

Vancomycin-Induced Stevens-Johnson Syndrome

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ABSTRACT

Stevens-Johnson syndrome is a rare immunologic reaction that may involve skin or various mucosal surfaces. The etiology may range from multiple pharmacologic agents to viral infections. Associated findings can range from minimal skin and mucosal involvement to extensive dermal exfoliation, nephritis, lymphadenopathy, hepatitis, and multiple serologic abnormalities. We report a 36 year-old caucasian male who developed a pruritic, raised maculopapular eruption on Day 17 of intravenous vancomycin for treatment of probable bacterial endocarditis. The vancomycin was discontinued. The patient had received a prosthetic aortic valve subsequent to acute rheumatic valve disease 20 years earlier, but had been well until development of endocarditis. The rash became more extensive to involve the torso, abdomen, legs, and arms. His fever persisted, and he developed neutropenia and eosinophilia. Axillary and inguinal lymphadenopathy, pharyngeal irritation, lip swelling, conjunctival injection, and elevated liver function studies also developed following cessation of the vancomycin. Eight days after eruption and fever began, corticosteroid therapy was instituted, with subsequent improvement of symptoms in less than 24 hours. Allergic reactions to vancomycin have included Stevens-Johnson syndrome rarely, and only one other case of adenopathy has been recorded. Most reactions have been in patients with severe renal insufficiency. We believe this patient is the first case of vancomycin-induced Stevens-Johnson syndrome in a previously healthy patient to be complicated by lymphadenopathy, hepatitis, and multiple serologic abnormalities. (Allergy and Asthma Proc 17:75-78, 1996)

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Vancomycin, a glycopeptide antibiotic, has been used with increased frequency in the past 10 years for serious infections due to methicillin-resistant strains of *Staphylococcus aureus*, coagulase-negative Staphylococci, and multiply resistant gram-positive organisms (such as *Corynebacterium jeikeium* and resistant strains of *Streptococcus pneumoniae*). In patients with intolerance or allergy to beta-lactam antibiotics, vancomycin is used for treatment of serious gram-positive infections and bacterial endocarditis. It is administered prophylactically for endocarditis during selected instrumentation, cardio-thoracic surgery, and for chemotherapy-induced granulocytopenia.¹⁻⁴

Adverse reactions to vancomycin most commonly reported are infusion-related side effects (such as "red-man" syndrome, "pain-spasm" syndrome, and hypotension). These reactions are considered to be due to nonimmunologic histamine release triggered by vancomycin. Other documented side effects have included ototoxicity, thrombophlebitis, nephrotoxicity, neutropenia, and rarely hypersensitivity reactions. This last category of hypersensitivity includes drug fever as well as cutaneous eruptions and is reported infrequently. Toxicities associated with vancomycin have diminished due to improved purification procedures and monitoring of drug concentrations.^{1,5,6}

We report a case of vancomycin-induced Stevens-Johnson syndrome in a patient receiving vancomycin for endocarditis. This case appears to be only the third report of vancomycin-induced Stevens-Johnson Syndrome and is the first to describe a symptom complex in a previously healthy patient of exfoliative dermatitis, hematologic changes with mild neutropenia and extreme eosinophilia, hepatic involvement, and extensive adenopathy.

CASE REPORT

A 36-year-old caucasian male was admitted to Northwestern Memorial Hospital, Chicago, Illinois, for treatment of possible bacterial endocarditis. He had a history of rheumatic fever and carditis at age 16 years requiring insertion of a prosthetic aortic valve. His health status

during the 20-year interval included only two hospitalizations for orthopedic procedures. He denied any recurrent illnesses other than occasional bouts of pharyngitis or herpes genitalis each year. He had discontinued his prophylactic amoxicillin 2 year earlier, but had received several short courses of antibiotic for minor upper respiratory illnesses and dental procedures in the months preceding his initial hospitalization. He denied illicit drug use. At the time of the first hospital admission, a diagnosis of endocarditis was suggested by continued low-grade temperature elevations and the new 3/6 diastolic blowing murmur and click. He was begun on prophylactic intravenous oxacillin and gentamicin, later to be changed to ampicillin and gentamicin at the recommendation of the Infectious Disease service. Blood cultures remained negative. A throat culture was negative for *Streptococcus pyogenes*. His HSV II infection was considered to be inactive.

