Vancomycin-induced neutropenia associated with anti-granulocyte antibodies

R.E. DOMEN, S. HOROWITZ

Abstract: Neutropenia is a rare complication associated with vancomycin, and the cause of this adverse reaction is not well understood. We report a case of vancomycin-induced neutropenia in which we were able to demonstrate anti-granulocyte antibodies. We also report the results of a bone marrow examination along with a brief review of the literature.

Vancomycin is a bactericidal antibiotic active against gram-positive cocci, but its most important use is in treating serious gram-positive infections in patients with penicillin allergy or penicillin-resistant staphylococcal and streptococcal infections. Neutropenia has rarely been reported in association with vancomycin, and the pathophysiology of this adverse reaction has not been delineated. We report a case of neutropenia and myeloid hypoplasia of the bone marrow associated with anti-granulocyte antibodies in a patient who received vancomycin. We also review the literature of vancomycin-induced neutropenia.

Case Report

The patient was a 36-year-old white male with a history of intravenous cocaine and alcohol abuse who presented with a three-week history of fever, chills, severe headache, general malaise, and weight loss. On admission to the hospital the patient had a temperature of 102°F and a white blood cell (WBC) count of 11.2 x 10^9/L with 70% neutrophils, 13% bands, 12% lymphocytes, and 5% monocytes. All tests for hepatitis A and hepatitis B were negative. The test for HIV was also negative. Prior medications included oral Keflex and penicillin without resolution of symptoms. Subsequent evaluation revealed methicillin-resistant Staphylococcus aureus endocarditis. On hospital day 2, intravenous vancomycin (1 gm every 12 hours) and gentamicin (80 gm every 8 hours) was started.

The hospital course was complicated by septic pulmonary emboli and epididymitis. On day 7, gentamicin was discontinued and medications were changed to intravenous vancomycin (500 mg every 6 hours) and oral rifampin (600 mg once daily). The WBC count was 11 x 10^9/L with 73% neutrophils and 0% bands. The WBC count continued to decrease and on day 28 was 3.3 x 10^9/L with 0% neutrophils and 1% bands, 24% monocytes, 68% lymphocytes, and 7% atypical lymphocytes. All antibiotics were discontinued and on hospital day 29 a bone marrow biopsy and aspiration were obtained. At the time of the bone marrow examination, the WBC count was 2.6 x 10^9/L with 1% neutrophils and 1% bands, 34% monocytes, 59% lymphocytes, and 5% atypical lymphocytes.

Bone marrow examination demonstrated a mild myeloid hypoplasia with a notable decrease in segmented neutrophils, and overall cellularity ranged from 25% to 50%. There were 2% blasts, 2% promyelocytes, 15% myelocytes, 6% metamyelocytes, 13% bands, 1% segmented neutrophils, 5% pronormoblasts and basophilic normoblasts, 41% polychromatic and orthochromatic normoblasts, 13% lymphocytes, and 2% plasma cells. Myeloid-to-erythroid ratio was 0.8 (normal 1.1–3.5). Special stains for bacteria, acid-fast bacilli, and fungi were negative.

On hospital day 30, the patient’s WBC count was 4.5 x 10^9/L with 14% neutrophils and 8% bands. The WBC count continued to increase, and on day 41 the WBC count was 6.3 x 10^9/L with 35% neutrophils and 7% bands, 1% basophils, 8% monocytes, and 49% lymphocytes. The patient was discharged well on day 42.

Materials and Methods

Studies to detect the presence of granulocyte-specific antibodies were performed with serum obtained on hospital day 28 (while the patient was still receiving vancomycin) and day 29 (24 hours after vancomycin...
was discontinued). The serum samples were tested for granulocyte antibodies by granulocyte agglutination (GA)\(^1\) and granulocyte immunofluorescence (GIF)\(^2\) with granulocytes obtained from eight normal individuals previously typed for granulocyte-specific antigens NA1, NA2, NB1, NB2, NC1, and 9a. The patient’s serum was tested in both assays with and without the addition of vancomycin to the test system (drug concentration in the GA assay was 0.1 mg/mL and 0.05 mg/mL in the GIF assay).

The presence of HLA antibodies in the serum of the patient was assessed by lymphocytotoxicity\(^3\) with a panel of 30 HLA-typed lymphocytes selected to represent the well-categorized HLAA and HLA-B locus antigens. If HLA antibodies were detected, the serum would then be absorbed with pooled platelets to remove this reactivity and the platelet-absorbed serum retested in GA and/or GIF for identification of granulocyte-specific antibodies.\(^4\)

**Results**

Both serum samples demonstrated a weakly reactive granulocyte-specific antibody in each of the assays used for antibody testing. Although a GA antibody was detected with one of the eight granulocyte panel cells, granulocyte antibodies were best demonstrated with the GIF assay, in which equivalent antibody activity was observed with all panel cells tested. Since no HLA antibodies were detected in the test specimens, the granulocyte antibodies were presumed to be granulocyte specific. Addition of drug to the GA and GIF test systems did not enhance or change the pattern or the strength of antibody activity in either assay.

