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Serum Sickness After Treatment With Rabbit Antithymocyte Globulin in Kidney Transplant Recipients With Previous Rabbit Exposure

Raghavender Boothpur, MD[1], **Karen L. Hardinger, PharmD**[2], **Rebecca M. Skelton, RN**[3], **Brunilda Lluka**[3], **Matthew J. Koch, MD**[3], **Brent W. Miller, MD**[3], **Niraj M. Desai, MD**[4], and **Daniel C. Brennan**[3]

[1] Barnes-Jewish Hospital, St. Louis, MO

[2] The Department of Pharmacy Practice, University of Missouri-Kansas City, Kansas City, Missouri

[3] The Department of Medicine, Washington University School of Medicine, St. Louis, MO

[4] Department of Surgery, Washington University School of Medicine, St. Louis, MO

Abstract

Serum sickness after rabbit anti-thymocyte globulin (ATG) has a reported incidence of 7–27% in kidney transplant patients. We describe four patients with previous exposure to rabbits who developed serum sickness after primary rabbit ATG induction. All patients presented with jaw pain. Three of four patients treated with plasmapheresis and steroids had prompt recovery and one patient treated with steroids had slower recovery. We performed a telephone interview of 214 patients contemporaneously transplanted between November 2006 and July 2008 regarding rabbit exposure. More than half of the patients had some type of previous rabbit exposure. There was a suggestion that patients with serum sickness were more frequently exposed to rabbits than those without. Jaw pain appears to be a hallmark symptom and treatment with plasmapheresis and steroids relieves symptoms more rapidly than steroids alone.

Introduction

Polyclonal antibodies are widely used in transplantation. They are prepared from horses and rabbits and can elicit an antibody response. In combination with complement, the foreign antigen and responding antibody can form circulating immune complexes that may deposit in tissues to cause serum sickness. Serum sickness is diagnosed clinically and has a reported incidence of 7–27% in kidney transplant patients 7–14 days after initiation of anti-thymocyte globulin (ATG)[1]. The reported incidence does not discriminate between use for induction or treatment of rejection or whether prior animal contact predisposes to serum sickness. We report four cases of serum sickness after induction with rabbit ATG (Thymoglobulin, Genzyme) without prior exposure to rabbit ATG. Each had remote exposure to rabbits prior to receiving rabbit ATG. To determine whether a prior history or type of rabbit exposure was predictive of

Corresponding Author: Daniel C. Brennan, MD, Washington University School of Medicine, 660 S. Euclid Avenue, Renal Division/ Campus Box 8126, St. Louis, Missouri 63110, Phone: 314-362-8351, Fax: 314-362-2713, brennan@wudosis.wustl.edu.

serum sickness, we queried patients, transplanted contemporaneously, regarding a history of exposure to rabbits.

Case Reports

Case 1

A 24 year-old Filipino woman received a living unrelated kidney transplant from her husband for endstage renal disease (ESRD) secondary to immunoglobulin (Ig) IgA-nephropathy. Induction immunosuppression consisted of rabbit ATG 2 mg/kg daily for three days and methylprednisolone 500 mg. Ten days after transplant she was admitted with fleeting diffuse skin rash with wheals, jaw, neck, bilateral knee, wrist, and elbow pain. She had a pet rabbit as a child. Her physical exam was remarkable for tenderness and decreased range of movement in affected joints. Laboratory data were remarkable for a white blood cell (WBC) count of 26,000/mm^3. She was diagnosed with serum sickness and treated with two sessions of plasmapheresis and methylprednisolone 500 mg intravenously with prompt resolution of her symptoms.

Case 2

A 20 year-old white woman with ESRD secondary to cystinosis and Fanconi syndrome who received a living unrelated kidney transplant 10-days prior to admission presented with arthralgias, jaw pain, fever, chills, nausea. She received induction immunosuppression with three doses of rabbit ATG (2 mg/kg/dose). She had extensive exposure to rabbits through raising and ingestion of rabbit. Her physical examination was remarkable for tenderness over multiple large joints. Laboratory data showed a WBC count of 17,600/mm^3. She was diagnosed with serum sickness. She received three plasmapheresis-treatments with prompt resolution of her symptoms. After discharge her serum complement C3 and C4 levels, obtained on admission, were 74 units (normal 83–185) and 15 units (normal 12–54), respectively.

Case 3

A 37 year-old white man with ESRD secondary to IgA-nephropathy who received a living unrelated kidney transplant 14-days prior to admission presented with acute onset of bilateral knee, hip, shoulder, back and jaw pain and myalgias. He received induction immunosuppression with three doses of rabbit ATG (2 mg/kg/dose) and methylprednisolone 500 mg. His social history was notable for contact with rabbits from hunting and ingestion. His physical exam showed limitation of range of motion in affected joints. Laboratory data showed WBC count of 29,500/mm^3. A diagnosis of serum sickness was made. He had prompt resolution of his symptoms after two plasmapheresis-treatments. After discharge his complement C3 and C4 levels, obtained on presentation, were found to be 82.7 (normal 83–185) and 5.4 units (normal 12–54) respectively. His serum anti–rabbit IgG was 8 micrograms/mL (normal less than 7).