On hospital Day 7, the original Bjork-Shiley aortic valve was replaced with a St. Jude aortic prosthesis. The diagnosis of endocarditis was confirmed at the time of surgery. Post-operatively, he experienced complete heart block thought attributable to extensive suture placement required to attach the new aortic valve prosthesis. Vancomycin 1 gram qd intravenous and digoxin 0.25 mg qd po were begun on hospital Day 10, when he was returned to surgery for placement of a permanent dual chamber pacemaker. The ampicillin and gentamicin were discontinued. The patient was discharged on hospital Day 15 to continue vancomycin 1 gram qd intravenously, digoxin 0.25 mg qd, coumadin 7.5 mg qd, and enalapril 5 mg bid.

On Day 12 of vancomycin, he continued to experience low-grade elevations of temperature. The intravenous vancomycin was increased to 1 gram bid. On Day 17 of vancomycin, the patient was noted to have fever to 39.4°C and chills. A raised erythematous rash was noted on his chest, with pain localized to an area over the sternum as well as the left mastoid region. Two days later, when the confluent macular erythema extended to the entire truncal area, he was readmitted with diagnosis of drug reaction, probably to vancomycin. His temperature on admission was 37.9°C, BP was 110/80. His physical exam was remarkable for an erythematous rash involving the trunk as well as the lower extremities bilaterally, and an intensified III/VI systolic ejection murmur. Laboratory studies included a WBC count of 2900, with 59% polys, 17% lymphs, 13% eos, and 10% monos. Hgb/Hct were 8.4/25.5. ESR was 60 mm/hr (nl < 20). BUN was 11 mg/dL (nl = 8–25); Creatinine was 1.2 mg/dL (nl = 0.7–1.8). Liver function studies revealed LDH was 304 U/L (nl ≤ 200), SGOT was 39 U/L (nl ≤ 30). Intravenous vancomycin was discontinued, and piperacillin and gentamicin were begun.

On the following day, the rash was less erythematous, but the patient reported sensations of pharyngeal irritation and tightness. The highest temperature recorded was 38.3°C. The WBC count was 2700 with 42% polys, 11% bands,

25% lymphs, 16% eos, and 6% monos; Hgb/Hct were 7.8/23.4. LDH was 305 U/L.

Forty-eight hours after discontinuing vancomycin and beginning piperacillin and gentamicin, the patient experienced increased throat tightness, lip swelling, and axillary and inguinal adenopathy. The rash again became extremely erythematous and pruritic, extending to face, ears, lower legs, soles of feet, arms, and palms of hands. The temperature peaked at 38.3°C, and all antibiotics were discontinued. Laboratory studies revealed a WBC count of 3600 with 30% polys, 12% bands, 19% lymphs, 28% eos, and 7% monos. Platelet count was 148,000. LDH was 305 U/L; SGOT was 62 U/L, Alkaline Phosphatase was 87 U/L. A Heterophile antibody was negative. Because of persistent mild neutropenia and extreme eosinophilia, a bone marrow examination was performed and revealed normal precursor cells, without evidence of malignancy. Viral cultures from the bone marrow specimen were negative at 3 weeks.

Following discontinuation of all antibiotics, the throat tightness and generalized cutaneous pruritus persisted. The axillary and inguinal adenopathy increased. The temperature remained at 38.3°C. The WBC count was 5600 with 50% polys, 14% lymphs, 28% eos, and 8% monos. ESR was elevated at 61 mm/hr. Coincidental penicillin hypersensitivity was evaluated, as future therapy with a penicillin derivative for endocarditis prophylaxis was anticipated for this patient and erythema had increased following piperacillin administration. Skin testing was performed using the major antigenic determinant, benzylpenicilloyl polylysine, and the minor determinants, benzyl penicilloate, potassium penicillin G, benzylpenicilloyl-N-propanolamine, and was negative.

