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CASE REPORT

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Guillain–Barre syndrome after antithymocyte globulin administration in a kidney transplant recipient: A case report and literature review

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Key Clinical Message

This report describes a rare case of developing Guillain–Barre syndrome (GBS) following receiving rabbit antithymocyte globulin (ATG) after kidney transplantation to prevent acute allograft rejection in a 34-year-old man. The patient presented severe pain in the right temporomandibular joint, fever, chills, myalgia, polyarthralgia, and bone pain. Twelve hours later, he developed quadriplegia, paresthesia, and a limited range of active motions in all extremities. No antecedent viral or bacterial infection was identified. The EMG/NCV evaluation displayed acute inflammatory sensory-motor polyneuropathy. After the administration of GBS treatment, the neurologic symptoms started to improve. Over a few days, the reflexes came back completely, and the patient was able to walk. To our knowledge, this is the second case report of ATG-related GBS after kidney transplantation.

KEYWORDS

antilymphocyte serum, antithymocyte globulin, Guillain–Barre syndrome, kidney transplantation, polyneuropathies

1 | INTRODUCTION

Guillain–Barre Syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy, accounting for an estimated 100,000 new annual cases worldwide.[1] It is typically characterized by progressive ascending symmetrical weakness and areflexia, tending to reach severe neurological involvement up to 3 weeks after initial symptoms.[1,2]

Rabbit or equine antithymocyte globulin (ATG) is an immunosuppressive drug used in kidney transplant recipients (KTRs) to prevent acute rejection by reducing cytotoxic T cells. The decreased T-cell response induced by ATG may increase the likelihood of autoimmune diseases such as GBS. Previously, only one patient was reported to develop GBS after ATG treatment after a renal transplant.[3] Here, we report a rare case of ATG-related GBS in a 34-year-old KTR 7 days after receiving the last dose of ATG.

2 | CASE REPORT

A 34-year-old man suffering from end-stage renal disease (ESRD) due to reflux nephropathy was admitted to our hospital for a kidney transplant. The patient had a history

of dialysis over the past 11 months and a total parathyroidectomy 10 months ago. The transplantation from a deceased donor was performed on the first day of admission. Afterwards, the patient received an intravenous (IV) methylprednisolone 1000 mg pulse, and prednisone 1 mg/kg was started. Mycophenolic acid (360 mg in the morning and 720 mg at night) and tacrolimus (2 mg in the morning and 3 mg at night) were also administered to prevent rejection. Moreover, a total of 400 mg (6 mg/kg) of IV rabbit ATG was administered over the next 6 days (two daily doses of 100 mg and four doses of 50 mg).

The primary response to renal transplantation was promising. The measurement of serum creatinine (Cr) revealed a daily decrease (from 11.8 to 1.26 mg/dL), no delayed (DGF) or slow graft function (SGF) was observed, and the urinary output was adequate. As the patient was improving, the prednisone dosage was reduced gradually to 15 mg/day. Seven days after the last dose of ATG, the patient suddenly complained of severe pain in the right temporomandibular joint, heaviness, and soreness in his right arm and hand. Two hours later, the patient developed fever (38.4°C), chills, myalgia, and bone pain. These symptoms were followed by severe arthralgia in the right shoulder, both wrists, both ankles, and both knees.

A physical examination revealed wheal-like lesions on both arms. No erythema and swelling were observed in the joints. Chvostek's and Trousseau's signs were negative. Other examination findings were also unremarkable. Fever and chills recurred hours later. The Doppler ultrasound of the transplanted kidney demonstrated no occlusion, and the resistive index (RI) was 0.54. The Doppler ultrasound of the extremities was normal. Infectious service consultation and a full sepsis work-up were performed. Urine culture (U/C) and blood culture (B/C) were sent. Chest x-ray and Cytomegalovirus (CMV) polymerase chain reaction (PCR) tests were done, and empirical IV meropenem 1 g (twice a day) and IV vancomycin 1 g (daily) were started. An IV methylprednisolone 250 mg pulse was administered. Oseltamivir 75 mg tablet (twice a day) was also prescribed to cover probable influenza. U/C, B/C, and CMV PCR were negative, and the chest x-ray was normal. The blood level of tacrolimus was 7.2 ng/mL (therapeutic range: 5–20 ng/mL).

Twelve hours later, the patient developed quadriplegia, paresthesia, and a limited range of active motions in all extremities. There were no accompanying symptoms, such as dysphagia, respiratory distress, diarrhea, vomiting, cough, and coryza. The examination showed areflexia in all extremities, and the Babinski sign on both sides was neutral. No sensory level was detected for paresthesia. The neurology service examined the case and suspected GBS. Accordingly, three sessions of plasmapheresis (every other day), IV methylprednisolone 250 mg pulse (daily for 3 days), intravenous immunoglobulin therapy (IVIG) 15 mg (daily for 2 days), and gabapentin 100 mg tablet (three times a day) for myalgia were administered. Cervical and brain magnetic resonance imaging (MRI) and electromyography and nerve conduction velocity (EMG/NCV) for all extremities were also performed. MRI findings were unremarkable. EMG/NCV displayed acute inflammatory sensory-motor polyneuropathy. Laboratory findings revealed a C3 of 62 mg/dL (normal range: 75–175 mg/dL) and a C4 of 18 mg/dL (normal range: 16–48 mg/dL).

