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Clinical Report

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Serum sickness following rabbit anti-thymocyte globulin for acute vascular renal allograft rejection

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Abstract
A simultaneous pancreas–kidney transplant recipient developed serum sickness manifesting with severe upper limb allodynia, arthralgia and myalgia 17 days following rabbit anti-thymocyte globulin (rATG) infusion for biopsy-proven vascular rejection. Rapid resolution of symptoms followed treatment with high-dose glucocorticoids. rATG is increasingly favoured over equine ATG in solid-organ transplantation, and although rATG has a superior safety profile, it is important to maintain a high index of suspicion for serum sickness.

Keywords: anti-thymocyte globulin; serum sickness; solid-organ transplant

Background

Over the last decade, rabbit-derived anti-thymocyte globulin (ATG) has been increasingly used in solid organ transplantation (SOT) to treat vascular rejection. Rabbit ATG (rATG) is a polyclonal antibody generated following the immunization of rabbits with human thymocytes, which target T-cell surface markers causing apoptosis and prolonged T-cell depletion [1]. Animal-derived therapeutic agents may be associated with serum sickness, a systemic hypersensitivity reaction mediated by circulating antibodies targeting foreign antigens. The antigen–antibody complex fixes complement and activates leucocytes, causing widespread tissue injury. Here, we present a case of serum sickness in an SOT recipient following the administration of rATG.

Case report

A 48-year-old patient presented with an unexplained rise in serum creatinine and lipase 10 months following simultaneous pancreas–kidney transplantation. The donor organs were a 3/6 human leucocyte antigen (HLA) antigen mismatch. A number of anti-HLA antibodies were detected on luminex single-bead antigen testing including a weak donor-specific antibody to A*02:01 (MFI 615). Primary graft function was observed, and immunosuppression with tacrolimus, mycophenolate mofetil and prednisolone was instituted. The early post-operative course was complicated by *Campylobacter jejuni* colitis and ureteric-stent-associated coagulase-negative *Staphylococcus* sepsis, the latter requiring a prolonged course of antibiotics. A protocol renal biopsy at 3 months was unremarkable.

A renal biopsy performed at the time of presentation confirmed borderline acute T-cell-mediated rejection with patchy tubulitis. Treatment with oral prednisolone resulted in only a transient improvement in serum creatinine and lipase. A repeat biopsy revealed acute vascular rejection (Type II) with changes suspicious for acute T-cell-mediated interstitial rejection. rATG was commenced at 3 mg/kg/day. The dose was reduced to 1.5 mg/kg/day after 3 days due to severe neutropaenia and ceased after a further 3 days. A single dose of granulocyte colony-stimulating factor (480 μg) was administered for persistent neutropaenia at a Day 10 post-initial dose of rATG.

Seventeen days following the first rATG dose, he presented with line-associated left arm superficial vein thrombosis and was commenced on intravenous flucloxacillin and therapeutic enoxaparin. Two days later, he became febrile and developed polyarthralgias involving shoulders, arms and back, resulting in near-complete immobility. Bilateral temporomandibular joint pain was striking. Clinical examination revealed severe allodynia in upper limbs bilaterally, rendering a complete neurological examination impossible. Limited lower limb examination showed preserved distal power and down-going plantars. There was no photophobia, neck stiffness or clouding of conscious state. An indwelling catheter was inserted for urinary retention. Antibiotic coverage was expanded to include vancomycin and ceftazidime; a ketamine infusion and morphine patient-controlled analgesia were commenced.

Laboratory data revealed a raised white cell count (WCC 17.4×10^9/L, range $4–11 \times 10^9$/L), neutrophilia (14.3×10^9/L; range $2–7.5 \times 10^9$/L) and elevated inflammatory markers (erythrocyte sedimentation rate 77 mm/h [<13 mm/h], C-reactive protein 148 mg/L [<5 mg/L]). Autoimmune and septic screen, including three sets of

blood cultures, were negative. Creatinine kinase levels were non-elevated. An urgent spinal MRI (magnetic resonance imaging) excluded an epidural abscess or paravertebral collection. A whole-body technetium^{99} bone scan revealed non-specific diffuse increased uptake surrounding both shoulders. Small collections in both shoulder joints were confirmed on ultrasound but repeated aspirations under imaging were unsuccessful.

Given the previous exposure to *C. jejuni* and concerns regarding neurological involvement, a single dose of intravenous immunoglobulin (0.4 mg/kg) was administered. Anti-GQ1b and anti-GM1 antibodies for the Guillain–Barre syndrome were negative. The patient deteriorated with ongoing fevers, worsening pain and increasing WCC up to 58.4×10^9/L. In the absence of compelling evidence for infection and the suspicion of serum sickness, he was commenced on high-dose prednisolone 60 mg/day, with a marked improvement of his symptoms within 24 h and was moving independently 3 days later.

Discussion

rATG is increasingly favoured over equine ATG, given its efficacy and superior safety profile [2]. To our knowledge, this is the first reported case of serum sickness post-rATG in an SOT recipient in Australia.

