

female patients, with first symptoms appearing on average at approximately 20.3 years of age.⁹ Although most patients with FXII-HAE described thus far have been Caucasians in studies of European populations,¹ increased rates of angioedema induced by ACE inhibition have been reported in African Americans.⁶ Curiously, our Brazilian patient is half Caucasian and half African. Then, we screened his sister, daughter, and granddaughter and found the deletion c.971_1018+24del72 only in his sister, although no family history had been previously reported.

In summary, we describe the case of a patient who was diagnosed with angioedema induced by ACE inhibitors at an advanced age, in whom a rare *F12* mutation was found to be likely responsible for FXII-HAE triggered by ACE inhibition. Considering the increasing number of patients under antihypertensive treatment, we suggest screening for exon 9 mutations encoding for *F12*, particularly for patients who present persistent edema episodes (other than facial edemas) after medication withdrawal and in men. This approach could be helpful in guiding the proper treatment of angioedema attacks and genetic counseling.

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Use of the basophil activation test in monitoring clinical tolerance after desensitization to brentuximab vedotin



Brentuximab vedotin is a monoclonal antibody-drug conjugate directed against the protein CD30¹. Brentuximab vedotin is indicated for treating patients with CD30⁺ Hodgkin lymphoma (HL) for which treatment with autologous stem cell transplant (ASCT) or 2 previous chemotherapy treatments have failed and when ASCT or chemotherapy are contraindicated.¹

Many hypersensitivity reactions (HSRs) produced by biologic agents have been seen, and their true incidence is unknown.² Desensitization is a method to counter HSRs from monoclonal antibodies in patients with no other adequate alternative options.³ Various desensitization protocols to brentuximab vedotin have been described.^{4–6} We describe a successful rapid desensitization to brentuximab vedotin in 3 patients with HL, refractory to several lines of chemotherapy and ASCT. This clinical tolerance to brentuximab vedotin is easily observed through the basophil activation test (BAT) as a decrease in activated basophils after desensitization as a treatment of HSRs.

Patient 1 was a 61-year-old man who presented with stage IIIB nodular sclerosis HL. The patient was treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) initially, with partial response. Subsequently, chemotherapy required rescue with etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP). He underwent ASCT without reaching remission. Finally, he was treated with brentuximab vedotin, 1.8 mg/kg infused every 21 days. The first infusion was well tolerated. However, within 15 minutes of infusion of the second dose, he developed pruritus, dyspnea, and rash, which was successfully controlled with steroids and antihistamines.

Patient 2 was a 29-year-old woman who presented with stage IIIB nodular sclerosis HL, refractory to several lines of chemotherapy, including ABVD and ESHAP. She responded partially to a gemcitabine and oxaliplatin regimen and underwent ASCT. Despite this, the patient experienced another relapse of disease, leading to initiation of brentuximab vedotin therapy. The first infusion was well tolerated, but with the second dose of brentuximab vedotin, she experienced itching in the hands and feet 5 minutes into the infusion and dyspnea at the end of administration. She responded well to dexchlorpheniramine, hydrocortisone, and methylprednisolone.

Patient 3 was a 48-year-old man who presented with stage IIA nodular sclerosis HL and was treated with an ABVD regimen followed by a ESHAP regimen and underwent ASCT without reaching disease remission. The patient was given intravenous brentuximab vedotin and tolerated the first dose. However, within 5 minutes of infusion of the second dose, he developed dyspnea, thoracic oppression, and syncope, which was successfully controlled with steroids and antihistamines.

Skin tests with brentuximab vedotin were performed in all cases. Skin tests consisted of prick tests using the undiluted drug (25 mg/mL) and of intradermal tests using serial dilutions (1:10, 1:100, 1:1,000). Positive and negative controls were performed with histamine and saline, respectively. Prick tests were examined at 20 minutes and intradermal tests at 15 minutes and 24, 48 and 72 hours; a result was considered positive when a wheal of 3 mm greater than negative controls was obtained. The results of skin prick tests with brentuximab vedotin were negative in all patients. However, the intradermal skin test results were positive in patient 1 (16 mm) and 3 (8 mm) at 1/100 dilution and in patient 2 (12 mm)

