

Successful desensitization of a patient with aplastic anemia to antithymocyte globulin

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ABSTRACT

Antithymocyte globulin (ATG) is a polyclonal gamma immunoglobulin derived from either rabbit or equine serum that serves as therapy for aplastic anemia; however, ATG causes serum sickness in up to 70% and anaphylaxis in up to 5% of recipients. Intradermal (ID) skin testing has been the primary technique used to evaluate for a preexisting Gell and Coombs type I hypersensitivity reaction to ATG. There are no data reporting the predictive value of delayed reactions to ID testing on the risk of serum sickness. This study was designed to establish the importance of epicutaneous and ID skin testing before the administration of ATG through a case report and literature discussion. We report a patient with severe aplastic anemia that was successfully desensitized to ATG after a negative epicutaneous skin test and positive ID skin test. The patient had neither systemic nor localized reactions during the desensitization. Desensitization to ATG in patients with positive epicutaneous skin testing has been shown to be associated with serious and potentially life-threatening complications and should only be considered when the benefits outweigh the risks. Epicutaneous skin testing should be considered in conjunction with ID skin testing when screening for potential sensitivity to ATG. Because of the serious risk of anaphylaxis, desensitization should be performed in an intensive care unit setting in conjunction with a physician familiar with drug desensitization and the management of anaphylaxis.

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Antithymocyte globulin (ATG) is a polyclonal γ -immunoglobulin derived from either rabbit or equine serum that serves as therapy to prevent graft versus host disease in renal transplant recipients.^{1–4} ATG is also regularly used to treat patients with severe aplastic anemia when they are not eligible for hematopoietic stem cell transplant because of existing comorbidities or lack of a histocompatible donor.^{5–7} Equine-derived ATG is thought to be more effective than rabbit-derived ATG for treatment of severe aplastic anemia; however, rabbit-derived ATG has also been successful in treating relapsed and refractory aplastic anemia.^{8,9} By suppressing T cells, ATG decreases immune-mediated attack on progenitor and hematopoietic stem cells, allowing the bone marrow to recover over a period of months.^{6,7} It is thought that ATG acts as a cytotoxic agent on T cells leading to cell death. It has been shown that ATG induces complement-dependent cell lysis.¹⁰ These released cytokines and chemokines cause a systemic inflammatory response often seen hours after beginning the infusion.^{11,12} Serum sickness after ATG therapy has also been reported.^{13–15} Other rarer and life-threatening reac-

tions occurring in fewer than 5% of patients include bradycardia, tachycardia, hypotension, seizures, and anaphylactic shock.^{16–18}

Anaphylactic shock, a Gell and Coombs type I hypersensitivity reaction, is a life-threatening reaction that occurs in a small number of patients that receive ATG.¹⁹ Because of this potential risk, pretesting with an intradermal (ID) skin test of diluted ATG (1:1000) is standard practice, starting with 0.2 mL and increasing to 0.5 mL to raise a 5-mm wheal.¹⁷ Epicutaneous skin testing was only recently recommended but has not historically been performed.^{17,20,21} There is scant literature comparing the efficacy of different techniques in the evaluation of type I immediate hypersensitivity reactions to ATG. A single study by Bielory *et al.*²² showed that epicutaneous skin testing with ATG has a greater specificity and positive predictive value. Here, we describe a man with severe aplastic anemia that was successfully desensitized to ATG after a negative epicutaneous skin test and positive ID skin test to ATG.

CASE REPORT

A 72-year-old man with dermatomyositis for over 40 years was found to be pancytopenic after ~5 months of methotrexate therapy. Aplastic anemia was confirmed after two bone marrow biopsies revealed hypocellularity. Because of his age and other comorbidities, he was not a candidate for a hematopoietic stem cell transplant.

