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CASE REPORT

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Successful desensitization to horse antithymocyte globulin for aplastic anemia: two case reports and literature review

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Abstract

Background Horse antithymocyte globulin (hATG) is an important therapeutic option for aplastic anemia (AA). However, hATG carries the risk of fatal anaphylaxis, and skin tests are performed to identify high-risk patients. We report on the successful desensitization of two AA patients with positive skin tests to hATG.

Case presentation Case 1: A 72-year-old man with a history of successful treatment with rabbit ATG was referred for pancytopenia. Neutrophil, reticulocyte, and platelet counts were 546 /μL, 32,000 /μL, and 19,000 /μL, despite the oral administration of eltrombopag and cyclosporine. Bone marrow biopsy showed hypocellularity, and he was diagnosed with relapsed severe AA. Case 2: A 69-year-old man was referred for anemia and thrombocytopenia, and diagnosed with non-severe AA. Neutrophil, reticulocyte, and platelet counts were 2,044 /μL, 23,000 /μL, and 37,000 /μL. Bone marrow biopsy revealed hypocellularity. Neither patient had a history of allergy, and the skin prick test (SPT) of hATG was negative, but the intradermal test (IDT) was positive. The result of the IDT in case 2 was reproducible. They received hATG desensitization under close monitoring of vital signs in our high-care unit. The protocol consisted of gradually increasing doses of hATG (four intradermal, two subcutaneous, and four intravenous (IV) push) and some premedications prior to administration of the full dose IV drip. They completed the course without developing any systemic allergic reactions.

Conclusions Despite the risk of anaphylaxis, hATG desensitization can be beneficial in AA patients with a positive skin test, especially when no alternative is available or hATG is preferred.

Keywords Aplastic anemia, Antithymocyte globulin, Desensitization, Skin test

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Background

Aplastic anemia (AA) is characterized by pancytopenia with hypocellular bone marrow (BM) in the absence of marrow fibrosis or the infiltration of malignancy. Antithymocyte globulin (ATG)-based immunosuppressive therapy (IST) is the standard treatment for severe AA (SAA) patients who are ineligible for transplantation, and non-severe AA (NSAA) patients who are transfusion dependent [1]. ATG is derived from either horse or rabbit, and horse ATG (hATG) has been reported to be equally or more effective than rabbit ATG (rATG) [2–6]. hATG has become available in Japan since 2023, providing a new treatment option for AA. hATG carries the risk of fatal anaphylaxis, and skin tests are performed to identify high-risk patients [7, 8]. Although desensitization has been attempted for high-risk patients in previous studies, to the best of our knowledge, there have been no reports from Japan. We report on the successful desensitization of two AA patients with positive skin tests to hATG.

Case presentation

Case1 72-year-old Japanese male who had the history of SAA 2 years prior was successfully treated with rATG and achieved full hematologic recovery. He had no history of allergy. He was referred for pancytopenia (WBC 1400 /μL, ANC 546 /μL, Hb 7.9 g/dL, PLT 19,000 /μL, reticulocyte count 32,000 /μL) and subcutaneous bleeding. Spinal MRI showed increased adipose tissue, and BM puncture revealed hypocellular marrow. Paroxysmal nocturnal hemoglobinuria (PNH) type blood cells were detected (PNH-R 0.003%, PNH-N 0.056%). He was diagnosed as relapsed SAA (severity criteria: stage 4), and a second IST using hATG was planned (hATG 40 mg/kg for 4 days). Skin tests were performed prior to hATG administration to evaluate the risk of anaphylaxis. Chlorpheniramine 10 mg was used as a premedication for platelet transfusion four days before the skin test, but no other antihistaminic drugs were used in the previous week, nor topical steroids were used during the previous three weeks. Skin prick test (SPT) with undiluted (50,000 μg/mL) hATG was negative. Intradermal test (IDT) using 0.02 mL of 1000-fold diluted (50 μg/mL) hATG showed a wheal with 8-mm diameter. This was more than 3 mm larger than that of the control (the same volume of saline showed a wheal with 3-mm diameter), so it was evaluated as positive. The administration of hATG was discontinued. However, cyclosporine and eltrombopag without ATG failed to resolve his transfusion dependency. hATG desensitization therapy was administered under close monitoring of vital signs in our high care unit, following the protocol of Millar and Wolanin et al. [9, 10] (Table 1). Acetaminophen 500 mg, chlorpheniramine 10 mg, famotidine 20 mg, and methylprednisolone 80 mg were administered as premedication before the start of desensitization and before the full dose. He completed four days of treatment without any local or systemic allergic reactions. Cyclosporine 40 mg/day and eltrombopag 100 mg/day, followed by darbepoetin alfa and G-CSF as supportive therapy, led to a partial response (PR).