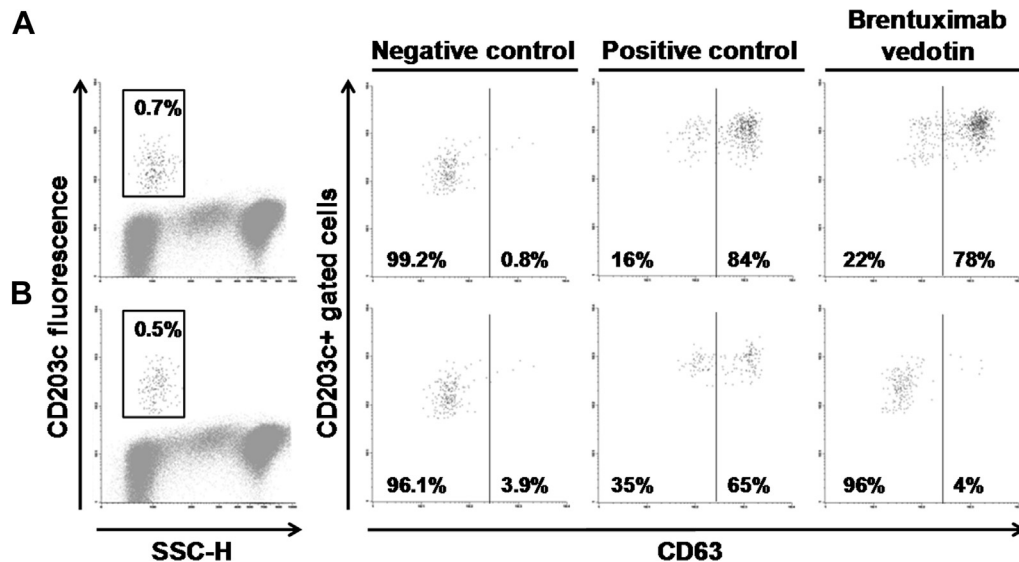


Figure 1. Basophil activation test results for patient 1. The percentage of basophils (SSC-low/CD203c-high) stimulated with brentuximab vedotin was 78% before desensitization (A) and decreased to 4% after desensitization (B). SSC-H indicates side scatter height.

at 1/10 dilution. The same tests were performed in 10 healthy controls, and skin test results were negative.

The BAT with brentuximab vedotin was also performed⁷ in all cases 15 days after the HSR. Results of the BAT with brentuximab vedotin were positive (>5%) in all patients; the percentages of activated basophils by brentuximab vedotin were 78% in patient 1 (Fig 1A), 15% in patient 2, and 18% in patient 3 (data not shown). The BAT with brentuximab vedotin results were negative in 2 patients who were treated with BV but without HSR to BV.

We consider that the patients presented a mast cell and IgE-mediated type 1 HSR based on the positivity of the skin test results and the BAT and the appearance of HSR at the second infusion implying a necessary sensitization. Because there was no therapeutic alternative in the patients, we planned to pursue brentuximab vedotin administration using a rapid desensitization 17-step protocol⁶ in patient 1 and 3 and 12-step protocol⁵ in patient 2.

Patients received premedication with dexamethasone (20 mg orally) and dexchlorpheniramine (5 mg intramuscularly) 1 hour before the beginning of the desensitization protocol. A total dose of 156 and 125 mg of brentuximab vedotin (1.8 mg/kg) was given as the 12-step⁵ and 17-step⁶ protocol, respectively, through increasing rate and concentration. The patients completed their infusion without difficulty. The patients were readmitted 21 days later to receive the third dose of brentuximab vedotin after the same desensitization protocol, and they completed the infusion without any difficulty and achieved complete remission.

After desensitization to brentuximab vedotin, at the end of the infusion, BATs were performed in all patients. The percentage of activated stimulated basophils with brentuximab vedotin decreased to 4% in patient 1 (Fig 1B), 0.7% in patient 2, and 2% in patient 3 (data not shown). All values are similar to their corresponding negative controls (3.9%, 0.4%, and 1.8%, respectively). Drug desensitization should be considered to continue the administration of biologic therapies after HSRs in cases in which an appropriate alternative does not exist.

