

Vancomycin Infiltrate-Induced Dermatitis Mimicking Bullous Cellulitis

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ABSTRACT

Extravasation of medications can manifest as tenderness, pain, tissue necrosis, and thrombophlebitis and lead to infection and severe long-term complications. Risk factors for leakage of medications include mechanical and pharmacologic mechanisms such as cannulation technique, vasoconstriction, and cytotoxicity. Well-known vesicants like anthracyclines, vinca alkaloids, and vasopressors are usually administered with proper caution. Often overlooked are many antimicrobial agents, which typically act via differences in osmolality and pH. Vancomycin harms the vascular wall by the latter (pH 2.5-4.5). Although similar in appearance to vancomycin hypersensitivity reactions (eg, linear immunoglobulin A bullous dermatosis), we present a patient whose dermatitis and subsequent cellulitis likely originated due to extravasation of the drug from the peripheral intravenous catheter. The visible dermatitis mimicked bullous cellulitis from toxin-producing *Staphylococcus aureus*, Group A *Streptococcus*, and gram-negative rods or anaerobes in the setting of neutropenia. Our case illustrates the importance of getting an appropriate history and recognizing non-infectious causes of rashes that mimic chronic infections.

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CASE PRESENTATION

A 67 year-old male presented to an outside facility with pneumonia and pancytopenia. Empiric intravenous vancomycin and piperacillin-tazobactam were started. Bone marrow biopsy revealed acute myeloid leukemia (AML). He was anxious to leave the hospital and pulled out the peripheral intravenous catheter (IVC) in his left forearm. Upon transfer to our facility he complained of ongoing pain in the left wrist and forearm at the site of the previous IVC, in addition to swelling and vesicular lesions that covered the area (Figure 1). Intravenous vancomycin, cefepime, clindamycin, and oral fluconazole and acyclovir were given. Wound and blood cultures were negative. As the area improved his regimen was de-escalated. Immediately after stopping vancomycin the bullae and erythema worsened, encompassing one-fourth of his palm and the lateral aspect of his hand. He experienced increasing pain and more limited range of motion of the wrist. Vancomycin was restarted and wound cultures were negative. Magnetic Resonance Imaging (MRI) of the forearm confirmed superficial cellulitis with no fluid collection or deeper tissue involvement. Over the next week the erythema, swelling, pain, and wrist function improved significantly. After 13 more days vancomycin was stopped. The hospital stay lasted 9 more days until cell count recovery, with no recurrence of cellulitis.

