Abstract

Thymoglobulin is a rabbit-derived anti-thymocyte antibody directed at T-cells and commonly used for induction immunosuppression therapy in solid organ transplantation, especially in immunologically high risk kidney transplant recipients. Despite its frequent use and efficacy, the heterologous makeup of thymoglobulin can induce the immune system resulting in serum sickness which typically presents with rash, fever, fatigue, and poly-arthralgia in the weeks following drug exposure. ATGAM is another anti-thymocyte antibody, targeting the same epitopes, but differs from thymoglobulin by the animal in which the preparations are generated (equine vs. rabbit). Herein, we present a case of a patient with a known history of thymoglobulin-induced serum sickness, who presented with evidence of acute cellular and vascular rejection at their 12-month post-operative visit. Given their immunologically high risk status, they were successfully treated with ATGAM with improvement in their rejection and kidney function. To the author’s knowledge, this is the first case report of successful administration of ATGAM in a patient with a documented history of thymoglobulin induced serum sickness, demonstrating a possible treatment option for acute rejection in patients with reactions to thymoglobulin.

Introduction

Antibody depleting therapy is now widely used in renal transplant medicine, both for induction therapy and the treatment of acute cellular rejection. In addition, antibody therapy allows for delayed exposure to nephrotoxic agents such as calcineurin inhibitors. Currently, thymoglobulin is the most commonly used induction agent in immunologically high risk renal transplant patients [1].Thymoglobulin is a polyclonal rabbit-derived antibody that causes lymphocyte depletion by acting at multiple antigenic sites, including molecules on the surface of T-cells and B-cells [2]. Following the use of antibodies for induction therapy, patients are typically given maintenance therapy with tacrolimus, mycophenolate and commonly, steroids. Despite data that shows fewer rejection and better graft survival using antibody induction, serious side-effects of thymoglobulin have been reported, including cardiopulmonary decompensation, respiratory distress syndrome, hematologic disorders, and serum sickness.
Equine Anti-Thymocyte Globulin (ATGAM) administration in patient with previous rabbit Anti-Thymocyte Globulin (Thymoglobulin) induced serum sickness: A case report

Serum sickness classically occurs in the setting of exposure to heterologous (non-human) serum proteins causing deposition of antigen-antibody complexes in vessels or tissues, resulting in activation of the complement cascade and recruitment of immune cells, specifically neutrophils. The cardinal symptoms of serum sickness include rash, fever, fatigue, and poly-arthritis. Treatment is primarily supportive: antihistamines for rashes and pruritus, and acetaminophen for fevers and arthralgias. In more severe cases, short courses of glucocorticoids can be administered; or in steroid resistant cases, plasmapheresis can be used [3]. In the event that a medication is identified as the causal agent, it is recommended to discontinue and avoid that medication in the future.

ATGAM is an anti-thymocyte globulin that differs from thymoglobulin by being produced in horses rather than rabbits. Typically, thymoglobulin is preferred over ATGAM in the U.S. as thymoglobulin has been associated with higher event free survival [4] and provided significant cost savings of when compared to ATGAM [5,6]. We present a case of a highly sensitized transplant recipient with prior serum sickness from thymoglobulin with severe vascular rejection.

Case Presentation

A 27 year-old G0P0, 5 foot, 130 lb, Caucasian woman presented with a chief complain of joint/body pains and weakness. She had a known history of ESRD from medullary cystic kidney disease, had failed a living unrelated donor kidney transplant (2008-2012) due to rejection and was now 10 days following a second (deceased donor) kidney transplantation. For her first transplant, she was given thymoglobulin for induction without any immunological adverse reactions. For her second transplant, she was also inducted with thymoglobulin, but only completed 2 doses (1.5 mg/kg each dose) because of neutropenia. After discharge from the hospital, she had been compliant with her medications. On post-transplant day 10, she presented to the ED with upper and lower extremity pain. On the prior day she had perioral swelling and pruritis of the upper and lower extremities that improved with Benadryl. She denied any tongue swelling, difficulty breathing, or rash. She described RLE>LLE sharp pain from knee to ankle that was worse with weight bearing, and no obvious swelling or redness. In addition, she had LUE pain that was aggravated by touch and movement and painful hands with a constant cramping sensation. Other symptoms included sweats, fevers, flushing, malaise, weakness, and night sweats. She denied cough, rhinorrhea, abdominal pain, or changes to urinary function.

Her outpatient medication list included Vitamin D3 2000 U daily, Acyclovir 400 mg BID, Amlodipine 10 mg daily, Aspirin 81 mg daily, Calcium Carbonate (200 mg elemental) TID, Clonidine 0.1 mg TID, Famotidine 20 mg BID, Mag ox 400 mg BID, Multivitamin daily, Mycophenolate 750 mg BID, Phosphate 750 mg TID, Prednisone 20 mg daily, Tacrolimus 5 mg BID, and Trimethoprim-Sulfamethoxazole 80-400 mg daily. Other medications included docusate 8.6-50, Ondansetron 4 mg BID, Oxycodone 5-15 mg QID, and Polyethylene glycol 17 mg to be taken on an as needed basis.

