Vancomycin-Induced Neutropenia Associated With Fever: Similarities Between Two Immune-Mediated Drug Reactions

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A 39-year-old woman being treated for osteomyelitis with vancomycin developed severe neutropenia and drug fever. After she discontinued therapy, both disorders quickly resolved. These adverse reactions have rarely been reported with vancomycin, and share many similarities with regard to clinical features and postulated mechanisms of induction. To our knowledge this is the first case documenting drug fever as a principal component of vancomycin-induced neutropenia, and provides further evidence in support of an immune-mediated mechanism. (Pharmacotherapy 1999;19(2):240–244)

Vancomycin is an antibiotic often administered to treat gram-positive bacterial infections that are resistant to other antimicrobial agents. It has been available for over 30 years, and experience has shown that it is both safe and clinically effective. Few alternatives are currently available for patients intolerant to vancomycin therapy. Adverse effects such as ototoxicity, nephrotoxicity, and infusion-related red man syndrome are well described. A less common adverse effect, vancomycin-induced neutropenia, is the subject of several case reports.1–15

Vancomycin-induced neutropenia typically occurs after 10 days or more of therapy and does not appear to be related to serum drug concentrations.16 On discontinuing therapy, white blood cell (WBC) counts and absolute neutrophil counts (ANCs) rapidly return to normal, usually within 2–5 days. Published case reports have not documented fever as a principal component of the disorder. Since both vancomycin-induced neutropenia and drug fever are postulated to be immune-mediated events, it is not surprising that fever may also result.17–19 The usual course of drug-induced fever mimics that of vancomycin-induced neutropenia, with delayed onset and rapid resolution of symptoms occurring when the offending agent is discontinued.

Case Report

A 39-year-old woman with sickle cell SS disease and a history of chronic osteomyelitis of the left ankle was admitted to undergo a right latissimus free flap to the left leg with segmentectomy, a procedure she had undergone 4 times in the past. One day before surgery she underwent an exchange transfusion, which was well tolerated. On hospital day 3 the bone was debrided and skin flap was performed. Three segments of bone were obtained and sent for culture. The surgery was completed without complication. Postoperatively the patient began therapy with aspirin 81 mg/day, patient-controlled analgesia with morphine, cefazolin 1 g and gentamicin 80 mg intravenously every 8 hours, folic acid 1 mg/day orally, heparin 5000 U subcutaneously twice/day, and acetaminophen as needed. White blood cell count before surgery was 6.5 x 10^3/mm^3, with hemoglobin 9.6 g/dl, and hematocrit 28%; temperature was 37.1°C.

On hospital day 5 the patient had a temperature of 38.3°C with WBC count 12.0 x 10^3/mm^3. On day 6 all three bone cultures were positive for growth of methicillin-resistant coagulase-negative Staphylococcus and Candida albicans. At that time gentamicin was discontinued, and vancomycin 1 g intravenously every 12 hours...
and oral fluconazole 400 mg/day were started. Patient-controlled analgesia was replaced with sustained-release morphine plus oxycodone for breakthrough pain. Cefazolin was inadvertently continued for 2 additional days. On hospital day 7 the patient remained febrile (38.5°C), with WBC count 7.2 x 10^3/mm^3 and hematocrit 28%. Heparin was discontinued.

The woman continued to be febrile with this regimen despite negative blood and sputum cultures, chest radiograph, and urinalysis. She reported feeling well, with fever as her only complaint. On day 13, WBC count was 4.0 x 10^3/mm^3 with ANC 2120/mm^3. One of three blood cultures drawn on day 9 grew out *C. albicans* on day 16. Maximum temperature at that time was 40.4°C.

The WBC count continued to fall to 2.1 x 10^3/mm^3 (ANC 378/mm^3) on day 17 and to 1.4 x 10^3/mm^3 (ANC 238/mm^3) on day 18. Vancomycin and fluconazole were then discontinued. The patient became afebrile within 48 hours, and both WBC count and ANC quickly rebounded to 2.6 x 10^3/mm^3 (ANC 234/mm^3) on day 20, 4.3 x 10^3/mm^3 (ANC 1548/mm^3) on day 21, and 6.4 x 10^3/mm^3 (ANC 2304/mm^3) on day 22 (Figure 1). Infectious causes of neutropenia such as acid-fast bacilli, Epstein-Barr virus, cytomegalovirus, and parvovirus B19 serologies were reported as negative.