During the second hospitalization for neutropenic fever within 1 month, it was decided that therapy with

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Table 1 Desensitization protocol for ATG

Dose*,#,\\$	Dilution (50 mg/mL)	Volume (mL)	Dosage (μ g)	Route of Administration
1	1:10,000	0.2	1	ID
2	1:1000	0.2	10	ID
3	1:100	0.2	100	ID
4	1:10	0.2	1000	ID
5	1:1	0.1	5000	Subcutaneous
6	1:1	0.2	10,000	Subcutaneous
7	1:1,000,000	2	0.1	i.v. push over 1 min
8	1:100,000	2	1	i.v. push over 1 min
9	1:10,000	2	10	i.v. push over 1 min
10	1:1000	2	100	i.v. push over 1–2 min
11	40 mg in 500 mL of 0.9% normal saline	500	160	2 mL/min for 10 min, and then 4 mL/min for the remainder of the bag
12*	Full therapeutic dose		1600	Infused at 2.5% of the total volume over the 1st hr ([total volume \times 0.025] – rate for the 1st hr) and then doubled rate for the 2nd hr, triple the rate for the 3rd hr and onward for the remainder of the bag

Source: Adapted from Ref. 15.

*The following premedication was given 30 min before ATG dose administration: diphenhydramine, 50 mg i.v.; acetaminophen, 650 mg p.o.; methylprednisolone, 40 mg (1 mg/kg) i.v.; and ranitidine, 50 mg i.v.

#Ranitidine, 50 mg i.v., was given every 8 hr after starting desensitization.

\\$Dosing interval, 15 min.

ATG = antithymocyte globulin; ID = intradermal; i.v. = intravenously; p.o. = by mouth.

ATG outweighed the risk of life-threatening complications. To test for preexisting hypersensitivity to ATG, per the ATG package insert, a 0.2-mL injection of equine ATG diluted to 1:1000 was placed ID.¹⁷ Immediately after placement, a wheal and flare reaction measuring 25.4 \times 50.8 mm occurred without accompanying respiratory distress, generalized urticaria, or other systemic symptoms. The measurement likely reflects the flare because the actual wheal size was not recorded. The separate measurement of wheal and flare of the ATG ID test was not recorded by the hematologist/oncologist. The reaction occurred despite the fact that the patient had been on prednisone since before his admission. His total white blood cell count on the day of the ATG ID test was 500, of which 400 were lymphocytes. An epicutaneous skin test to full strength ATG performed 5 days later was nonreactive with a positive 8 \times 8-mm wheal/30 \times 30-mm flare histamine control and nonreactive saline control. Complete blood count the day before was still very low at 200, of which 200 were lymphocytes. Given that there was no significant change in his white blood cell count or prednisone use, the ATG ID test was not repeated. Additional epicutaneous skin testing to horse dander (Greer Laboratories, Lenoir, NC) was negative.

The risk, benefit, and alternate therapies were discussed with the patient and written informed consent

to proceed with ATG desensitization was obtained. A desensitization regimen was adapted from the University of Washington Medical Center and existing literature (Table 1).¹⁵ The patient was not taking an angiotensin-converting enzyme inhibitor or β -adrenergic blocking medication. At the time of the desensitization he was taking 40 mg of prednisone daily. In preparation for desensitization, he was transferred to the intensive care unit for close observation, where emergency medications and resuscitation equipment were close at hand. He was premedicated with diphenhydramine, ranitidine, acetaminophen, and methylprednisolone before the initial ID dilution was administered. Ranitidine was given every 8 hours thereafter (Table 2). The acetaminophen was added to prevent any potential serum sickness symptoms such as fever (Table 2).

A series of increasing dilutions of ATG were administered ID, subcutaneously, and, finally, intravenously with 15-minute intervals between each dose (Table 1). Throughout the increasing concentrations he developed neither a localized nor systemic reaction. Before dose 12 he was premedicated again with diphenhydramine, acetaminophen, and methylprednisolone. Rescue medications at the bedside were not needed and the patient transitioned to full therapeutic dosing within 1 day. He finished 3 additional days of contin-

Table 2 Premedication

Medication	Dosing (mg)	Route of Administration	Interval
Diphenhydramine	50	i.v.	30 min before desensitization and before administration of full therapeutic dosage*
Acetaminophen	650	p.o.	
Methylprednisolone	40 (1 mg/kg)	i.v.	
Ranitidine	50	i.v.	

*Ranitidine was also given every 8 hr after the initial dose.

i.v. = intravenously; p.o. = by mouth.

uous ATG infusion to complete the course of therapy. Sadly, 4 weeks after successful completion of ATG therapy, he died from fungal septicemia.

