Case Report

Group A Streptococcal bacteraemia and necrotizing faciitis in a renal transplant patient: a case for intravenous immunoglobulin therapy

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Introduction

Acute infectious diseases in immunocompromised patients are potentially life threatening. This report deals with a Gram-positive, Gp. A streptococcal (Streptococcus pyogenes) (GAS) bacteraemia, complicated by necrotizing fasciitis, in a renal transplant patient. Conventional antibiotic therapy together with intravenous (i.v.) gammaglobulin led to a complete recovery, without having to resort to debilitating surgical debridement.

Case

A 37-year-old female was admitted with a 12-h history of fever together with epigastric and right shoulder pain.

Relevant past history included end-stage renal failure, secondary to diffuse proliferative glomerulonephritis complicating systemic lupus erythematosus. Peritoneal dialysis had been carried out for 6 months until August 1998 when she received a cadaver-donor renal transplant. ‘Triple therapy’ (prednisone, azathioprine, and tacrolimus) was initiated. At 3 months post-transplant renal function was good (serum creatinine: 1.2 mg/dl). In January 2001, renal function deteriorated (serum creatinine: 2.3 mg/dl). A closed biopsy of the transplanted kidney revealed acute cellular rejection. I.v. methylprednisolone (500 mg) was given on 3 consecutive days. During those 3 days numerous attempts were made to cannulate veins for the methylprednisolone therapy. On the day after the last ‘bolus’ the patient was admitted.

On admission the patient was in obvious distress. Vital signs included: blood pressure 160/90 mmHg, pulse rate 90/min, temperature 38.2°C, respiratory rate 22/min. There were no skin lesions. The right arm was held in elbow-flexion and in contact to the lateral chest wall. Active movements of the right shoulder were extremely painful, but the shoulder joint was not oedematous, red, or hot. The right arm showed no signs of phlebitis and no axillary lymphadenopathy was felt. No pericardial friction rub was heard and no tenderness over the transplanted kidney was elicited. A known diastolic murmur of aortic insufficiency was heard.

Immediately investigations revealed a normal urinalysis, leucocytosis 25 400/mm³ (bands 5%, neutrophils 90%), serum albumin 30 g/l, stable renal function, and a normal chest X-ray. An ultrasound of the right shoulder showed no intra-articular or bursal fluid and a transthoracic echocardiogram demonstrated aortic insufficiency but no valvular vegetations or pericardial fluid.

Azathioprine was stopped, prednisone dosage increased and i.v. cloxacillin (8 g/day) was started. On the second day the patient was worse. Although haemodynamically stable, there was no improvement in her pain, and tenderness was marked over the superior postero-lateral aspect of the right chest wall. Thrombocytopenia (80 000/mm³) and a metabolic acidosis (pH 7.30, HCO₃ 18 mmol/l) were observed for the first time. During the morning of this second day, blood cultures revealed large numbers of a Gram-positive cocci. I.v. vancomycin (1 g) was given. A CT of the chest showed a large soft tissue swelling of the
right chest wall, extending from just under the right axilla to the diaphragmatic area (Figure 1). CPK levels were normal. During that same afternoon the blood-borne cocci were identified as GAS. The diagnosis at this stage was GAS bacteraemia and necrotizing fasciitis of the chest wall. I.v. clindamycin (900 mg, three times a day) and ceftriaxone (2 g/day) were initiated and all other antibiotics stopped.

On the third day of hospitalization the patient was still febrile (38–38.5°C) and a markedly tender, swollen, and erythematous area was noted, for the first time, over the right lateral neck area. However, the patient looked improved, vital signs were stable, and the peripheral white cell count was down (13 000/mm³, with no young cells). Surgical intervention, with debridement of the chest wall and neck area, was felt to be too mutilating for this patient and as a final non-invasive therapeutic resort i.v. gammaglobulin (Omr-IgG-am 5% i.v., Omrix, Israel; 0.4 g/kg/6 h) was given.

On the following day, there was a marked improvement in the patient’s condition. She was afebrile, and both the chest wall tenderness and neck swelling were far better. I.v. gammaglobulin, at the same dose, was given for a second consecutive day. Debridement was felt to be unwarranted at this stage.

Improvement continued over the following few days. Chest wall pain resolved and full shoulder movements returned. Clindamycin was stopped after 9 days, and the patient was discharged after 14 days (having lost 4 kg body weight, but with a rising serum albumin level). Renal function remained excellent and ‘triple therapy’ could be re-introduced. Currently, 3 months after this acute infectious illness the patient is doing well. In retrospect, the patient mentioned that she had shaved her axillary areas 2–3 days prior to admission.