Fluconazole was restarted 4 days after it was discontinued (day 22), and one double-strength trimethoprim-sulfamethoxazole tablet twice/day was started on day 23. The patient received a 6-week outpatient course of these antibiotics, and did well without further fever or neutropenia.

### Discussion

The incidence of vancomycin-induced neutropenia is estimated to be approximately 2%, and does not seem to be related to serum drug concentrations. It was proposed that impurities in the original formulation may have contributed to the toxicity; however, a retrospective study of 98 patients from 1974–1981 who received reformulated vancomycin also revealed a 2% incidence. A retrospective review of 49 surgical patients found vancomycin-associated neutropenia to occur much more frequently, with 18% of patients developing leukocyte counts below 4.0 x 10^3/mm^3, and 8% having severe neutropenia defined as an ANC less than 1000/mm^3. Although the likelihood of vancomycin being the causative agent in these patients is uncertain, it may suggest that this adverse effect is underrecognized.

A number of cases of vancomycin-associated neutropenia have been reported in the literature, the first dating back to the late 1950s. Many of these included patients receiving concomitant drugs also known to have neutropenia as a side effect, making the contribution of vancomycin uncertain. The high risk associated with neutropenia also made it difficult to confirm vancomycin as the causative agent by rechallenge. One patient was rechallenged without recurrence, but the duration of rechallenge was only 5 days, and most patients required 2 or more weeks of therapy before becoming neutropenic.

In addition to delayed onset, vancomycin-induced neutropenia has always been reported as reversible, with complete resolution taking place in 2–5 days. Besides the question of rechallenge, it also remains uncertain whether these patients can be successfully desensitized once the initial bout of neutropenia is resolved. This is an important question due to the limited number of alternative therapies that are available for serious gram-positive infections. One report in the literature documented successful administration of colony-stimulating factors to allow continuation of vancomycin in two patients who became neutropenic during therapy.

The pattern of neutropenia in our patient was consistent with reported cases (Table 1). The reaction appeared after 12 days of vancomycin and resolved approximately 72 hours after the drug was discontinued.

In general, drug-induced neutropenia may be the result of either immune-mediated destruction of neutrophils or a direct suppressive effect on bone marrow. The mechanism of vancomycin-induced neutropenia remains unclear, but much evidence supports an immune-mediated event. Examinations of bone marrow aspirates have

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### Figure 1. Time course of WBC count, ANC, and temperature curve in relation to drug therapy. WBC = white blood cell count; ANC = absolute neutrophil count; Tm = maximum daily temperature; cfz = cefazolin; tmp/smx = trimethoprim-sulfamethoxazole.
been inconsistent, with reports ranging from granulocytic hypoplasia\textsuperscript{9, 14, 15} to normal myeloid precursor cells with slight hypocellularity\textsuperscript{4} and granulocytic hyperplasia with normal maturation.\textsuperscript{3} Granulocytic hyperplasia is more consistent with peripheral destruction of leukocytes than bone marrow suppression. In addition, the rapid recovery of neutrophils commonly seen in vancomycin-induced neutropenia suggests that bone marrow is not significantly damaged.\textsuperscript{22}

Further evidence supporting immune-mediated destruction of neutrophils is found in a number of published case reports. In one series, antineutrophil antibodies were isolated from the serum of three patients.\textsuperscript{13} Others also reported the presence of antineutrophil antibodies.\textsuperscript{14} More evidence for an immune-mediated mechanism was the discovery of a positive lymphocyte transformation test in a patient with suspected vancomycin-induced neutropenia, which suggests sensitization of lymphocytes to the agent.\textsuperscript{11} In contrast, one investigator failed to isolate antibodies in a patient despite using two different assays.\textsuperscript{3} However, this cannot rule out an immune-mediated contribution, as antibodies may be difficult to detect in routine practice and are rapidly cleared once drug is withdrawn.\textsuperscript{23, 24}

Additional mechanistic insight can be gained from examining patients with vancomycin-induced neutropenia for clinical signs of hypersensitivity reactions. Two case reports described skin rashes consistent with an allergic response associated with onset of neutropenia. Both rashes quickly resolved once the agent was discontinued.\textsuperscript{5, 7} Eosinophilia also was reported in at least three patients.\textsuperscript{4, 22} The simultaneous

