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A Case of Hypersensitivity Syndrome to Both Vancomycin and Teicoplanin

Drug hypersensitivity syndrome to both vancomycin and teicoplanin has not been previously reported. We describe here a 50-yr-old male patient with vertebral osteomyelitis and epidural abscess who developed hypersensitivity syndrome to both vancomycin and teicoplanin. Skin rash, fever, eosinophilia, interstitial pneumonitis, and interstitial nephritis developed following the administration of each drug, and resolved after withdrawing the drugs and treating with high dose corticosteroids. The vertebral osteomyelitis was successfully treated with 6-week course of linezolid without further complications. Skin patch tests for vancomycin and teicoplanin was done 2 months after the recovery; a weak positive result for vancomycin (10% aq.,+at D2 and +at D4 with erythema and vesicles; ICDRG scale), and a doubtful result for teicoplanin (4% aq.-at D2 and±at D4 with macular erythema; ICDRG scale). We present this case to alert clinicians to the hypersensitivity syndrome that can result from vancomycin and teicoplanin, with possible cross-reactivity, which could potentially be life-threatening.

Key Words : *Drug Hypersensitivity; Patch Tests; Vancomycin; Teicoplanin; linezolid*

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INTRODUCTION

Drug hypersensitivity syndrome is a severe, idiosyncratic multi-system reaction caused by drugs, defined by the clinical triad of fever, rash and internal organ involvement (1). It is potentially life-threatening with significant morbidity. Drug hypersensitivity syndrome due to glycopeptide antibiotics, such as vancomycin or teicoplanin, is a rare phenomenon. While cases of suspected drug hypersensitivity syndrome due to vancomycin have been reported previously (2-4), only one case of drug hypersensitivity syndrome due to teicoplanin has been reported in literature (5). Here, we describe a patient with vertebral osteomyelitis and an epidural abscess who developed hypersensitivity syndrome to both vancomycin and teicoplanin.

CASE REPORT

A 50-yr-old man with a long-standing history of low back pain presented with rapidly increasing pain and mild fever persisting for a month following the third session of acupuncture. His medical history included alcohol-related Child-Pugh class A liver cirrhosis. Examination at a local orthopedic clinic revealed tenderness at the lumbar spine. His initial body temperature was 37.5℃. Complete blood count was normal except for mild anemia (Hgb 11.0 g/dL) and leucocytosis ($11.8 \times 10^3/\mu L$). The ESR value was 58 mm/hr. Blood chemistries showed increased C-reactive protein (CRP) (2.3 mg/dL [0-0.5]) and mild derangement in liver function (bilirubin 0.9 mg/dL [0.2-1.2], alkaline phosphatase 388 IU/L [30-115], AST 95 IU/L [0-40], ALT 45 IU/L [0-40]). L-spine MRI showed the possibility of infectious vertebral osteomyelitis with epidural abscess extending to the paravertebral area.

After blood was taken for culture, he was empirically started on vancomycin intravenously at a dose of 1 g every 12 hr. Blood cultures were negative. His body temperature dropped below 37℃ after the fifth day of vancomycin treatment. On day 18 of vancomycin treatment, he presented with a generalized maculopapular rash and his body temperature rose

up to 39°C. The blood chemistry showed increased CRP (12.1 mg/dL [0-10]) and creatinine (2.2 mg/dL [0.7-1.4]) level. The white blood cell count was $16.9 \times 10^3/\mu L$ and the eosinophil count was 1,605/μL. The ESR was 55 mm/hr. Vancomycin was stopped and intravenous ceftriaxone was started at a dose of 1 g every 8 hr for 2 days. Because he remained febrile and the skin rash persisted and desquamated, all antibiotics were withdrawn. Gradually, skin rash improved and he became afebrile. The follow-up L-spine MRI showed slight improvement of the vertebral osteomyelitis and epidural abscess. Four days after discontinuing all the antibiotics, he was started on teicoplanin intravenously at a dose of 600 mg every 48 hr. However, on the third day of teicoplanin treatment, a generalized cutaneous maculopapular rash developed accompanied by respiratory and gastrointestinal symptoms; non-productive cough, dyspnea, wheezing, abdominal pain, nausea and vomiting. Crackling sounds were heard on both lung fields. The white blood cell count was $15.2 \times 10^3/\mu L$ and the eosinophil count increased to 3,648/μL. The serum creatinine level was elevated up to 4.4 mg/dL and the CRP level was 12.85 mg/dL. The chest radiography and chest computed tomography scan suggested the possibility of a hypersensitivity pneumonitis. All drugs were stopped and he was referred to our department.