DISCUSSION

Our patient was successfully desensitized without any localized or systemic reactions, which is inconsistent with other published case reports. Most patients reported in the literature develop serum sickness, systemic reactions, and, occasionally, anaphylaxis during and after desensitization.^{12,15,18} It is possible that premedication before and during desensitization attenuated the chemokine- and cytokine-associated symptoms.¹⁸ It is more likely the patient had a false positive ID skin test that was confirmed with negative epicutaneous skin test. It is also important to note that the published desensitization protocol that was used differs significantly from the usual doubling doses every 15 minutes used in most other desensitization protocols.

A recent case report described a patient who began a similar desensitization protocol after a positive ID skin test.¹⁵ He developed anaphylaxis after advancing to continuous ATG infusion at full therapeutic dosing.¹⁵ An epicutaneous test was never performed on this patient before desensitization. In the body of literature reviewed regarding ATG hypersensitivity, few patients were ever tested with an epicutaneous skin test.^{11,12,15,18}

In the realm of allergy and immunology, epicutaneous skin testing to determine type I hypersensitivity has been associated with greater specificity, although lower sensitivity in comparison with ID skin testing, and is therefore used as the technique of choice in testing.^{20,23–25} There are a few important exceptions in which ID testing after epicutaneous skin testing is considered the standard for diagnosis. These exceptions include venom, penicillin, and local anesthetic allergies.^{24–26} Only one study in 1988 by Bielory²² was found comparing the reliability of epicutaneous and ID skin testing for ATG hypersensitivity. In that study of 36 patients with bone marrow failure, 3 had positive epicutaneous skin tests to ATG and 35 were positive by ID skin testing. Of the three patients with positive

epicutaneous skin tests, all had positive ID skin tests. One of those patients was successfully desensitized, another decided to pursue alternative therapy, and the third died during desensitization. The other patients with negative epicutaneous but positive ID skin tests were all successfully desensitized.²² Although the power of this study is low, there is a striking difference in positive predictive value between epicutaneous and ID skin testing.

Our patient initially had an ID skin test as recommended by the ATG package insert. Subsequently, an epicutaneous skin test was placed after review of the literature indicated a potential higher risk of adverse events in patients with a positive test. One explanation for why epicutaneous testing may be more predictive of anaphylaxis than ID testing is a potential higher level of specific IgE. In this setting less antigen is needed to elicit a positive response. It is possible that our patient was successfully desensitized after showing evidence of sensitization by ID testing. It is also possible that the patient had a false positive ID skin test because one may expect that the patient would have suffered localized or systemic side effects as is frequently seen in successful desensitizations.²⁷ Another explanation is that patients with a negative epicutaneous skin test but positive ID test can better tolerate desensitization because of a lower state of hypersensitivity. It can be difficult to determine the validity of skin testing when an epicutaneous and ID test differ. There is scant literature regarding testing for ATG hypersensitivity; however, the existing study and case reports indicate that epicutaneous skin testing has a superior positive predictive value whereas ID skin testing may carry a higher false positive rate or identify patients with milder hypersensitivity. To prevent patients who would benefit from ATG from seeking alternative therapies based solely on a positive ID skin test, it appears that epicutaneous skin testing should be considered in the evaluation of type I immediate hypersensitivity reactions and factor into the decision to proceed with desensitization.

During the preparation of this article, the recommendations in the ATG package insert were revised to

include epicutaneous testing and ID testing before administration of ATG.¹⁷

CONCLUSION

Desensitization to ATG is associated with serious and potentially life-threatening complications and should only be considered when the benefits outweigh the risks. Epicutaneous skin testing should be considered in conjunction with ID skin testing when screening for potential sensitivity to ATG. If the epicutaneous test was positive, our decision to proceed with desensitization may have been different, based on previous reported experience. Review of the data suggests that patients with a negative epicutaneous skin test but positive ID skin test are able to tolerate desensitization. Because of the serious risk of anaphylaxis, desensitization should be performed in an intensive care unit setting in conjunction with a physician familiar with drug desensitization and the management of anaphylaxis.

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