<table>
<thead>
<tr>
<th>Patient Description</th>
<th>Days of Vancomycin before Onset (nadir\textsuperscript{a})</th>
<th>Additional Drugs</th>
<th>Time to WBC Recovery</th>
<th>Fever During Vancomycin Therapy</th>
<th>Rapid Fever Resolution after Discontinuing Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-year-old man with vertebral osteomyelitis\textsuperscript{22}</td>
<td>20 (WBC 1800/mm\textsuperscript{3})</td>
<td>Gentamicin, triamterene-HCTZ</td>
<td>4 days</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>67-year-old woman with cellulitis, sepsis\textsuperscript{11}</td>
<td>17 (WBC 2300/mm\textsuperscript{3}, ANC 1200/mm\textsuperscript{3})</td>
<td>Phenytoin, furosemide, insulin, acetaminophen</td>
<td>5 days</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2-year-old boy with endocarditis\textsuperscript{10}</td>
<td>15 (WBC 1400/mm\textsuperscript{3}, ANC 459/mm\textsuperscript{3})</td>
<td>Gentamicin, cefotaxime, penicillin G</td>
<td>5 days</td>
<td>39.2°C</td>
<td>Afebrile 5 days after DC</td>
</tr>
<tr>
<td>37-year-old man with neutropenic fever\textsuperscript{9}</td>
<td>14 (WBC fell from 2000 to 600/mm\textsuperscript{3}, with ANC 0)</td>
<td>Mezlocillin, tobramycin, TMP-SMX</td>
<td>2 days</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>59-year-old woman with chronic prostatic hip infection\textsuperscript{6}</td>
<td>27 (WBC 1700/mm\textsuperscript{3})</td>
<td>Netilmicin, cimetidine, phenylbutazone, cefazolin</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>48-year-old man with rheumatic disease\textsuperscript{5}</td>
<td>15</td>
<td>Diphenhydramine</td>
<td>“Prompt”</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>32-year-old man with endocarditis\textsuperscript{5}</td>
<td>30</td>
<td>Rifampin, furosemide, digoxin</td>
<td>7 days</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>61-year-old man with osteomyelitis\textsuperscript{4}</td>
<td>37</td>
<td>Gentamicin, propoxyphene, acetaminophen, heparin, digoxin, methicillin, indomethacin</td>
<td>“Quickly”</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>55-year-old man, paraplegic, with osteomyelitis, endocarditis\textsuperscript{4}</td>
<td>24 (WBC 2100/mm\textsuperscript{3})</td>
<td>Heparin, codeine, flurazepam</td>
<td>2 days</td>
<td>38.1°C</td>
<td>Yes</td>
</tr>
<tr>
<td>10-year-old girl with endocarditis\textsuperscript{2}</td>
<td>35 (WBC 500/mm\textsuperscript{3})</td>
<td>Folic acid, heparin gentamicin, penicillin G, erythromycin, rifampin,</td>
<td>3 days</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>39-year-old woman with osteomyelitis\textsuperscript{5}</td>
<td>12 (WBC 1400/mm\textsuperscript{3}, ANC 234/mm\textsuperscript{3})</td>
<td>Cefazolin, fluconazole, gentamicin, morphine, folic acid, aspirin</td>
<td>3 days</td>
<td>40.4°C</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Defined as white blood cell count less than 2500/mm\textsuperscript{3} after starting vancomycin therapy.

\textsuperscript{b}Our patient.

WBC = white blood cell count; HCTZ = hydrochlorothiazide; ANC = absolute neutrophil count; TMP-SMX = trimethoprim-sulfamethoxazole; NR = not reported; DC = discontinue.
appearance of drug fever in our patient provides additional evidence of an immune-mediated hypersensitivity mechanism.

In addition to the onset of neutropenia, our patient's clinical course was defined by a febrile period characteristic of drug fever (Figure 1). Drug fever is defined as an elevated body temperature that coincides with administration of a drug but subsides once the agent is discontinued. The first critical evaluation of the literature on drug fever was an analysis of 51 episodes diagnosed between 1959 and 1986, together with 97 published case reports. Only one case of vancomycin-induced fever was identified and it is not known if this occurred before or after reformulation of vancomycin.

Despite frequent use, very few cases of vancomycin-induced drug fever have been reported in the literature. The earliest report, published in 1962, found an incidence of approximately 5%, but this was not supported by subsequent publications. In a retrospective study from 1974–1981, none of 98 patients experienced a sustained fever. One developed transient fever with wheezing and chills after the first dose of vancomycin. Another patient developed a fever while receiving both vancomycin and rifampin; both drugs were discontinued and the fever subsided. Another case report described a 37-year-old woman receiving long-term hemodialysis and had an unexplained, persistent low-grade fever for 6 weeks that was believed to be associated with vancomycin.