Under the diagnosis of drug hypersensitivity syndrome with hypersensitivity pneumonitis and nephritis, methylprednisolone was started with 30 mg every 6 hr. After 3 days of the treatment, the serum creatinine decreased to 1.6 mg/dL and the eosinophil count decreased to 136/μL. The respiratory and gastrointestinal symptoms disappeared, and skin rash and fever improved. The L-spine MRI showed aggravated osteomyelitis and paravertebral abscess. Endoscopic surgery was done for curettage. Microscopic examination and culture studies of the resected bony tissue were negative for microorganisms. PCR study for *Mycobacterium tuberculosis* was negative. After the surgery, linezolid was started at a dose of 600 mg every 12 hr. Prednisolone was slowly tapered over 2 weeks. The patient was successfully treated with 4 weeks of intravenous and 2 weeks of oral linezolid without further complications.

The skin patch tests for vancomycin and teicoplanin was done 2 months after the hypersensitivity syndrome resolved. The patch tests showed a weak positive result for vancomycin (10% aq.,+at D2 and +at D4 with erythema and vesicles; ICDRG scale), and a doubtful result for teicoplanin (4% aq. –at D2 and ±at D4 with macular erythema; ICDRG scale). Patch tests for ceftriaxone and 27 other control drugs showed negative results. The patch tests with 10% aq. vancomycin and 4% aq. teicoplanin were done in 20 control patients who had experienced drug hypersensitivity to drugs other than vancomycin and teicoplanin, and they all showed negative results to vancomycin and teicoplanin.

DISCUSSION

Hypersensitivity syndrome, or drug rash with eosinophilia and systemic symptoms (DRESS), is a well known finding with anticonvulsants and sulfonamide drugs (6). Bocquet and his group proposed a criteria for the diagnosis for DRESS syndrome: cutaneous drug eruption, hematological abnormalities (eosinophilia more than 1.5×10^9/L or presence of atypical lymphocytes) and systemic involvement (adenopathies more than 2 cm in diameter or hepatitis or interstitial nephritis or interstitial pneumonitis or carditis) (6, 7). The patient presented here meets the criteria: skin rash resulting in exfoliative dermatitis, eosinophilia, interstitial pneumonitis, and possible interstitial nephritis suggested by azotemia.

Severe adverse drug reactions such as drug hypersensitivity syndrome caused by vancomycin is a rare phenomenon with only few cases reported in literature, despite its relatively more frequent incidences of cutaneous hypersensitivity reactions (2-4). Drug hypersensitivity syndrome due to teicoplanin has been reported in only one case recently (5). The diagnosis was made on the basis of signs and symptoms associated with the syndrome which rapidly resolved after withdrawal