Eight days after discontinuation of vancomycin, and 10 days after development of the erythematous rash, the patient continued to have a nonblanching, maculopapular rash with edema and cutaneous desquamation on the lower extremities. He also developed conjunctival injection, palatal petechiae, and epigastric distress. The axillary and inguinal adenopathy became tender to palpation. The temperature remained elevated to 39.2°C. The WBC count was 8500 with 37% polys, 8% bands, 21% lymphs, 28% eos, and 4% monos. LDH was 377 U/L. SGOT was 77 U/L. Alkaline Phosphatase was 139 U/L. Intravenous methylprednisolone 60 mg Q 6 hr, and diphenhydramine 50 mg prn were begun as therapy for the Stevens-Johnson Syndrome.

Within 18 hours after initiating steroid therapy, the patient reported a subjective decrease in adenopathy tenderness, pruritus, and malaise, as well as a decrease in the cutaneous erythema. The temperature had decreased to 37.2°C and remained at that level or lower until discharge. The WBC count was 7800 with 35% polys, 19% bands, 34% lymphs, 1% eos, and 3% monos. ESR had declined to 33 mm/hr. The liver function studies remained elevated, with an LDH of 382 U/L. SGOT of 188 U/L. Alkaline Phosphatase was 232 U/L.

Fourteen days after discontinuing vancomycin, and 7 days after beginning methylprednisolone therapy, the patient was discharged. He was to receive Prednisone 60 mg daily for 1 week and continue prednisone with a gradually tapering dose recommended, using his clinical status as a guide. The laboratory studies at the time of discharge included a WBC count of 11,000 with 77% polys, 1% bands, 15% lymphs, and 5% monos. ESR was now 24 mm/hr. The adenopathy and edema slowly resolved over the following two weeks. The eosinophilia did not return on subsequent counts.

DISCUSSION

Our case differs from the other two reported cases of vancomycin-induced Stevens-Johnson syndrome in that the patient had normal renal function and had been well before his present hospitalizations. Clinical findings were compatible with the diagnosis of Stevens-Johnson syndrome. The complex of multiple cutaneous, mucosal, and systemic symptoms and signs our patient experienced are listed in Table I. Our patient developed a cutaneous eruption and fever on Day 17 of vancomycin therapy that evolved into Stevens-Johnson syndrome and persisted for 8 days until methylprednisolone therapy was begun.

A review of previously reported cases of vancomycin-related Stevens-Johnson syndrome and other serious cutaneous reactions revealed the average time from initiating vancomycin therapy to the appearance of an eruption was 17.5 days, with a range of 2 to 31 days. The average duration of the reactions following cessation of the drug was 23.5 days, with a range from 2 days to 2 months.⁷⁻¹⁷

Vancomycin was suspected initially as the cause of the fever and erythematous rash in this patient. Other possibilities included concurrent medications used (coumadin, digoxin, and enalapril), viral infection, endocarditis, or neoplasm. He had a history of HSVII infection, but denied any recent lesions. On admitting examination, no herpetic lesions were documented. Other viral studies for HSVII, Epstein-Barr virus, and cytomegalovirus, as well as viral

cultures, were negative. No renal dysfunction was documented. No malignancy was found.

Skin testing for vancomycin was not performed. The patient did not display a Type I hypersensitivity IgE-mediated reaction, but rather an immunological reaction considered to be of a Type III or Type IV hypersensitivity. No well-defined standards are available for vancomycin skin testing.^{18,19} A vancomycin challenge^{12,16} to evaluate reproducible symptoms was not performed due to severity of the present reaction. The eruption had worsened with administration of piperacillin. Concurrent immediate hypersensitivity (Type I) to penicillin was excluded as a complicating factor by performing prick and intradermal skin testing with the major and minor determinants of penicillin. The tests were nonreactive. Other medications received (digoxin, coumadin, and enalapril) have not been associated with development of Stevens-Johnson syndrome, to our knowledge. His clinical improvement occurred before discontinuation of digoxin. He continued to receive coumadin.

