
NONCARDIOGENIC PULMONARY EDEMA IN A PATIENT RECEIVING VANCOMYCIN AND OXYCODONE-ACETAMINOPHEN

Vancomycin is the drug of choice for hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections.¹ With the accelerating spread of community-acquired MRSA, vancomycin currently continues to serve as initial empirical therapy.² The drug is not benign, and severe adverse reactions have been reported in addition to red man syndrome. Among them is an immunologic IgE-mediated hypersensitivity reaction.³ The combination of opiates and vancomycin has been reported to potentiate this capillary leak reaction.⁴ We describe a patient with a nonallergic drug hypersensitivity reaction to vancomycin who developed life-threatening pulmonary edema after receiving 1 dose of vancomycin and oxycodone-acetaminophen.

Case Report

A 57-year-old man presented to the emergency department with redness, pain, and swelling of the fourth digit of his right foot of 2 days' duration, with temperatures to 101.8°F. Because outpatient treatment of common cellulitis with a previous 2 days of amoxicillin-clavulanate failed, the patient was admitted to the hospital for intravenous antibiotic drug treatment for the presumptive diagnosis of community-acquired MRSA cellulitis.

On admission, the patient's temperature was 100.7°F, with tachycardia at a heart rate of 101/min. Blood pressure was 155/80 mm Hg, and arterial oxygen concentration was 96% on room air while breathing 12 respirations per minute. Other laboratory values included a white blood cell count of 7.6 k/mm³, 78% neutrophils, 15% lymphocytes, 0.8% eosinophils, erythrocyte sedimentation rate of 31 mm/h, and a creatinine level of 1.1 mg/dL. A chest radiograph was clear. After cultures, the patient was given vancomycin, 1 g infused over 1 hour, and oxycodone-acetaminophen, 5 and 325 mg, for pain. The vancomycin infusion was completed after 90 minutes. Four hours later, the patient experienced sudden hypoxia and hypotension without fever. On examination, he was obviously dyspneic, with altered mentation. Arterial oxygen concentration on room air was 84%, and he had diffuse crackles in both lung fields. The patient denied chest pain. Absent were wheezes, rashes, pruritus, lip or throat swelling, and drooling. A portable chest radiograph showed acute pulmonary edema. Serial electrocardiograms remained negative for ischemia, and 3 sets of cardiac enzyme biomarkers were negative. B-type natriuretic peptide concentration, seen to be elevated in heart failure, was within the reference range. Arterial blood gas analysis demonstrated respiratory alkalosis and moderate hypoxia, with a normal alveolar-arterial oxygen

gradient. The patient was given intravenous furosemide, 40 mg twice in 6 hours; diphenhydramine, 25 mg; and famotidine, 20 mg. He was switched to linezolid. Empirical treatment for pulmonary embolus was initiated with enoxaparin, with negative findings on a subsequent computed tomographic angiogram. Echocardiography confirmed no abnormalities. His tryptase level returned to 2.05 ng/mL (reference range, 0.0–11.4 ng/mL) and his IgE level to 94.0 kU/L (reference range, 0.00–127.0 kU/L) (Mayo Medical Labs, Rochester, Minnesota).

The patient's dyspnea markedly improved in the next 12 hours, with radiographically confirmed resolution of pulmonary edema. The patient was discharged taking clindamycin. Blood cultures remained negative.

Discussion

We maintain that the pulmonary edema observed 4 hours after completion of the vancomycin infusion cannot be anaphylactic or red man syndrome but rather is an atypical nonallergic drug hypersensitivity reaction to vancomycin. This was not an anaphylactic reaction because the patient was definitely vancomycin naive and, therefore, had no previously formed IgE antibodies. He also lacked the skin manifestations of pruritus, urticaria, maculopapular rash, and angioedema. There was no nasal congestion, bronchospasm, arrhythmias, nausea or vomiting, or peripheral eosinophilia. The patient's condition resolved without the administration of epinephrine. Although elevated IgE levels are not always found in anaphylaxis, this patient had a normal total IgE level 5 hours after the completion of vancomycin infusion. Elevated tryptase concentration remains a marker of anaphylaxis,⁵ but this patient's level was low normal. Although a nonallergic drug hypersensitivity reaction is also a mast cell-mediated release of histamine, bradykinins, and other cell mediators that cause capillary leak, this mechanism may explain this patient's pulmonary edema. Unlike anaphylactic reactions, nonallergic drug hypersensitivity reactions can occur on first administration of a drug.