The recent development of the quantification of basophil activation by flow cytometry represents a new opportunity for the diagnosis of drug allergies⁸ as a step before the provocation test. It is also useful in food allergy⁸ to monitor the effectiveness of immunotherapy,⁸ desensitization procedures,^{9,10} and the study of allergic processes in which the existence of specific IgE cannot be detected by conventional methods. The BAT has proven to be a

reliable and valid candidate marker to oral desensitization to cow's milk⁹ and egg¹⁰ allergy. We observed a decrease in antigen-specific CD63 basophil expression of brentuximab vedotin induced in our patients at the end of the brentuximab vedotin desensitization protocol.

In conclusion, the BAT continues to be a useful in vitro tool for the study of drug allergic disease. In addition, the BAT could be able to monitor allergen-specific basophil responses induced by a desensitization treatment in HSRs to brentuximab vedotin. However, studies that involve a larger number of patients will be required to assess the safety and efficacy of this approach to BAT.

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A case of green tea (*Camellia sinensis*) imbibement causing possible anaphylaxis



Tea is one of the oldest produced beverages and has been consumed since 2700 BC.¹ Green tea's popularity is increasing among consumers with its production expected to increase to 2.97 million tons a year by the year 2023.¹ Anaphylaxis caused by tea produced from the Compositae family has been reported in the literature.² To date, no cases of anaphylaxis from green tea, which is produced from *Camellia sinensis*, have been reported. We describe the first possible case of IgE-mediated anaphylaxis caused by imbibement of green tea.

A 20-year-old woman with no history of asthma, anxiety, or occupational exposure to green tea presented as an outpatient to our allergy clinic with a constellation of symptoms after consuming brewed green tea. She has imbibed green tea in the past without any reaction. Approximately 15 minutes after consuming green tea, she began to experience throat swelling, throat pruritus, sore throat, hoarse voice, shortness of breath, and nasal congestion. Her symptoms were more severe during subsequent consumption of green tea. The patient had a total of 2 episodes. She first noticed these symptoms 6 months before she presented to our clinic, and her symptoms would last up to 3 hours during each episode. She tried taking acetaminophen during 1 episode without any relief from her symptoms. She denied ingesting any alcohol, medications, or exercising before drinking the green tea. She never activated emergency medical services or went to the emergency department for her symptoms. She denied any reactions to other foods, including caffeine. The patient was given an epinephrine auto-injector for use during any subsequent anaphylactic reaction caused by green tea.

A Celestial brand green tea pod was used for skin prick tests (SPTs). Dry green tea leaves from the pod were weighted on an analytical balance. Two milliliters of sterile diluent was added to 200 mg of dry green tea leaves and allowed to cold steep for 10 minutes before use. The resultant is a 1/10 (wt/vol) heterogeneous solution of green tea. SPTs of the solution, sterile diluent, and histamine were performed on 5 healthy individuals without known green tea allergies to determine and verify nonirritant concentrations. All participants tested positive only to the histamine +4 (4- to 6-mm wheals) after 15 minutes. No irritation was reported by the participants or seen on examination around the 3 sample sites.

A SPT in the patient elicited a 6-mm wheal with a 61-mm flare (Fig 1). The SPT was performed to food allergens based on her history, and the results were nonreactive, including chocolate and coffee. The results of ImmunoCap for tea (f222) IgE, an in vitro assay for IgE to fermented black tea or blend of several black teas, were negative.

The patient had respiratory symptoms after each subsequent imbibement of green tea. The presentation fits the one-system category of anaphylaxis or other category of anaphylaxis as

discussed in the most recent practice parameters for anaphylaxis.³ As such it supports the possible diagnosis of anaphylaxis to green tea, especially with positive SPT results.

Cases of anaphylaxis from the ingestion of caffeine have been reported with supportive history and positive SPT results.⁴ Caffeine is a known component of green tea, and our patient had a nonreactive SPT result to caffeine and a history of consuming caffeine-containing products, other than tea, without developing any symptoms.

Herbal teas, such as peppermint tea, are prepared from various parts (roots, leaves, flowers, and fruits) of herbs.⁵ In contrast, green and black teas are prepared based on the level of fermentation from leaves from the same tea shrub, *Camellia sinensis*.⁶ Shirai et al⁷ describe food allergy to green tea in patients with a history of occupational asthma and question whether occupational exposure was necessary for sensitization in these cases. Tanaka et al⁸ describe one case of occupational hypersensitivity pneumonitis.



Figure 1. Skin prick test result for green tea with 6-mm wheal and 61-mm flare.