The clinical course of drug fever mimics that of vancomycin-induced neutropenia, with delayed onset and rapid resolution following discontinuation of the offending agent. Drug fever typically has its onset after 7 days or more of therapy and resolves within 48–72 hours, as occurred in our patient. It is thought to be dosage independent and is occasionally accompanied by eosinophilia. It is difficult to distinguish drug fever clinically from bacteremic infections or other febrile disorders. Many assume the pattern to be one of sustained fever. However, many patients do not have a fever pattern that might be considered typical. In one evaluation, a fever pattern was reported in 62% of 92 patients. Most patterns were characterized as either hectic (41%) or remittent (28%), and only a few patients experienced rash (18%) or eosinophilia (22%). It is important to realize that antipyretics are frequently given and may mask the underlying fever.

Numerous mechanisms have been identified by which specific drugs may induce fever and can be classified into broad categories: extension of pharmacologic action, altered central or peripheral thermoregulation, drug administration, idiosyncratic reactions, and immune-mediated hypersensitivity reactions. The last is the most common mechanism. It results in formation of drug-antibody immune complexes, lymphocyte sensitization, and release of fever-inducing lymphokines. Classic signs of allergic reactions such as eosinophilia, urticaria, and anaphylaxis are generally not features of this disorder.

The appearance of neutropenia and fever in our patient was likely due to vancomycin based on its abrupt resolution after drug discontinuation and a negative fluconazole rechallenge. The time of onset and abrupt resolution of symptoms are consistent with literature reports. Two other agents that rarely cause neutropenia and could not be completely ruled out were fluconazole and cefazolin, although their contribution seems unlikely. Fluconazole is unlikely due to the negative rechallenge, and cefazolin was discontinued more than a week before onset of the reaction, after less than 5 days of therapy. It is also unlikely that fever was the result of fungal infection, as it appeared while the patient was receiving fluconazole and resolved after fluconazole was discontinued. If fever was the result of fungemia despite fluconazole therapy, it would not be expected to resolve rapidly once the antifungal was discontinued. Cefazolin also reportedly causes drug fever, but is an unlikely cause in our patient based on the time course.

Because hypersensitivity reactions to vancomycin are rare, descriptions of both vancomycin-induced neutropenia and drug fever are limited to case reports. Further understanding may be obtained by evaluating β-lactam-induced neutropenias. The β-lactams have perhaps the best-described allergic reaction data, and both penicillin-induced neutropenia and drug fever have been studied extensively and are documented to have been caused by immune-mediated mechanisms. In fact, in a number of patients both disorders have occurred simultaneously. Therefore, it may not be surprising that the two would occur simultaneously in our patient due to a similar hypersensitivity reaction.

As drug molecules are often too small to act as antigens themselves, they must act as haptons, binding to a larger molecule in order to be recognized as immunogenic substances. The
most commonly cited mechanism involves the drug or a metabolite first binding to a host protein, either an extracellular protein or part of a cellular wall, such as the wall of a neutrophil. This drug-protein complex functions as an antigen against which antibodies are synthesized, and an antigen-antibody immune complex forms. The immune complex triggers the activation of complement, leading to destruction of the neutrophil. During this process lymphocytes are sensitized and many pyrogenic substances may be released, resulting in reactions such as fever.\(^{19}\)

An immunologic mechanism such as this is consistent with the disorder in our patient, as well as case reports describing rash, eosinophilia, and laboratory findings of sensitized lymphocytes and antineutrophil antibodies.

Based on our patient’s clinical course and a review of the literature, it is most likely that neutropenia and drug fever were induced by vancomycin. Case reports of the reaction have failed to examine the role of drug fever. Although several have noted patients to be febrile while receiving vancomycin, the course of fever and its correlation to therapy were not described in sufficient detail to allow for analysis.\(^{3,5,10}\) Future case reports should continue to focus on concurrent clinical symptoms that may provide clues to the underlying mechanism of neutropenia. Although a small number of bone marrow aspirate results have been inconsistent, available data favor an immune-mediated mechanism. This includes the discovery of antineutrophil antibodies sensitized lymphocytes and concurrent hypersensitivity reactions such as skin rash, eosinophilia, and now drug fever. Further laboratory and clinical evidence will be necessary to confirm this immune-mediated mechanism.

References
