

Unfortunately, the patient had a left middle cerebral artery ischemic stroke several days after her second brain biopsy examination. She was transitioned to hospice and expired a few days later. Postmortem brain uncus and parietal tissue for PCR testing were positive for human Coxsackie virus B3, with positive VP2, VP4, and 5' untranslated region. The VP2 and VP4 sequences showed 93% nucleotide identity with the human Coxsackie virus B3. Thus, her final cause of death was determined to be diffuse meningoencephalitis secondary to human Coxsackie virus B3 owing to an immunocompromised state.¹

We hypothesize that this patient's previous treatment with rituximab for Evans syndrome caused persistent profound B-cell lymphopenia and secondary hypogammaglobulinemia, predisposing her to EM. Although she also had a splenectomy, asplenia is not considered a high-risk condition for EM.

The present case adds to an increasingly recognized, but incompletely understood, association between rituximab therapy and EM. Rituximab is a chimeric monoclonal antibody targeting CD20, which is expressed on B cells from the late pro-B-cell to memory B-cell stage.⁶ Given the absence of CD20 expression on plasmablasts and plasma cells, most patients treated with rituximab develop only transient, mild hypogammaglobulinemia and naive B-cell recovery occurs by 12 months,⁷ with memory B-cell recovery after recapitulating normal B-cell ontogeny.

Increased susceptibility to enteroviral infections has been observed in primary immunodeficiencies associated with defective B- and T-lymphocyte interactions such as X-linked agammaglobulinemia, hyper-IgM syndrome, and major histocompatibility class II deficiency.⁸ In X-linked agammaglobulinemia, congenital absence of B lymphocytes is associated with defective antigen presentation and decreased ability of B lymphocytes to sequester and destroy circulating virus.⁴ In contrast, patients with common variable immunodeficiency typically retain circulating B cells and are at lower risk for EM.^{9,10} Therefore, in patients with persistent marked B lymphopenia after rituximab, we would predict an increased risk of EM similar to patients with X-linked agammaglobulinemia.

Routinely obtaining immunoglobulin levels and peripheral B-cell numbers before and after rituximab treatment should be considered to monitor for pre-existing and secondary immunodeficiency. Prompt immunoglobulin replacement intravenously or intrathecally should be initiated in patients with persistent B-cell absence because this might avert severe EM infections in these high-risk patients. As the present case illustrates, immunoglobulin replacement might be inadequate salvage therapy in established EM.

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Allergic reaction to chlorpheniramine maleate

Antihistamines are commonly used in the management of allergic diseases. Their safety, effectiveness, and reliability have already been proven.¹ Allergic reactions to antihistamines are extremely rare, even when used on a frequent and daily basis. In addition to adverse effects, these drugs may cause some allergic reactions, including fixed-drug eruption, urticaria, angioedema, and anaphylaxis.^{2,3} This report presents a systemic reaction to chlorpheniramine maleate that was found through skin tests.

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Thamiris Palacios, DO*
Luther Bartelt, MD†
William Scheld, MD†
M. Beatriz Lopes, MD, PhD‡
Sarah M. Kelting, MD‡
Steven Holland, MD§
W. Ian Lipkin, MD||
Phenix-Lan Quan, PhD||
Larry Borish, MD*,¶
Monica Lawrence, MD*

*Division of Asthma, Allergy and Immunology

†Division of Infectious Disease

Department of Medicine

‡Department of Pathology

University of Virginia School of Medicine

Charlottesville, Virginia

§Laboratory of Clinical Infectious Diseases

National Institute of Allergy and Infectious Diseases

Bethesda, Maryland

||Center for Infection and Immunity

Mailman School of Public Health of Columbia University

New York, New York

¶Department of Microbiology

University of Virginia School of Medicine

Charlottesville, Virginia

TVP9Z@hscmail.mcc.virginia.edu

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A 37-year-old woman was admitted to the allergy and immunology clinic 3 weeks after a systemic reaction composed of widespread pruritus, redness of the neck, palpitation, and dyspnea. Her symptoms emerged within minutes after intravenous administration of chlorpheniramine maleate.

She had a medical history of ischemic heart disease and hyperlipidemia for 5 years and received antihyperlipidemics, β -blockers, and acetylsalicylic acid smoothly during this time. She also had an unverified history of penicillin allergy since her childhood.



Figure 1. Facial and neck erythema after skin test with CM.

