CLINICAL VIGNETTE

Antithymocyte Globulin Desensitization in a Rabbit Allergic Patient

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A 62-year-old male presented with hypoxic respiratory failure and progressive ground glass opacities on imaging. Past medical history includes interstitial lung disease due to chronic hypersensitivity pneumonitis status post bilateral lung transplant with coronary artery bypass, secondary hypogammaglobulinemia, type 2 diabetes, paroxysmal atrial fibrillation, history of cerebrovascular accident and prior deep vein thrombosis. The patient was empirically started on antibiotics given his immunosuppressed state, and pulmonary embolism was ruled out. He underwent bronchoscopy with bronchoalveolar lavage which was unremarkable for infection. However, the biopsy showed evidence of fibrosis and bronchiolitis obliterans syndrome. The lung transplant team was concerned for rapidly progressive rejection despite mycophenolate and tacrolimus. He was given three days of high dose methylprednisolone followed by oral prednisone. He persisted to have high flow oxygen requirements and underwent plasma exchange and four days of intravenous immunoglobulin. Despite this, he continued to have significant high flow oxygen requirements. Eventually, the lung transplant team recommended rabbit antithymocyte globulin (ATG) for suspected rapidly progressive rejection. Allergy & Immunology service was consulted as the patient has a reported rabbit allergy.

With regard to his rabbit allergy, the patient recalls his first clinical reaction twenty years ago with a pet rabbit. He held his rabbit and approximately thirty minutes after, he developed bilateral eyelid angioedema, itchy eyes and chest tightness. Several years ago he had hugged his son who had been playing with a pet rabbit and experiencing a near identical reaction with periorbital edema and chest tightness. Both reactions were treated with antihistamines, not epinephrine. The Allergy & Immunology service also inquired about horse allergy given the possibility of the use of horse antithymocyte globulin (ATG). The patient reported after horseback riding, eighteen years ago he had a significant asthmatic reaction necessitating nebulizer treatment.

The patient has a history of allergic rhinitis and asthma with sensitization to tree and grass pollens, cat, and dog. He also reports clinical reactions to rabbits and horses. He was on subcutaneous allergen immunotherapy for five years in 1990's. Since completing allergen immunotherapy, he has not used daily allergy or asthma medications other than after cat or dog exposures.

Given his history, skin testing was considered to rabbit ATG itself, and rabbit and horse antigens. The patient had no response to histamine skin prick control, rendering skin testing invalid. Pressing concern for treatment with ATG, serum IgE to rabbit was obtained before the lab would result. The prolonged high dose steroid therapy the patient received could suppress serum IgE testing. A multidisciplinary discussion was held between the lung transplant service, Allergy & Immunology service, and the inpatient pharmacy regarding rabbit ATG desensitization for use of rabbit ATG in lung transplant rejection. There were concerns regarding possible increased serum sickness reactions with horse ATG, and the patient's reported clinical history of horse allergy.

Risks of ATG desensitization including life-threatening anaphylaxis and cytokine release reactions were reviewed with the patient in addition to the benefits in the treatment for transplant rejection. Informed consent was obtained. With inpatient pharmacist input regarding the stability of rabbit ATG, minimal administration rates and consideration of prior desensitization protocols, a desensitization protocol was developed (Table 1). The patient was premedicated with cetirizine, famotidine, montelukast, and methylprednisolone and underwent successful desensitization over approximately eleven hours. The patient received an additional six days of ATG therapy per the lung transplant team with decreasing oxygen requirements and was discharged to an acute rehabilitation unit.

Discussion

Antithymocyte globulin (ATG) consists of polyclonal anti-lymphocyte immunoglobulin purified from rabbit or horse serum.[1] This immunoglobulin is directed against human T lymphocyte surface antigens which subsequently induces significant lymphocyte reduction.[1] ATG was used for induction of immunosuppression prior to stem cell transplant and renal transplant.[1,2] It has also been used as treatment for steroid refractory acute cellular rejection in lung transplant, and to prevent the progression of and possibly reverse the effects of chronic lung allograft dysfunction.[3,4]

While ATG is a valuable drug in transplant medicine, it is not without risks. ATG is from heterologous serum, and it carries significant risk for adverse reactions. Such reactions include type I hypersensitivity including anaphylaxis, cytokine release reactions with symptoms such as fever, chills, back pain, as well as hemolytic anemia or other cytopenias, and possible serum