Frequently reported infusion-related cutaneous reactions to vancomycin, such as "Red-man/Red-neck" syndrome, are found to occur if one gram of vancomycin is infused in less than 60 minutes in adults.²⁰ One patient experienced symptoms attributed to "Red-man" syndrome after a single vancomycin dose. With successive doses, he developed more severe symptoms of angioedema, fever, and tachycardia, despite changes in infusion rate and premedication with cyproheptadine. These symptoms resolved with cessation of the infusions. His basophils displayed *in vitro* IgE-mediated histamine release when mixed with vancomycin.¹⁷

Other less frequently reported cutaneous reactions to vancomycin include maculopapular rashes,⁷ exfoliative erythroderma,^{8,9} various types of vasculitis,^{10,11} Linear IgA Bullous Dermatitis,¹² Stevens-Johnson syndrome,^{13,14} and Toxic Epidermal Necrolysis.^{15,16} The more severe cutaneous eruptions may represent a spectrum of disease mediated by immunological mechanisms involving both immune complex formation in the skin and cell-mediated immunity as proposed for Erythema Multiforme Complex²¹ and Necrotizing Venulitis.²² The initial presentation of the eruption may not be predictive of the final, fully evolved dermatitis. A patient developed a pruritic, vesicular eruption between the fingers of both hands 2 days after the initial dose of vancomycin was given through intraperitoneal dialysis. The reaction did not progress, and weekly vancomycin therapy was continued. Two weeks later, a maculopapular rash developed. By 3 weeks, it progressed to erythema multiforme, and eventually an exfoliative dermatitis.⁹ Impaired renal function, acute or chronic, was a common underlying factor in most of these patients, allowing prolonged elevation of serum vancomycin concentrations. Adenopathy⁸ and liver function abnormalities¹⁵ have been reported very rarely in vancomycin-induced cutaneous syndromes. Although the published reports were generally of solitary cases, a manufacturer had received 15 spontaneous reports of patients experiencing Stevens-Johnson syndrome possi-

TABLE I

Associated Symptoms of Vancomycin-Induced Stevens-Johnson Syndrome

Fever to 39.4°C
Chills/malaise
Pain/spasm: outer ears and sternum
Exfoliative erythrodermatitis: generalized, greater prominence over extremities
Edema: face, extremities
Conjunctival injection
Palatal petechiae
Lymphadenopathy: inguinal, axillary, cervical
Hepatitis
Neutropenia
Eosinophilia

bly associated with the use of vancomycin. One patient also had lymphadenopathy, and five patients also had hepatitis. These cases have occurred from the time of market introduction of vancomycin through December 31, 1994 (personal communication, Jennifer L. Riggins, Pharm D., Division of Medical Information, Lilly Research Laboratories, Indianapolis, Indiana, June 22, 1995).

The treatment of the serious cutaneous eruptions included cessation of the vancomycin in all cases. Three patients developed skin lesions while receiving systemic corticosteroids for their underlying diseases. Antihistamine alone or in combination with a steroid were the usual therapies. In two patients treated with prednisone, attempts to taper dosage resulted in recurrences of the initial maculopapular rash and eosinophilia,¹⁴ or erythema.¹⁵

In this patient, the onset of the rash occurring after 17 days of antibiotic therapy, the continued symptoms after discontinuation of the drug, and the resolution of the cutaneous toxicity of Stevens-Johnson syndrome followed the typical 3 to 4-week time course, as in the other reported cases of vancomycin-induced eruptions. The patient's cutaneous lesions and abnormal liver functions tests, with the exception of a persistent elevation of the LDH, had resolved by Day 17 of prednisone administration. This patient's sign/symptom complex as listed in Table I illustrate the complete range of the toxicities that occurred in this patient.

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