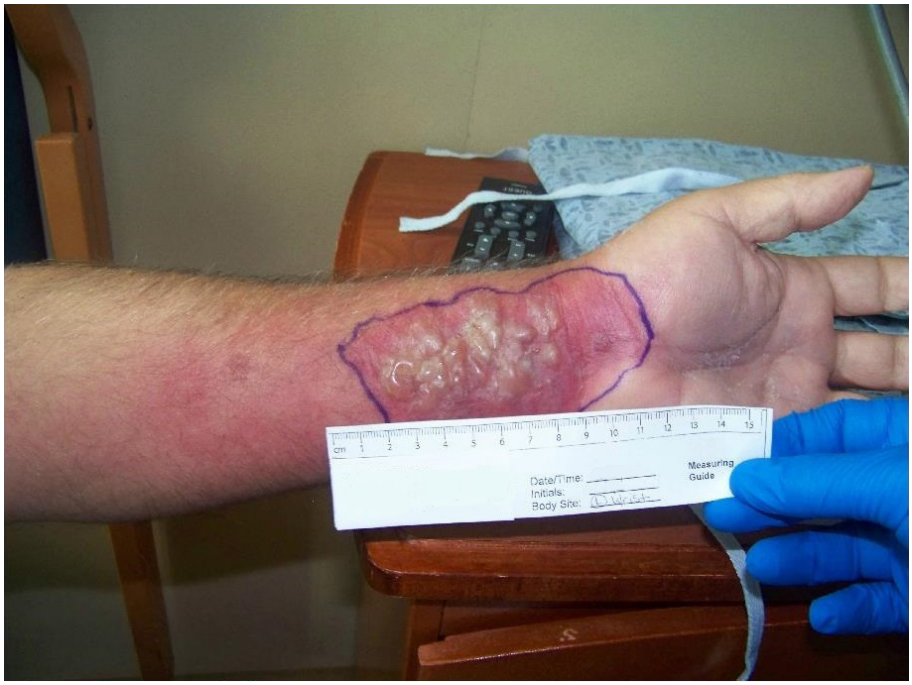
DISCUSSION

Vancomycin is a tricyclic glycopeptide antibiotic that inhibits bacterial cell wall synthesis, blocking glycopeptide polymerization by tightly binding to the D-alanyl-D-alanine segment of the cell wall precursor.[1] The bactericidal agent also alters cell membrane permeability and ribonucleic acid (RNA) synthesis and has activity against most common aerobic and some anaerobic gram-positive bacteria, such as *Staphylococci*, *Streptococci*, *Enterococci*, *Listeria*, *Diphtheroids*, and *Actinomyces*.[2] Due to its low pH that typically ranges from 2.5-4.5, vancomycin can be an irritant or vesicant to tissue and should therefore be given by a secure intravenous route of administration.[3,4]

Vancomycin was first isolated from the fungus *Streptomyces orientalis* in 1957 and gained Food and Drug Administration (FDA) approval a year later in 1958. Since this time, the drug has been associated with a wide array of adverse reactions. Initial versions of the product contained vast amounts of impurities and were brown in color, earning it the nickname "Mississippi Mud."[5] The contaminants led to increased rates of neprho- and oto-toxicity in early trials with the agent.[5,6] These complications were far less frequent with the use of subsequent formulations of vancomycin that were purer in composition. Still, utilizing the agent, especially at high serum concentrations or concomitantly with other nephro- and oto-toxic medications, can be detrimental to renal and auditory function.[3] Reversible neutropenia has been known to occur, usually after therapy of extended duration (≥ 1 week) or high cumulative dose (> 25 gram).[3] Thrombocytopenia (via induction of platelet-reactive antibodies) and agranulocytosis, although rare, have been reported.[3,7]

Additionally, vancomycin has been associated with several adverse cutaneous side effects. In most cases, these occurrences

FIGURE 1. Vancomycin infiltrate-induced dermatitis mimicking bullous cellulitis and causing ongoing pain, swelling, and vesicular lesions.



resulted from the systemic administration of vancomycin and ensuing immunological reactions to the agent. If administered too rapidly, an acute release of vasoactive mediators like histamine can result in the pseudoallergic drug reaction known as "red-man syndrome," which is commonly accompanied by flushing, rash, hypotension, dyspnea, wheezing, urticaria, and pruritus.[8] Other vancomycin-induced complications involving the soft tissue include Stevens-Johnson syndrome (SJS),[9] toxic epidermal necrolysis (TEN),[10] leukocytoclastic vasculitis,[11] drug rash with eosinophilia and systemic symptoms syndrome (DRESS Syndrome),[12] and linear immunoglobulin A bullous dermatosis (LIBD).[13] Despite offering a wealth of data on these dermatologic adverse reactions associated with vancomycin, the literature provides relatively limited reports of information regarding the extravasation of the chemical itself.[4,14,15]

If vancomycin extravasation is suspected or occurs, the infusion should be stopped immediately. However, the cannula or needle should only be removed after attempting to aspirate as much of the drug and surrounding fluid as possible, drawing back 3 to 5 mL of blood.[16,17] If feasible, the affected limb can be elevated in order to reduce swelling and promote lymphatic resorption of the agent. A cold compress can be administered for 20 to 30 minutes to reduce subsequent inflammation and potential necrosis.[18] The process can be repeated every 4 to 6 hours for the next 24 to 48 hours.[18] If local inflammation and erythema occurs, 1% hydrocortisone cream can be applied every 6 hours for 7 days or as long as symptoms persist.[16,19] A critical but often neglected point of management is action taken to appropriately document the event. Denoting a line of demarcation with an indelible pen, taking photographs of the affected area, and detailing the size and appearance of the injury are three such steps.[19] These items will be included in medical record notes and incident reports and more importantly serve as the baseline for which treatment progression and recovery are based on.

