e00020–16.
- 4 Santos J, Fernández A, Arana C, *et al*. [Bacteremia and recurrent arthritis caused by *Streptococcus pyogenes* in a heroin addict with AIDS]. *Enferm Infecc Microbiol Clin* 1994;12:390–2.
- 5 Ejlersen T, Prag J, Pettersson E, *et al*. A 7-month outbreak of relapsing postpartum group A streptococcal infections linked to a nurse with atopic dermatitis. *Scand J Infect Dis* 2001;33:734–7.
- 6 Rasmussen M. Recurrent sepsis caused by *Streptococcus pyogenes*. *J Clin Microbiol* 2011;49:1671–3.
- 7 Dooling KL, Crist MB, Nguyen DB, *et al*. Investigation of a prolonged Group A Streptococcal outbreak among residents of a skilled nursing facility, Georgia, 2009–2012. *Clin Infect Dis* 2013;57:1562–7.
- 8 Johnson DR, Kurlan R, Leckman J, *et al*. The human immune response to streptococcal extracellular antigens: clinical, diagnostic, and potential pathogenetic implications. *Clin Infect Dis* 2010;50:481–90.
- 9 Dale JB, Seyer JM, Beachey EH. Type-specific immunogenicity of a chemically synthesized peptide fragment of type 5 streptococcal M protein. *J Exp Med* 1983;158:1727–32.

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