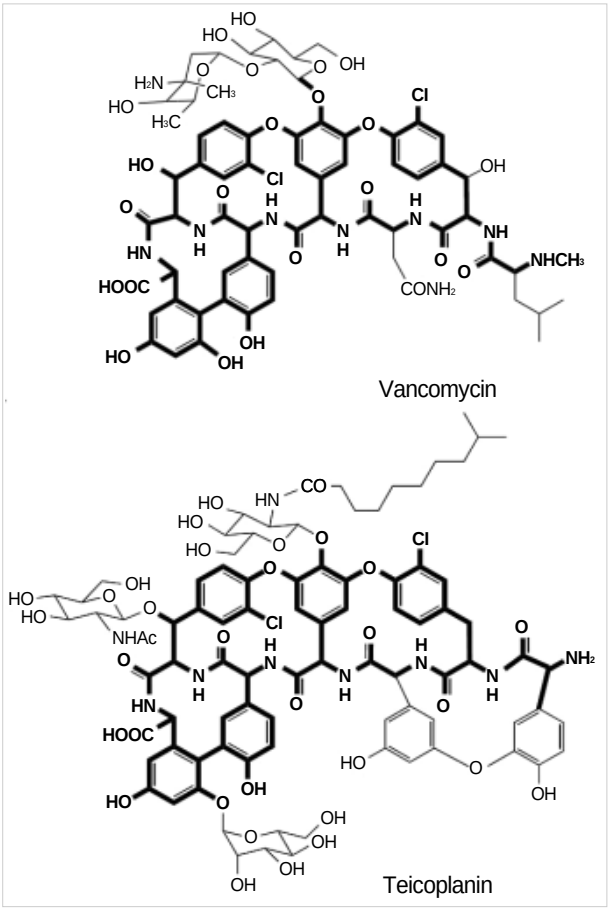

Fig. 1. Chemical structures of vancomycin and teicoplanin. The core common to these molecules is shown in bold (Adapted from Van Babeke F. Curr Opin Pharmacol. 2004; 4: 473).

of the drug. Our patient had not only the hypersensitivity syndrome to vancomycin, but also to teicoplanin. Improvement of the maculopapular skin rash and pyrexia after discontinuation of vancomycin, worsening of the skin lesions and newly developed respiratory and gastrointestinal symptoms after starting teicoplanin clearly suggest that both of these drugs caused hypersensitivity syndrome. The symptoms and signs of hypersensitivity syndrome diminished after removal of all antibiotics and starting treatment with high dose corticosteroids.

It has been reported on the possible allergic cross-reactivity between vancomycin and teicoplanin in a few previous reports; maculopapular rash (8), erythrodermic rash (9), vasculitis (10), and drug fever after vancomycin induced red man syndrome (11). Only one report showed positive patch tests for both vancomycin and teicoplanin in a patient with hypersensitivity to vancomycin. However, teicoplanin was not used and its potential hypersensitivity was not determined (12). Our case clinically suggested a possible cross-reactivity between these glycopeptide antibiotics in the hypersensitivity syndrome. The reason for this cross-reactivity is unclear, but it may well be due to the fact that both of these antibiotics share the similar glycopeptide structure (Fig. 1).

Previous reports used 4% diluted teicoplanin (12) and 0.05-5% diluted vancomycin in the patch tests (12, 13). However, the optimal concentration of vancomycin in the patch tests has not yet been established. We used 10% diluted vancomycin in the patch test because 10% dilution is the most commonly used concentration used in drug patch tests. We have done the patch tests with 10% aq. vancomycin and 4% aq. teicoplanin in 20 control patients who had not experienced any type of hypersensitivity reaction against vancomycin or teicoplanin, and they all showed negative results. Our experience supports that 10% diluted vancomycin can be used in patch tests.

Linezolid is reported to be an effective agent in treating patients with osteomyelitis due to linezolid-susceptible Gram positive bacteria, who are intolerant to vancomycin or have resistant Gram-positive infection (14). Despite the absence of identifiable microorganisms in our patient, empirical targeting of Gram (+) bacteria and the use of linezolid resulted in successful treatment of the vertebral osteomyelitis and epidural abscess.

We present this case to alert clinicians to the hypersensitivity syndrome that can result from both vancomycin and teicoplanin, which may present as a life-threatening emergency. Furthermore, we suggest the possible cross-reactivity of these glycopeptide antibiotics in the hypersensitivity syndrome and show that linezolid is an effective and safe alternative.

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