Furthermore, red man syndrome is unlikely given that it is an infusion-related complication that resolves with infusion rate slowing. This patient's symptoms occurred hours after the vancomycin infusion ceased. In addition, he lacked the classically associated rash, flushing, pruritus, chest pain, and muscle spasms.

Opiates can potentiate mast cell degranulation with concurrent administration of vancomycin,⁴ yet we would have expected an immediate or severe reaction around the time of administration, not hours later. And although this patient had an acute febrile illness suggestive of bacteremia, this remains very unlikely because repeated blood cultures remained negative.

For the reasons elucidated, this patient likely did not experience anaphylaxis but rather an atypical nonallergic

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drug hypersensitivity reaction. With the increasing epidemiologic burden of community-acquired MRSA, health care professionals must remain vigilant for this uncommon delayed vancomycin reaction because it can lead to life-threatening pulmonary edema and possibly other capillary leak phenomenon.

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OBSERVATIONS ON THE MECHANISM OF OMALIZUMAB AS A STEROID-SPARING AGENT IN AUTOIMMUNE OR CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

Previous observations suggest that chronic idiopathic urticaria or angioedema (CIU/A) in some cases results from autoantibodies against the high-affinity IgE receptor (IgEfcR) or IgE.^{1,2} An association is present between thyroid autoantibodies and CIU/A³ and between a positive autologous skin test result and thyroid autoimmune disease.⁴ Activation of donor basophils by immunoglobulin IgG from patients with CIU/A supports an autoimmune basis for this disorder.⁵

Omalizumab (Xolair), a humanized monoclonal antibody, prevents IgE binding to IgEfcR and may be a novel therapy for CIU/A.^{6,7} We previously described a patient with a dual diagnosis of oral corticosteroid-dependent asthma and CIU/A who received omalizumab for her asthma⁸ followed

Table 1. Laboratory Values Before and After Omalizumab Therapy in Patient A

Component	Before omalizumab	After omalizumab
Basophil cd203c, %	5.5 (reference range, <5)	9.0
Thyrotropin, mIU/L	0.92 (reference range, <5.5)	22.1
Antithyroglobulin, ng/mL	326 (reference range, <60)	620
Antimicrosomal antibodies, ng/mL	210 (reference range, <33)	814
Total IgE, µg/L	169	288

by sustained clinical improvement in both CIU/A and asthma. This patient and others described in additional reports had paradoxical worsening of urticaria immediately after injection of omalizumab.^{9,10}

Subsequently, 6 additional patients in our practice with dual diagnosis of asthma and CIU/A have received the medication without exacerbations of urticaria or anaphylaxis, in all cases experiencing a significant improvement in both CIU/A and asthma. One of these additional patients (denoted patient A, data shown in Table 1) had evidence of thyroid autoimmunity (thyroid peroxidase and antithyroglobulin antibodies; Quest Diagnostics, Wallingford, Connecticut) before or during therapy. The serum from patient A was also positive for donor basophil cd203c activation (R. Harbeck, MD, National Jewish Medical and Research Center, Denver, Colorado).

Patient A, a 22-year-old woman, was referred for evaluation of worsening allergies, asthma, and urticaria. She had a history of seasonal allergies, asthma, and endometriosis treated with oral contraceptives but otherwise was in good health. The results of skin prick testing were positive for seasonal and perennial allergens, and pulmonary testing showed reversible obstruction consistent with her history of asthma. She required 40 to 60 mg/d of prednisone for control of wheezing and hives in addition to nonsedating antihistamines and continued to require weekly visits to the emergency department for wheezing treated with epinephrine, albuterol, and additional corticosteroids. Laboratory test results were otherwise negative for other systemic illness, including negative antinuclear antibody and pregnancy testing. Symptoms did not improve with multiple steroid-sparing therapies, including a month of low-dose thyroid hormone (levothyroxine, 50 µg/d) and subsequently 2 weeks of low-dose cyclosporine (2 mg/kg of cyclosporine A, divided twice daily).

Therapy with omalizumab was associated with a rapid reduction and subsequent elimination of oral steroid requirement noted in the first month. Additional basophil activation testing after 6 months of omalizumab therapy showed that serum factors capable of triggering mast cell and basophil release had not decreased but in fact had increased, almost

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