The admission physical exam was notable for the following vitals: Temperature 102.2F, BP 114/70, HR 113, respirations of 18, and 100% O2 saturation on room air. She was alert and oriented, talking and breathing comfortably with no evidence of facial or oral edema, no wheezes or pulmonary crackles. Her abdomen was appropriately tender around the surgical site, but was otherwise benign. Though able to move all extremities equally, she had diminished grip, wrist, hip, knee, and ankle strength (4/5) due to pain and refused to stand. The initial laboratory workup showed a WBC of 11.02 K/cu mm, neutrophil predominance at 86%, hemoglobin 9.1 g/dL, hematocrit 27.1%, platelet count of 138 K/cu mm. Her chemistry panel showed potassium of 5.6 mmol/L (sample was hemolyzed), creatinine 0.86 mg/dL (baseline), calcium of 8.3 mg/dL, ionized calcium of 1.23, and an albumin of 3.4 g/L. The AST at 56 U/L, but remainder
of the liver panel was otherwise unremarkable. Her urine was notable for moderate blood and 100 mg/dL protein. The LDH, lactic acid level and creatinine kinase were normal. Cultures of the blood and urine were negative. She had a low CD3 at 144 per mm³, but normal CD4 count. Her EKG, CXR and renal ultrasound with doppler were unremarkable. Given her persistent symptoms and concern for serum sickness, she was treated with a single plasmapheresis dose and started on a 3 day course of prednisone 100 mg/day while awaiting culture results. Pain and symptoms resolved rapidly with treatment and her infectious workups were negative.

Over the next months, her renal course was complicated by BK viremia and recurrent rejection despite being on maintenance therapy with steroids, mycophenolate and tacrolimus. Her 12 month post-transplant surveillance biopsy revealed evidence of acute cellular and vascular (CCTTII) rejection which prompted immunosuppressive augmentation. Given her history of serum sickness with rabbit anti-thymocyte globulin, she was given equine anti-thymocyte globulin (ATGAM) 15 mg/kg/day x 7 days and a steroid pulse. The goal was to complete 7-10 days of ATGAM, but the 8th dose was reduced to 500mg and discontinued after in the setting of thrombocytopenia [73k]. During administration there was no evidence of serum sickness, or hypersensitivity reactions. Following ATGAM administration she had a return to the baseline serum creatinine of 0.7 mg/dL and a follow-up biopsy after 1 month showed significant improvement in inflammation and decreased evidence of rejection when compared to the pre-ATGAM biopsy.

Discussion

Induction therapy with anti-lymphocyte antibodies has many benefits including a reduced risk of acute rejection and longer allograft survival (7-10). However, the use of non-human antibodies carries risk of alloimmunization against the non-human immunoglobulins. Serum sickness usually results following foreign antigen presentation in the setting of delayed clearance and primary antibody response [11]. Common presentation includes fevers (>101°F) with arthralgias 1-2 weeks after therapy without other overt signs or symptoms of infection or allergic reaction.[11] Other common presentations include persistent arthralgias or acute renal failure, erythematous morbilliform rash, or less commonly neurological involvement [12].

In patients who develop serum sickness, treatment is highly effective in reversing all symptoms, thus emphasizing the importance of timely recognition and accurate diagnosis. Furthermore, the 1-2 week post therapy initiation timeline is helpful given the overlap between medication side effects and serum sickness symptoms. Diagnosis can be difficult if not already on the differential secondary to lack of diagnostic and laboratory criteria. Lundquist et al have attempted to gather presenting symptoms and formulate four major criteria including: 1) >7 days since initial drug (thymoglobulin) administration, 2) Persistent high fevers (>101°F), 3) Persistent arthralgias/arthritis, and 4) Positive heterologous antibodies on ELISA. Minor criteria included (+/-) acute renal failure, rash, trismus, and low serum complement [13]. Other laboratory data such as inflammatory markers are not included because while they may be elevated, they are not specific enough.

Risk factors for development of serum sickness include previous history of serum sickness, exposure to animal derived serum, injection with large quantities of antiserum, and those with frequent exposure to horses or rabbits as these conditions pose possible exposure to antigens contained within anti-thymocyte preparations [13].

The diagnosis of serum sickness in our patient was made based on the temporal relationship between symptoms onset, thymoglobulin administration, her clinical manifestations, laboratory studies, as well as the absence of other infectious or immunologic causes to explain her symptoms. She developed serum sickness following
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her second exposure to thymoglobulin (rabbit protein) and due to the occurrence of cell mediated rejection with endothelialitis, she required stronger immunosuppression. This is the setting in which we would normally use Thymoglobulin and instead chose to use ATGAM (horse protein). We suspected that there would be no cross-reactivity of her anti-rabbit antibodies with the horse immunoglobulin. In fact, she did not have a reaction to ATGAM and it helped to reverse her rejection, as evidenced by the followup biopsy. A history of serum sickness is known to be a risk factor for subsequent reactions [14] and in this case a change in species appeared to be protective.

Regan et al investigated the rates of sensitization based on IgG levels and found that sensitizations levels in those who received thymoglobulin were similar to those who received ATGAM; however, ATGAM sensitization lasted longer than thymoglobulin when patients were compared at 90 days [15]. Despite the patient’s history of serum sickness, she tolerated ATGAM well.

There are multiple case reports of serum sickness with thymoglobulin; however, there are no case reports to our knowledge documenting the successful administration of ATGAM in a patient with documented thymoglobulin induced serum sickness. Given the successful administration, there may be a role for ATGAM for the treatment of severe rejection in patients with thymoglobulin associated serum sickness.

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