**Discussion**

Infection by GAS is the most common cause of bacterial pharyngitis, and can also be responsible for cellulitis, erysipelas, rheumatic fever, and glomerulonephritis. GAS bacteraemia is on the increase over the last 20 years, especially in the young adult population [1]. An important portal of entry is skin trauma (i.v. drug abusers, burns, herpes zoster infections), and HIV-infected patients are far more prone to GAS bacteraemia than the general population [2].

GAS can lead to fulminant disease for a number of reasons. First, the filamentous M-protein, anchored to the cell membrane, has antiphagocytic properties. Secondly, GAS is capable of producing pyrogenic exotoxins (‘superantigens’). These exotoxins can bind to a specific segment of the T-cell receptor, causing an overwhelming T-cell production of TNFα, IL-1, and IL-6 and subsequent tissue destruction, organ failure, and the toxic shock syndrome [3].

Necrotizing fasciitis complicating GAS bacteraemia (‘streptococcal gangrene’) is a toxic infection of the subcutaneous tissue that results in the progressive destruction of both fascia and fat. It is associated with a mortality rate of 30–40%. Unexplained severe pain and tenderness, with a conspicuous absence of inflammatory signs, is characteristic of GAS fasciitis [4]. Erythema and bullae of the overlying skin are late signs, indicating extensive disease. Early diagnosis is dependent on an accurate bacterial identification and CT/MRI to show extent of the soft tissue involvement. Fine needle aspiration is not needed to confirm diagnosis. An overlap exists between fasciitis and myositis, but myositis causes muscle to become exquisitely tender and indurated, and can spread over several hours to contiguous muscle groups [5].

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**Fig. 1.** Axial non-contrast CT scan of the chest (mediastinal window) showing soft tissue density in the right axilla. There is increased thickness of the right periscapular musculature.
elevated serum CPK is a clue to the presence of myositis.

The therapeutic cornerstones in GAS bacteremia are a combination of antibiotics, early, aggressive and repeated surgical debridement of infected subcutaneous tissue and muscle, and the administration of i.v. gammaglobulin. GAS are susceptible to beta-lactam antibiotics, but penicillin alone can fail in these patients because of the presence of a large inoculum size and because GAS has an ability to reduce bacterial expression of penicillin binding proteins during their ‘stationary growth phase’ [6,7]. On the other hand, clindamycin has an efficiency not affected by the inoculum size, inhibits both M-protein and exotoxin productions and is, therefore, highly recommended at the earliest suspicion of GAS bacteremia [4].

Surgical attempts to remove all necrotic tissue and fascia and should be performed at an early stage of the disease. Sudarsky et al. [8] argue that further surgery should be undertaken 24 h after initial exploration, but, at the very least, repeated debridement must be considered in all patients who fail to improve after their initial surgery.

I.v. gammaglobulin contain neutralizing antibodies against the circulating ‘superantigens’, and are capable of reducing plasma levels of TNF-a and IL-6 in these patients [9–11]. Information regarding the efficacy of i.v. gammaglobulin in GAS bacteremia was scarce until the recent publication of the Canadian Streptococcal Study Group in 1998 [11–14]. In that work, Kaul et al. [11] compared survival in 21 consecutive patients with Streptococcal toxic shock syndrome given i.v. gammaglobulin to that of 32 control patients who did not receive i.v. gammaglobulin. Thirty-day survival for i.v. gammaglobulin treated patients was 67%, as compared with only 34% in the control patients. The odds ratio for survival associated with i.v. gammaglobulin therapy was 8.1 (95% confidence interval, 1.6–45; \( P = 0.009 \)).

This observed patient highlights a number of important points in the diagnosis and management of GAS bacteremia, complicated by fasciitis. Axillary hair shaving or i.v. cannulation should be performed with care in immunosuppressed patients. Beware of the toxic and feverish patient who complains of severe pain, yet the physical examination confusingly does not reveal positive signs. Dual antibiotic therapy combined with i.v. gammaglobulin may lead to cure without surgical intervention, even if i.v. gammaglobulin is not given immediately [12]. As always, however, a single case report does not provide absolute proof of the efficacy of i.v. gammaglobulin therapy in this patient, but i.v. gammaglobulin therapy should be considered as a possible therapeutic agent in all patients with GAS bacteremia.

References


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