Case2 A 69-year-old Japanese male with no history of allergy. He was referred for pancytopenia (WBC 2800 /μL, ANC 2044 /μL, Hb 6.7 g/dL, PLT 37,000 /μL, reticulocyte count 23,000 /μL). BM puncture revealed hypocellular marrow. PNH-type blood cells were detected (PNH-R 0.021%, PNH-N 0.043%). Because there were no agents that could have induced AA, he was diagnosed as NSAA (severity criteria: stage 3). Since he was transfusion dependent, the first IST with hATG (hATG 40 mg/kg for 4 days) was planned. To identify the risk of anaphylaxis, a skin

Table 1 Desensitization protocol for hATG

Dose*	ATG concentration (mg/mL)	Volume (mL)	Dosage (μg)	Route of Administration
1	0.05	0.02	1	intradermal
2	0.5	0.02	10	intradermal
3	5	0.02	100	intradermal
4	50	0.02	1,000	intradermal
5	25	0.2	5,000	subcutaneous
6	50	0.2	10,000	subcutaneous
7	0.00005	2	0.1	intravenous push over 1 min
8	0.0005	2	1	intravenous push over 1 min
9	0.005	2	10	intravenous push over 1 min
10	0.05	2	100	intravenous push over 1 - 2 min
11	0.08 (40 mg in 500 mL of 0.9 % normal saline)	500	40,000	intravenous drip at 2 mL/min for 10 min, and then 4 mL/min for the remainder of the bag
12	1 - 4	10 - 40 mL/kg	Full therapeutic dose (40 mg/kg)	intravenous drip at a rate of 2.5% of the total volume during the 1st hour, the doubled rate for the second hour, and the tripled rate thereafter

* Dosing interval, 15 min.

test was performed prior to hATG administration with the same method as in case 1. No antihistamines had been used for 1 week, and no topical steroids had been used for more than 3 weeks. SPT was negative and IDT was positive because of a wheal with 10 mm-diameter, which was at least 3 mm larger in diameter than the control (the same volume of saline showed a flare with 4-mm diameter, Fig. 1). Considering the possibility of false positives, IDT was repeated contralaterally with similar findings. Desensitization therapy was administered in the same method as in Case 1. Although a wheal was observed as a local adverse reaction during the dose escalation phase, desensitization was continued as there were no changes in vital signs. He successfully completed four days of hATG treatment without any systemic allergic reaction. Subsequently, we obtained a PR.

Discussion and conclusions

We successfully performed hATG desensitization to two high risk AA patients with SPT negative and IDT positive, following the protocol of Millar and Wolanin et al.