Case 4

A 51 year-old white man with ESRD from IgA-nephropathy, who received a one-haplotype match living related transplant 25-days prior to admission, presented with acute onset of fever, jaw pain and bilateral hip and shoulder pain. Induction immunosuppression included 1 mg/kg of rabbit ATG initiated intraoperatively, 2 mg/kg of rabbit ATG post-operatively on days 1 and 2 and methylprednisolone 500 mg. He had a history of raising, hunting and ingesting rabbits. Pertinent positives on physical examination included limited range of motion of the affected joints. Laboratory data showed a WBC count of 19.5/mm^3. He was diagnosed with serum sickness and treated with 500 mg of methylprednisolone and discharged home on a

tapering dose of prednisone with gradual improvement in his symptoms. After discharge complement levels obtained at the time of presentation were found to be normal.

Discussion

Diagnosis of serum sickness is a clinical diagnosis. Symptoms include fever, arthralgia, lymphadenopathy and rash. Typically serum sickness affects multiple large joints, occasionally joints involving the spine, or the temporal-mandibular joint[2, 3]. One important finding is that serum sickness presented as jaw pain along with polyarthralgias in all patients.

The diagnosis is supported by detection of heterologous antibodies to horse or rabbit IgG,[4] which we investigated and found in one patient. In severe cases, low levels of complement C3 and C4 may be present. We obtained complement levels in 3 of the 4 patients and confirmed low complement levels in two. The heterologous antibody and complement levels were not available until after treatment and discharge. The fourth patient presented later, with less severe symptoms, and normal complement levels and was treated less aggressively with slower resolution of his symptoms. This supports that the diagnosis is made clinically and institution of therapy should begin before supportive evidence is available.

Serum sickness can be treated with high dose steroids or plasmapheresis. High-dose corticosteroids have side effects: glucose intolerance, weight gain, hypertension, poor wound healing, peptic ulcer disease, increased susceptibility for infections, and viral reactivation. Treatment with plasmapheresis was associated with prompt resolution of symptoms, supporting their use as first-line therapy[1, 5].

Risk factors for serum sickness include higher levels of heterologous protein, type of preparation and prior exposure to the antigen. Pre-induction anti-rabbit antibodies have been detected in approximately 10% of patients who never received polyclonal antibodies prior to testing[6, 7]. In the one patient in whom we measured anti-rabbit IgG, the level was elevated modestly. Complement levels were low.

To explore the relationship between prior rabbit exposure and serum sickness after treatment with rabbit ATG, we performed a telephone interview of 240 contemporaneous patients who underwent de novo transplants and rabbit ATG induction between November 2006 and July 2008, Of these 214/240 (89%) were able to be contacted. We estimated a sample size between 24–116 to provide 80% power with an alpha of 0.05 based on the published incidence of serum sickness of 17% ± 10% to determine an association with rabbit exposure[1]. The Fisher's exact test was used to evaluate all categorical variables. All statistical tests were two-tailed. This study was approved by the Washington University School of Medicine Human Research Protection Office.

One-hundred ten patients (51%) had some type of rabbit exposure with one or more of the following: 43 (20%) had rabbits as pets, 19 (9%) raised rabbits, 34 (16%) hunted rabbits and 48 (22%) had ingested rabbit. Serum sickness was significantly associated with having raised rabbits (1.0% no vs. 10.5% yes, P=0.04) or ingested rabbit (0.6% no vs. 6.3% yes, P=0.04). While any type of rabbit exposure (0% no exposure vs. 3.6% exposure, P=0.1), previously having pet rabbits (1.8% no vs. 2.3% yes, P=0.9) and hunting rabbits (1.1% no vs. 5.9% yes, P=0.1), were not associated with serum sickness.

Limitations are that we did not measure circulating immune complexes, anti-rabbit IgM or IgG antibody or serum complement levels in all patients with or without exposure to rabbits. There was no clinical indication to do so, and stored samples were not available for analysis.

Over the past 13 years we have induced over 1600 patients with rabbit ATG, and have diagnosed serum sickness after de novo exposure in 4, for a rate of 0.25%. Thus, the number needed to treat (NNT) to observe serum sickness would be 400. Our low rate of serum sickness compared to the published literature may be because we limited our analysis to de novo recipients of rabbit ATG, limited the dose of rabbit ATG (average 6 mg/kg) and duration (1–7 days) of exposure compared to higher accumulative doses (>10 mg/kg) and durations up to 21 days, which are regimens that have been used historically. We also start cyclosporine or tacrolimus by post-operative day 4 rather than delaying commencement of these agents as historically practiced when polyclonal induction is used.

In conclusion, more than 50% of kidney transplant patients at our center had a history of exposure to rabbits prior to transplantation. A history of raising or ingesting rabbits was associated with an increased risk of serum sickness after de novo exposure to rabbit ATG. Serum sickness is uncommon and does not warrant avoiding rabbit ATG even among those with a history of rabbit exposure. Jaw pain was common to all patients with serum sickness and should be elicited in the history. Treatment with plasmapheresis was rapidly effective and should be considered as first-line treatment for serum sickness after de novo exposure to rabbit ATG.

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