**Discussion**

Including the present case, we were able to find 16 well-documented and reported cases of vancomycin-related neutropenia.\(^5-17\) Three additional unclear cases have also been reported,\(^18\) but those patients had also received courses of penicillin or cephalosporins, which have been reported to cause neutropenia. In another confusing case,\(^19\) the neutropenia resolved while the patient was still receiving vancomycin.

In 15 of the 16 well-documented cases, as with our patient, the neutropenia did not occur until two to six weeks after continuous intravenous administration of vancomycin, and in all 16 cases the neutropenia was quickly reversible after discontinuation of the drug. As in our case, the neutrophil count usually began to rise within 24 hours after the last dose of vancomycin. Patients with renal failure, however, may not manifest the neutropenia until several weeks after vancomycin is discontinued.\(^9-15\)

Although our patient had received gentamicin, it was discontinued more than three weeks prior to the nadir of his neutropenia. We found only one well-documented case of gentamicin-induced neutropenia in a search of the English language literature.\(^20\) The neutropenia in that patient appeared after seven days of receiving gentamicin, and recovery was evident within three days after the drug was discontinued.

It is also highly unlikely that rifampin was the cause of our patient’s neutropenia, although he was receiving this drug at the time neutropenia developed. Most reported cases of neutropenia associated with rifampin have been in tuberculosis patients who were also receiving daily isoniazid and ethambutol.\(^21\)

In addition to our case, six other reported cases of vancomycin-induced neutropenia have had detailed bone marrow examinations. The bone marrow findings have been variable. Our patient’s bone marrow showed mild myeloid hypoplasia with a shift to less mature forms, and maturation arrest with only a rare segmented neutrophil seen. Others have reported either granulocytopenia with maturation arrest,\(^16\) or severe myeloid hypoplasia.\(^5,15\) On the other hand, Kaufmann et al.\(^11\) noted hyperplasia of the granulocytic series with normal maturation of all myeloid precursors, and West\(^17\) reported only slight hypocellularity with normal myeloid precursors and no bone marrow suppression.

The mechanism of vancomycin-induced neutropenia is unclear, but it may be an immunologic reaction. Serum specimens taken from our patient while he was neutropenic, and either during vancomycin administration or shortly after its discontinuance, demonstrated the presence of granulocyte-specific antibodies. Unfortunately, specimens prior to his neutropenia or following its resolution were not available for granulocyte antibody testing. Nor were we able to demonstrate technically the presence of “drug-dependent” granulocyte antibodies, since the presence or absence of drug in the test system had no effect on the antibody profile observed. Nevertheless, the presence of granulocyte-specific antibodies did coincide with a paucity of mature granulocyte forms in the bone marrow from this patient. Granulocytopenia secondary to increased peripheral destruction usually is associated with a marrow showing normal or increased numbers of granulocyte precursors,
with band and segmented forms virtually absent from the marrow.

Anti-granulocyte antibody studies have been reported in only five cases. Weitzman and Stossel 18 found anti-neutrophil antibodies in the sera of three patients who had received vancomycin; however, all were also receiving cephalosporins, which have been associated with anti-granulocyte antibodies. Kauffman et al. 11 were unable to detect anti-neutrophil antibodies with two different methods in a patient receiving only vancomycin. Milsteen et al. 15 were also unable to demonstrate vancomycin-dependent leukoagglutinins. The possibility of a hypersensitivity reaction to vancomycin is indirectly supported by observations of skin rashes, 9,15 peripheral blood eosinophilia, 15,17 and vancomycin-induced lymphocyte transformation. 14 Interestingly, a recent report has demonstrated vancomycin-dependent antibodies associated with thrombocytopenia. 22 Therefore, drug-dependent antibodies should be considered as a cause of any unexplained cytopenia.

In conclusion, we have demonstrated the presence of granulocyte-specific antibodies in a case of vancomycin-induced neutropenia. This suggests that, at least in some cases, vancomycin-induced neutropenia may have an immunologic basis. Neutropenia is becoming recognized as an infrequent complication of vancomycin therapy that is easily reversible by withdrawal of the drug. In order to guard against this potential complication, we suggest that the WBC count and differential be monitored in all patients receiving long-term vancomycin therapy.

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References


Ronald E. Domen, MD, Miller Memorial Blood Center, 1465 Valley Center Parkway, PO. Box 2867, Bethlehem, PA 18016; Susan Horowitz, MD, University of South Florida College of Medicine, Tampa, FL 33612.