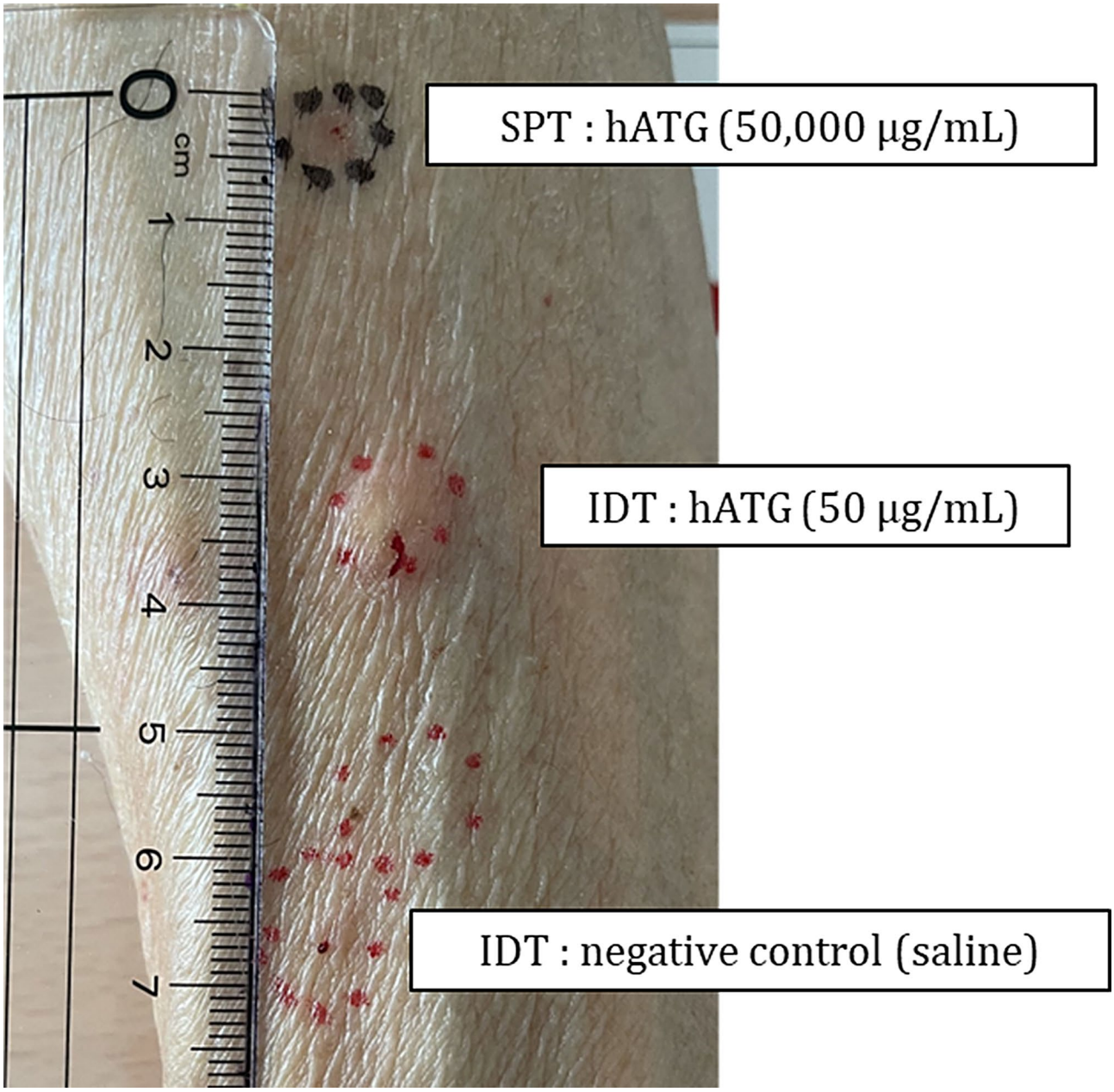

Fig. 1 The results of the skin tests in case 2 are shown. Skin prick test (SPT) with undiluted (50,000 μg/mL) hATG was negative. Intradermal test (IDT) using 0.02 mL of 1000-fold diluted (50 μg/mL) hATG was positive because of a wheal which were at least 3 mm larger in diameter than the negative control (the same volume of saline). IDT was repeated contralaterally with similar results

Table 2 Literature review on desensitization to hATG

	n	Age	Sex	Skin prick test	Intradermal test	Systemic reactions accompanying skin tests	Outcome of desensitization
Tsai 2018 [14]	1	59	female	negative	positive; 13 mm wheal (5 μg)	N/A	success
Wolanin 2015 [9]	1	72	male	negative (Additional test)	positive; 25.4 × 50.8 mm wheal and flare (50 μg/mL, 0.2 mL)	without accompanying respiratory distress, generalized urticaria, or other systemic symptoms	success
Demir 2015 [15]	8	median: 12.9 (7 - 19)	male: 6 female: 2	8/8 negative	4/8 positive; 10-11 mm (50 μg/mL, 0.02-0.05 mL) 2/4 positive; 8-10 mm (500 μg/mL, 0.02-0.05 mL) 3/3 positive; 11-18 mm (5000 μg/mL, 0.02-0.05 mL)	N/A	8/8 success (4/8 side effect; Urticaria, fever, Headache, Arthralgia)
Hall 2006 [16]	1	15	male	N/A	positive; 14 mm wheal and flare (0.1 μg)	without wheezing or difficulty breathing	success (developed wheal)
Ferdman 2004 [17]	1	17	male	N/A	positive; 20 mm wheal (50 μg/mL, 0.1 mL)	postural dizziness and hypotension (81/44 mm Hg)	success (generalized urticaria developed, symptoms did not progress beyond the urticaria and resolved after the infusion ended)
Millar 2000 [10]	2	63 and 46	male: 1 female: 1	N/A	2/2 positive; 11 × 11 mm wheal and flare (50 μg/mL, 0.1 mL) 10 × 10 mm wheal and flare (50 μg/mL, 0.1 mL. repeat 50 μg/mL, 0.02 mL)	N/A	2/2 failure (dizziness, dyspnea, tachycardia, hypotension, and decreased pulse oximetry measurement / anaphylactic reaction, tachycardia and hypotension)
Bielroy 1988 [11]	1	6	female	positive; 2×2 mm wheal (50,000 μg/mL)	positive; 7 × 8 mm wheal and 36 × 37 mm ring of erythema (5,000 μg/mL, 0.02 mL)	No complications	success