During regular follow-ups, she was scheduled for a coronary angiography by the cardiology clinic. Because of the possible penicillin allergy, a premedication was planned to avoid a possible radiocontrast media allergy. An ampoule of chlorpheniramine maleate was administered intravenously before the coronary angiography process, and then the reaction in question occurred. She was intravenously treated with 40 mg of methylprednisolone and improved within an hour.

At the allergy clinic, she was questioned regarding a possible antihistamine allergy. One week after that, a basophil activation test (BAT) and skin tests with chlorpheniramine maleate (45.5 mg/2 mL) were performed. In the BAT, CD203c and CD63 were used as activation markers. The values of the percentage of active basophils after *in vitro* stimulation with chlorpheniramine maleate (PABivs) and stimulation index (SI; the ratio of PABivs to the percentage of basal active basophils [PABbas]) were analyzed with flow cytometry. The BAT result was considered positive if the PABivs was greater than 5% and the SI was greater than 2.⁴ The BAT results were attained as PABbas equal to 4.1, PABivs with 1/10 dilution of chlorpheniramine maleate equal to 6.4, PABivs with 1/100 dilution of chlorpheniramine maleate equal to 5.3, PABivs with 1/1,000 dilution of chlorpheniramine maleate equal to 3.2, SI with 1/10 dilution of chlorpheniramine maleate equal to 1.5, SI with 1/100 dilution of chlorpheniramine maleate equal to 1.29, and SI with 1/1,000 dilution of chlorpheniramine maleate equal to 0.78. Ultimately, the BAT produced a negative result.

Skin tests were performed with incremental dilutions of chlorpheniramine maleate.⁵ Histamine and saline were used as positive and negative controls. Negative results were found for the prick tests with 1/100 dilution (0.227 mg/mL), 1/10 dilution (2.27 mg/mL), and undiluted form (22.75 mg/mL) of chlorpheniramine maleate, as well as the intradermal test with 1/1,000 dilution (0.022 mg/mL) of chlorpheniramine maleate. However, the intradermal test with 1/100 dilution of chlorpheniramine maleate produced a positive result (a wheal of 3 × 3 mm and a flare of 8 × 10 mm). In addition, systemic symptoms, including excessive fatigue, blurred vision, palpitation, burning and itching on the neck and face, and numbness in the hands and arms, occurred within minutes. This concentration was proven to be nonirritating in 10 healthy control subjects, and at least 4 of them were premenopausal women older than 30 years.

A physical examination revealed neck and facial erythema and edema of the uvula (Fig 1). The patient had a heart rate of 120/min, a blood pressure of 190/120 mm Hg, and a respiratory rate of 16/min. This was considered an anaphylactic reaction, and she was treated with 40 mg of methylprednisolone intravenously and 4 L/min of oxygen by mask immediately. Within 15 minutes, her symptoms gradually decreased, and her blood pressure and heart rate were measured as 135/75 mm Hg and 84/min, respectively. Adrenalin was not administered right away because of the initial vital signs. Forty-five minutes later her physical and vital findings returned to normal. A laboratory evaluation, including complete blood cell count, erythrocyte sedimentation rate, liver and kidney function tests and electrolytes, was performed within 1 hour, and all results were normal. Tryptase and histamine levels were not measured during the reaction, but subsequently serum tryptase level was measured as being 3 ng/mL (<11.5 ng/mL). She was kept under observation for 4 hours and then discharged with an epinephrine autoinjector. Meanwhile, skin testing with antihistamines other than the chlorpheniramine maleate was offered, but the patient did not accept. She was informed to avoid all forms of antihistamines and drugs that contain antihistamine and to return to our clinic immediately in the event of any situation that required antihistamine treatment.