After the administration of GBS treatment, the myalgia and neurologic symptoms started to improve. Over a few days, the reflexes came back completely, and the patient was able to walk. The blood level of tacrolimus measured 8.0 ng/mL before discharge. Finally, the patient was discharged with prednisone 25 mg daily, mycophenolic acid (360 mg in the morning and 920 mg at night), tacrolimus (2 mg in the morning and 3 mg at night), trimethoprim/sulfamethoxazole 400/80 mg daily, amlodipine 5 mg daily, valganciclovir 900 mg daily, and calcium/vitamin D3 500 mg/400 IU.

3 | DISCUSSION

GBS is believed to be associated with an antecedent illness caused by inflammation through a mainly T cell-mediated autoimmune mechanism or a clinical condition with immune dysfunction.[4,5] In most patients, a viral or diarrheal infection, commonly caused by CMV or *Campylobacter jejuni*, preceded the illness, followed by neurological symptoms. Prior CMV infection is the most common viral cause of GBS, presented in 66% of patients.[2,6] Immunosuppressed individuals, including solid organ transplant recipients, are more prone to infections, resulting in higher mortality and morbidity than the general population.[7,8] Although GBS is rare in solid organ transplant patients, CMV-related GBS has been previously reported in heart, liver, and renal transplant recipients.[6,9,10] A systematic review of 17 cases of GBS after renal transplant by Ostman et al. revealed that the most common antecedent infection in KTRs was caused by CMV, with 12 cases involved.[11] Acute infection, re-activation, and re-infection of CMV can prompt the GBS. The time between the kidney transplantation and the initial symptoms of CMV-related GBS ranged from 27 days to 7 years.[11,12] In our case, the neurological symptoms initiated about 2 weeks after the kidney transplant. We examined the patient for an antecedent viral or bacterial infection, and U/C, B/C, and CMV PCR tests were all negative.

Organ transplant recipients receive an immunosuppressive regimen immediately after transplantation to prevent graft rejection or autoimmune diseases. These drugs are not believed to be a risk factor for the development of demyelinating polyradiculoneuropathy because there are reports that confirm their benefits in the treatment of GBS, or chronic inflammatory demyelinating polyneuropathy (CIDP), as well as the development of GBS after stopping these drugs such as steroids.[13] On the other hand, the incidence of GBS among this population is considerably lower than in the general population, which may be explained by the protective effect of immunosuppressive treatment against immune-mediated diseases.[11]

However, two cases of GBS associated with the calcineurin inhibitors cyclosporine and tacrolimus were previously reported in KTRs.[6,14] Cyclosporine was also related to GBS in a lung transplant recipient,[10] and tacrolimus was reported to be the cause of three cases of CIDP.[15] In this case, our patient tolerated tacrolimus, mycophenolic acid, and prednisone well without any significant adverse effects. The serum level of tacrolimus was within the normal range during the treatment. In addition, he was discharged on an immunosuppressive regimen including prednisone, mycophenolic acid, and tacrolimus and had no neuromuscular complaints at follow-up visits. All the facts together, the tacrolimus could not be the cause of GBS in our patient.

ATG seemed to reduce the cellular immune response by depleting cytotoxic T cells and by releasing hematopoietic growth factors.[16] Decreased cellular immunity due to impaired cytotoxic T cells, which generally limit B-cell activation but permit the development of hematopoietic progenitor cells, may increase the possibility of autoimmune disorders. Although there are reports of autoimmune disorders such as thyroid disease,[17] hemolytic anemia,[18] and fibrosing alveolitis[19,20] after ATG, only 2 cases of GBS after administration of ATG have been previously reported: one after renal transplantation[21] and the other in treating aplastic anemia.[13] Our patient received a total of 400 mg of ATG over 6 days, and the neurologic symptoms manifested 7 days after the last dose of ATG. The temporal ratio and beginning of the patient's symptoms after administration of ATG, as well as an absence of other causes such as antecedent infection, strengthened the clinical suspicion of ATG-related GBS, which could be associated with serum sickness.

Consequently, ATG treatment in renal transplant recipients could be associated with the development of GBS. Physicians should be aware of this significant complication of ATG administration in KTRs and think about autoimmune polyneuropathies like GBS or CIDP when the patients develop neurological symptoms.

AUTHOR CONTRIBUTIONS

Farnaz Tavakoli: Conceptualization; investigation; writing – review and editing. **Davood Dalil:** Data curation; investigation; software; supervision; writing – original draft; writing – review and editing. **Fatemeh Yaghoubi:** Conceptualization; investigation; project administration; writing – review and editing. **Seyyed Mohammad Hosseini:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

The Research Ethics Committee of Tehran University of Medical Sciences approved all procedures performed in the current case report with the approval number IR.TUMS.SHARIATI.REC.1402.057.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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