Vancomycin is not the sole antimicrobial agent that can cause significant injury via extravasation, or inadvertent leakage of medications with vesicant properties that can potentially lead to infection and other severe long-term complications.[4] In general, medications that induce harm when exposed to tissue can be classified as irritants or vesicants. Irritants typically produce self-limiting, local symptoms such as pain, tightness, inflammation, and phlebitis at the injection site or associated vein.[20] However, they rarely cause long-term complications and do not result in tissue necrosis.[20] On the contrary the leakage of a vesicant is much more toxic, resulting in severe and possibly irreversible effects including blistering, sloughing, and deep tissue destruction or death.[20] Although most are known to be irritants, some antimicrobials have been classified as vesicants in select cases.[4,19,20,21]

In addition to vancomycin, antimicrobials such as acyclovir, amphotericin, gentamicin, piperacillin-tazobactam, penicillin, pentamidine, cefotaxime, metronidazole, ciprofloxacin, doxycycline, ampicillin, erythromycin, foscarnet, nafcillin, oxacillin, ganciclovir, tetracycline, and trimethoprim-sulfamethoxazole

have all been associated with tissue irritation or damage through varying mechanisms.[4,18,19,21,22] Hyperosmolar agents, such as nafcillin and ampicillin, are one such source of injury. Introducing a hypertonic substance into the tissue causes an osmotic shift of fluid from the intracellular space to the extracellular space, leading to cell volume dysregulation, cellular transport dysfunction, reactive oxygen species formation, protein and deoxyribonucleic acid (DNA) damage, and apoptosis.[18,23] Exposure to agents with a nonphysiologic pH is detrimental as well. It is thought that alkaline compounds like acyclovir, [24] trimethoprim-sulfamethoxazole,[25] and ganciclovir[26] can penetrate deep into tissues and cause the formation of dissociated hydroxide ions that can lead to protein dissolution, collagen destruction, cell membrane compromise, and apoptosis.[18] When exposed to tissues, acidic agents such as doxycycline[27] and ciprofloxacin[22] may cause vasoconstriction, edema, eschar formation, cellular desiccation, and coagulative necrosis that result from hydrogen ion donation and the reductive capacity of the acid anion salt.[18] With its acidic pH of 2.5-4.5, vancomycin falls under the latter of these mechanisms.[3]

The method and duration of vancomycin administration can precipitate further complications. In comparison to intermittent dosing, continuous infusion of vancomycin keeps the drug in contact with the endothelial wall for extensive periods of time and can increase the risk of catheter-related thrombosis. Gullet et al[28] conducted a study that identified vancomycin as the most important risk factor for this event. Fifteen of sixteen patients who developed central venous catheter-related thrombosis had received continuous high-dose vancomycin, and the likelihood of occurrence rose with larger doses and durations of therapy.[28] Phlebitis is a common occurrence with the utilization of a peripheral line, occurring in up to 3-13% of patients with such access.[14] Given its low pH,[29] vancomycin is extremely likely to cause irritation when it comes in contact with the vascular wall. Hence the most probable cause of our patient's dermatitis and resultant bullous cellulitis was the extravasation of the drug with the indwelling peripheral IVC as he pulled it out. Although some of the aforementioned hypersensitivity reactions such as LIBD could be quite similar in appearance, they were ruled out of the differential when repeated and prolonged re-administration of vancomycin over the course of patient's stay did not result in worsening of the cellulitis. Further, LIBD is a diffuse rash not localized on the site of infusion. The patient's wound also mimicked erysipelas, a superficial cellulitis usually caused by group A β-hemolytic *Streptococci*.[30] Five percent of cases are complicated by bullae, necrosis, or hemorrhage. This bullous involvement signifies possible coinfection with *Staphylococcus aureus* (often methicillin-resistant) or anaerobic microorganisms and is associated with a prolonged disease and treatment course.[30]

If vancomycin is administered through a peripheral line, it is important to be aware of and routinely search for any signs of extravasation and phlebitis. This especially holds true in scenarios involving patients such as ours, where immunosuppression can delay the appearance of symptoms and allow more damage to occur due to a blunted immune response. In conclusion, when tissue damage occurs at the site of a peripheral IVC, consider non-infectious causes such as extravasation of the antimicrobial which may mimic a severe infection.

DISCLOSURES

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