According to the patient, she had never used any antihistamine previously. Therefore, it is possible to explain this reaction with a missing anamnesis or a cross-reactivity with other drugs, such as histamine₂ (H₂)–receptor blockers and common cold drugs that contain antihistamines. Some authors stated that urticarial lesions, depending on antihistamine use, were related to cysteinyl leukotrienes.³ However, immunologic mechanisms have rarely been found. In some cases, prick test positivity with mizolastin and loratadine and intradermal test positivity with cetirizine and diphenhydramine supported an IgE-mediated mechanism.^{6–9} Chlorpheniramine maleate is a first-generation H₁-antihistamine and structurally resembles histamine. Therefore, chlorpheniramine maleate can easily change the inactive status of its receptor to active.⁶ In this type of reaction, metabolite haptenization and abnormal metabolic pathways have also been implicated.¹⁰ BATs have already been performed with many drugs, and positive results were obtained with neuromuscular blocking agents and β -lactam antibiotics.⁴ In the literature, no study has been performed of antihistamine allergy evaluated with BATs. Although the result was negative, this case is unique because for the first time to our knowledge an antihistamine allergy was evaluated with a BAT in which both CD203c and CD63 were used as activation markers. In this case, despite the negative BAT result, intradermal test positivity and early emerging symptoms supported a possible type 1 hypersensitivity reaction to chlorpheniramine maleate. Although antihistamines are known to be safe drugs, they may cause adverse drug reactions even if used during skin tests. Currently, the BAT is not widely accepted as a diagnostic tool. The BAT may be used as a complementary tool to skin tests, but this should be confirmed with further drug allergy studies, including antihistamines.

Fevzi Demirel, MD

Mustafa Gulec, MD

Ozgur Kartal, MD

Sait Yesillik, MD

Abdullah Baysan, MD

Ugur Musabak, MD

Osman Sener, MD

Division of Immunology and Allergic Diseases

Department of Internal Medicine

Gulhane Military Medical Academy and Medical School

Ankara, Turkey

fedemirel@gata.edu.tr

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Second episode of near-fatal angioedema in a patient treated with everolimus



Angioedema is defined as localized and self-limiting cutaneous and mucosal swelling. Upper airway swelling may critically compromise the airway, requiring intubation or even emergency tracheostomy to prevent death. There are different causes of angioedema, such as the intake of drugs, allergies, or lack of the complement C1 inhibitor (C1-INH).¹ Angioedema is often associated with urticaria and may be idiopathic.

A recent classification of angioedema without wheals distinguishes idiopathic histaminergic (or mast cell-mediated) angioedema from idiopathic nonhistaminergic angioedema, acquired angioedema related to angiotensin-converting enzyme inhibitors (ACEIs), hereditary forms of C1-INH deficiencies, and acquired angioedema with C1-INH deficiency.² In acquired angioedema related to ACEIs and C1-INH deficiency, increased bradykinin levels are involved in the pathogenesis of swelling. Angioedema has been reported as an adverse effect of both ACEI and mTOR inhibitors (mTORIs).^{3–5}

We present a case of a 51-year-old woman who had received a kidney transplant and developed near-fatal drug-induced angioedema twice, first caused by an ACEI and then 10 years later due to treatment with mTORI (everolimus). She had a medical history of polycystic kidney disease and had received 3 kidney transplants. Initially, she was treated with the combination of cyclosporine and mycophenolate as immunosuppressants. As antihypertensive treatment, she was treated with the combination of ramipril, 2.5 mg/d, and atenolol, 50 mg/d, which she tolerated well for years. One month after starting treatment with ramipril, 5 mg/d, she was admitted to the emergency department with a swollen and edematous tongue and difficulty speaking. She was diagnosed as having acquired angioedema related to ACEIs and treated with intravenous hydrocortisone, antihistamine, and adrenaline inhalation without improvement. Three hours later, she had respiratory impairment with stridor. Oral endotracheal intubation was attempted but was complicated because of the severity of the laryngeal edema; therefore, she received an emergency tracheostomy. She experienced asphyxia and 30 seconds of asystolia. After approximately 36 hours, the edema subsided. She remained in the hospital for several weeks because of complications secondary to the tracheostomy. The antihypertensive regimen was changed to nifedipin and atenolol, and she had no relapse of angioedema. Deficiency of C1-INH was excluded based on measurement of C1-INH antigenic and functional levels.

During the next 10 years, she developed multiple nonmelanoma skin cancers facilitated by the long-term use of immunosuppressive treatment with cyclosporine and mycophenolate. Therefore, the

immunosuppressive regimen was switched from cyclosporine and mycophenolate to everolimus and mycophenolate. After 2 months of treatment, she was admitted to the emergency department with a swollen tongue, angioedema of her lips, and difficulty speaking (Fig 1). Also at this time, she did not respond to traditional anti-allergic therapy with intravenous hydrocortisone, antihistamine, and adrenaline inhalation. After 2 hours she developed stridor, and an oral endotracheal intubation was performed. It was concluded that she probably had everolimus-induced nonhistaminergic angioedema. Her C1-INH antigenic and functional levels were



Figure 1. A 51-year-old patient with a kidney transplant and everolimus-induced angioedema of the orofacial area.

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