N/A : Not Applicable

[9, 10]. hATG rarely causes fatal anaphylaxis [11]. Skin testing is considered useful in identifying patients at high risk of anaphylaxis, and the U.S. Food and Drug Administration (FDA) strongly recommends skin testing prior to administration [7]. On the other hand, the British Society of Hematology (BSH) recommends intravenous infusion test administration instead of skin tests because of the high incidence of false-positive and false-negative results [1]. In Japan, both skin tests and intravenous infusion tests are available, but if a skin test is positive, a change in the treatment plan should be considered on the risk-benefit balance [8]. Given that elderly patients are a risk factor for severe anaphylaxis [12], we chose skin testing to identify risk. Although strategies when positive skin tests for hATG are have not been established, desensitization is one therapeutic approach for immediate IgE-mediated drug hypersensitivity reactions such as anaphylaxis [13].

In a literature review, hATG desensitization was performed in 15 patients (Table 2). IDT was performed in all patients before administration and was positive in all cases [9–11, 14–17]. SPT was performed before administration in 11 patients, and one patient was positive. Thirteen patients were successfully desensitized. Of the 13 patients who successfully desensitized, six patients had symptoms of wheals, fever, headache, and arthralgia during desensitization but were able to complete the administration. In the two cases where desensitization failed, anaphylaxis was observed in both cases. SPT was not performed in the two cases with anaphylaxis and in the two cases with wheals and urticaria during desensitization. It has been reported that a case of death due to anaphylaxis was positive for SPT [11].

SPT is the most reliable and cost-effective tool for the diagnosis of type I immediate-type IgE-mediated allergy, being safe, high in sensitivity and specificity, and used in the initial approach. IDT should be considered in patients with a strong clinical suspicion of immediate IgE-mediated allergy and a negative SPT. Compared with SPT, IDT has a lower positive predictive value because of its increased sensitivity but lower specificity. Factors such as infants and the elderly, and the use of antihistaminic drugs can cause false negative results [18].

Both cases had a negative SPT and a positive IDT. Although it is possible that the IDT results were false-positives, we performed desensitization because we could not rule out a potential risk of anaphylaxis. Wolanin et al. emphasized the importance of SPT and suggested that patients who are SPT negative and IDT positive may tolerate desensitization [9]. Our results support this opinion.

While it is an option for allogeneic hematopoietic stem cell transplant (HSCT), long-term survival rates are only about 70% in patients over 40 years of age due to comorbidity and treatment toxicity, even with allogeneic HSCT from HLA-matched sibling donors (MSD) [19]. The BSH guidelines recommend IST as the first-line treatment for elderly AA patients, and allogeneic HSCT should be considered for those who do not respond to first-line IST [1]. Another issue for elderly AA patients is the limited availability of MSD. In light of these facts, the indication for allogeneic HSCT should be carefully considered. In our cases, the patients were ineligible for allogeneic HSCT due to age and lack of MSD.

Although there is a risk of anaphylaxis, in cases where no alternative is available or where hATG is preferred, hATG desensitization can be beneficial for AA patients who are SPT negative and IDT positive, under close monitoring of vital signs.

Abbreviations

hATG	Horse antithymocyte globulin
AA	Aplastic anemia
SPT	Skin prick test
IDT	Intradermal test
IV	Intravenous
BM	Bone marrow
ATG	Antithymocyte globulin
IST	Immunosuppressive therapy
SAA	Severe aplastic anemia
NSAA	Non-severe aplastic anemia
rATG	Rabbit antithymocyte globulin
PNH	Paroxysmal nocturnal hemoglobinuria
PR	Partial response
FDA	Food and Drug Administration
BSH	British Society of Hematology
HSCT	Hematopoietic stem cell transplant
MSD	Matched sibling donors

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Author contributions
SY and MO designed the study, acquired the data, analyzed and interpreted the data. SY wrote the first draft of the manuscript. MO and TI advised on the interpretation of the cases and revised the manuscript. DI, KK, RF, and KM supervised the writing of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of the Kameda Medical Center (Numbers: 24 – 006). Informed consent for this report was obtained from the patient.

Consent for publication
Consent for publication was obtained from the patient.

Competing interests
The authors declare no competing interests.

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