sickness.[2] Though type I IgE-mediated anaphylactic reactions are rare, there have been fatal reactions to ATG reported.[1] Anaphylaxis has been reported to both equine-derived ATG, and rabbit-derived ATG.[5] The manufacturer for equine ATG recommends skin testing prior to administration on the package insert, as a positive skin test may suggest increased risk of systemic allergic reaction.[6] The insert notes to "seriously consider alternative forms of therapy" with a positive skin test.[6] However, the predictive value of pre-treatment skin test has not been established. Interestingly, the manufacturer for rabbit-derived ATG notes that the product is "contraindicated in patients with history of allergy or anaphylactic reaction to rabbit proteins or to any product excipients" but does not recommend pretreatment skin testing.[7] There is a reported case of severe life-threatening anaphylaxis to rabbit ATG that may have been prevented had investigation for rabbit sensitization been performed prior to administration.[1] In this case, a 24 year old male with an atopic history including allergic rhinitis and asthma, drug allergy to vancomycin and latex allergy, underwent renal transplant.[1] The patient received induction of general anesthesia. Forty-five minutes later, rabbit ATG was started with plans to be given over eight hours. However, three minutes into administration the patient developed significant hypotension, bradycardia, hypoxia and required epinephrine and chest compressions. The patient secondarily developed a generalized rash and wheezing. He was transferred to the ICU and transplant was deferred. The patient was subsequently hospitalized for allergy testing to determine the causative drug, though ATG was highly suspected. History obtained retrospectively noted he had symptoms of asthma and angioedema around rabbits. The patient underwent skin testing to all agents used in anesthesia induction which were negative, and additionally an intradermal test for colloid allergy was negative. He had a positive skin prick test to ATG, as well as to standardized extracts of rabbit and horse. Serum IgE to rabbit dander and rabbit serum proteins were also positive. The authors concluded that the patient had severe life-threatening anaphylaxis to rabbit ATG due to rabbit protein allergy.[1] This exemplifies the need for detailed history of atopy prior to ATG use, particularly regarding any history of reactions to rabbit and horse. It also implies that skin testing to both rabbit ATG and rabbit standardized antigen should be strongly considered prior to use of the drug, particularly in cases of atopy. With increasing prevalence of rabbit sensitization with rabbits as household pets, it is important to systematically investigate rabbit sensitization prior to the use of pharmaceutical products containing rabbit proteins.[1]

There are multiple cases of evaluation and desensitization to ATG, some more successful than others. For example, Northwestern University Allergy-Immunology Division reported four cases of evaluation for, and in some cases, desensitization to ATG.[2] Among the four reported cases, one patient who had prior successfully received ATG, subsequently had pretreatment skin testing with pseudopods at next admission, and given the positive skin test with the patient's medical comorbidities, desensitization was not pursued due to concern the patient may not tolerate anaphylaxis were it to occur. Another patient with aplastic anemia, desensitization was recommended following a positive skin test as benefits were determined to outweigh risks in this case. However, after the patient successfully tolerated intradermal, subcutaneous and intravenous injection portions of the desensitization, the patient developed erythema with papules and with attempt to increase the already slowed infusion rate, the patient developed anaphylaxis with hypotension, hypoxia and tachycardia, necessitating multiple doses of epinephrine, intravenous fluids, steroids, diphenhydramine and dopamine to maintain recovery.[2] The third case reported was a patient with aplastic anemia with a negative pretreatment skin test to ATG. However, developed both mixed IgE-mediated and symptoms of cytokine release syndrome within several hours of the first dose. Only one of the four patients evaluated for ATG managed to undergo eighteen hours of the dose-escalating desensitization protocol prior to developing allergic-like symptoms that necessitated stopping the infusion.[2] These cases illustrate the difficulties in evaluating ATG allergy and the risks associated with desensitization.

Our patient, had no response to histamine control on skin testing. This was likely due to prolonged high dose steroids and critical illness. Skin testing in the inpatient setting may lead to negative skin test responses for several reasons including systemic steroids, older age, use of histamine H2-receptor antagonists inpatient.[8] Because the patient had a clinical history strongly suggestive of rabbit allergy, and due to the inability to risk stratify with skin testing, the patient underwent desensitization to rabbit ATG.

Standard management of IgE-mediated drug allergies include the use of an alternative agent that is equally effective but immunologically unrelated to the culprit drug. If there is no equally effective alternative, standard desensitization protocols have been reported for many drugs including antibiotics and chemotherapy. Desensitization induces a temporary tolerance for a course of treatment.[9] There are few cases for desensitization to ATG given significant risks, and varying protocols based on dose, restrictions on administration rates and the length of time needed to provide varying doses. This case serves as an example of multidisciplinary cooperation to successfully deliver a high risk therapeutic to a high-risk patient. It emphasizes need to obtain a thorough history of atopy prior to administering either equine or rabbit ATG, and using this history and skin testing in risk stratification to determine how and if ATG should be administered.

TABLE 1. Antithymocyte globulin (ATG) continuous desensitization infusion protocol				
ATG concentration (mg/mL)	Rate (mL/hr)	Infusion time (mins)	Interval dose (mg)	Cumulative dose (mg)
0.0004	0.5	20	0.0001	0.0001
0.0004	1	20	0.0001	0.0002
0.0004	2	20	0.0003	0.0005
0.0004	4	20	0.0005	0.001
0.004	1	20	0.001	0.002
0.004	2	20	0.003	0.005
0.004	4	20	0.005	0.01
0.004	8	20	0.011	0.021
0.04	2	20	0.027	0.048
0.04	4	20	0.053	0.101
0.04	8	20	0.107	0.208
0.04	16	20	0.213	0.421
0.4	8	20	1.067	1.488
0.4	10	20	1.333	2.821
0.4	20	20	2.667	5.488
0.4	40	354.42	94.512	100

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