Serum sickness is classically described as a constellation of fever, rash, arthritis and glomerulonephritis [3], but there are no universal diagnostic criteria. Several case series have noted arthralgias, joint effusions and trismus to be prominent features, all which were observed in this case [4–6]. The most striking presenting feature in this case was that of severe allodynia necessitating the use of potent intravenous analgesics and markedly elevated WCC. Snow *et al.* [7] described a small case series of patients with serum sickness, where synovial fluid analysis demonstrated high inflammatory indices, corresponding with elevated serum WCC. Other reports have noted a significant prevalence of abdominal and cutaneous findings [4, 5, 7, 8], which were absent in this case. Neurological involvement, although reported [9], is uncommon.

Serum sickness classically occurs 7 to 14 days post-exposure, correlating with antibody class switching from IgM to IgA; however, in renal allograft recipients, it has been reported up to 30 days post-rATG exposure [6, 7]. Such a delay in presentation may be explained by ongoing immunosuppressive therapy.

The diagnosis of serum sickness is a clinical one with biochemical changes providing supportive evidence. Inflammatory markers may be raised but are often unhelpful in differentiating this from other diagnoses. Complement levels may be either elevated or depressed [6, 7]. Acute kidney injury is commonly seen; however, interpretation of renal function in this case was confounded by the recent history of graft rejection. Some series have used anti-heterologous antibody titres to aid diagnosis [5, 10].

Treatment of ATG-induced serum sickness involves high-dose corticosteroids or plasmapheresis in steroid-resistant patients [5]. Some have used plasmapheresis as a first-line therapy [11]. There are no proven methods of predicting serum sickness development. As in our patient, serum sickness can occur independent of acute hypersensitive reactions to rATG. Prin Mathieu *et al.* [12] measured ATG immunoglobulin levels pre- and post-first dose of ATG: they found that 8.9% of the patients had pre-dose antibodies, with sensitization increasing rapidly to 71% post-dose, but found no correlation between pre-immunization and occurrence of serum sickness. Another case series observed an association between previous rabbit exposure (raising or ingesting rabbit) and increased risk of serum sickness after *de novo* exposure to rATG [6].

The incidence of serum sickness varies depending on the antigen, with most reports citing a frequency of 1.6–7.5% in SOT recipients receiving rATG [4, 5, 7]. With an increasing use of rATG within Australia, it is anticipated that more cases of serum sickness will emerge. Clinicians need a high index of suspicion for serum sickness to enable prompt treatment with corticosteroids, which leads to rapid and permanent symptom resolution.

Conflict of interest statement. None declared.

References

1. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med* 2004; 351: 2715–2729
2. Chang SH, Russ GR, Chadban SJ *et al*. Trends in adult post-kidney transplant immunosuppressive use in Australia, 1991–2005. *Nephrology (Carlton)* 2008; 13: 171–176
3. Von Pirquet CF, Schick B. *Serum Sickness*. Baltimore: Williams & Wilkins, 1951
4. Buchler M, Hurault de Ligny B, Madec C *et al*. Induction therapy by anti-thymocyte globulin (rabbit) in renal transplantation: a 1-yr follow-up of safety and efficacy. *Clin Transplant* 2003; 17: 539–545
5. Tanriover B, Chuang P, Fishbach B *et al*. Polyclonal antibody-induced serum sickness in renal transplant recipients: treatment with therapeutic plasma exchange. *Transplantation* 2005; 80: 279–281
6. Boothpur R, Hardinger KL, Skelton RM *et al*. Serum sickness after treatment with rabbit antithymocyte globulin in kidney transplant recipients with previous rabbit exposure. *Am J Kidney Dis* 2010; 55: 141–143
7. Snow MH, Cannella AC, Stevens RB *et al*. Presumptive serum sickness as a complication of rabbit-derived antithymocyte globulin immunosuppression. *Arthritis Rheum* 2009; 61: 1271–1274
8. Bielory L, Gascon P, Lawley TJ *et al*. Human serum sickness: a prospective analysis of 35 patients treated with equine antithymocyte globulin for bone marrow failure. *Medicine (Baltimore)* 1988; 67: 40–57
9. Pham PT, Pham PM, Miller JM *et al*. Polyclonal antibody-induced serum sickness presenting as rapidly progressive descending paralysis. *Transplantation* 2007; 83: 1657
10. Lundquist AL, Chari RS, Wood JH *et al*. Serum sickness following rabbit antithymocyte-globulin induction in a liver transplant recipient: case report and literature review. *Liver Transpl* 2007; 13: 647–650
11. Christiaans MH, van Hooff JP. Plasmapheresis and RATG-induced serum sickness. *Transplantation* 2006; 81: 296
12. Prin Mathieu C, Renoult E, Kennel De March A *et al*. Serum anti-rabbit and anti-horse IgG, IgA, and IgM in kidney transplant recipients. *Nephrol Dial Transplant* 1997; 12: 2133–2139

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