A rare case of oxacillin-induced leukocytoclastic vasculitis

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ABSTRACT

Leukocytoclastic vasculitis is a pathology whose mechanisms are associated with the process of vascular inflammation. It is estimated that up to 24% of the cases of vasculitis are drug-related, with beta-lactam antimicrobials being one of the pharmacological groups commonly associated with this adverse outcome. Oxacillin, a semisynthetic penicillin, has a beta-lactam ring that confers biological activity and is most frequently associated with reports of leukocytoclastic vasculitis. However, similar cases related to this antimicrobial are rare, with only three cases identified in the literature. Against this background, we report a fourth case of leukocytoclastic vasculitis in a 56-year-old man, on oxacillin treatment, who developed the vasculitis on the 3rd day of antimicrobial use. In addition to oxacillin suspension, he was treated with 125 mg/day of intravenous methylprednisolone for seven days, followed by 20 mg/day of oral prednisone for four days, resulting in satisfactory remission of the skin lesions and no new adverse outcomes. This case provides further evidence supporting the potential causal relationship between the use of oxacillin and the development of leukocytoclastic vasculitis, albeit a rare occurrence. The positive response to therapeutic interventions, such as oxacillin suspension and corticosteroid treatment, underscores the effectiveness of these approaches in addressing this complication.

Keywords: Oxacillin, Beta-Lactams, Vasculitis leukocytoclastic cutaneous, Drug-related side effects and adverse reactions, Case reports.

INTRODUCTION

Leukocytoclastic vasculitis is a condition characterized by inflammation of the blood vessels, resulting in generalized symptoms, such as arthralgia, myalgia, fever, and, most commonly, purpuric skin lesions, with or without pain, in the lower and upper limbs, and whose triggering factors are diverse: neoplasms, chemical agents, infectious agents, and drugs are some examples[1]. Although the cause of leukocytoclastic vasculitis is idiopathic, it is estimated that up to 24% of cases are related to drug use, with the groups most frequently involved in this adverse outcome being sulfonamides, nonsteroidal anti-inflammatory drugs, and beta-lactam antimicrobials[2].

Oxacillin is a semisynthetic penicillin from the isoxazolylpenicillin group, with broad activity against gram-positive cocci and several species of gram-positive bacteria, whose chemical structure has a beta-lactam ring that gives it biological activity[3]. Despite the presence of this ring, which places it in a pharmacological group frequently associated with cases of leukocytoclastic vasculitis, reports of vasculitis associated with the use of oxacillin are rare. Only three reports associating this antibacterial agent with adverse outcomes were found in the scientific literature[2,4-5]. Generally, its clinical management consists of the suspension of the drug associated with the adverse outcome and, in some cases, the administration of systemic corticosteroids is necessary[5].

Given the significance of this case in enhancing the understanding and clinical management of leukocytoclastic vasculitis, the objective of this study is to present a fourth clinical case involving oxacillin-induced leukocytoclastic vasculitis and outline the therapeutic measures employed to resolve this issue. This study was previously approved by the Ethics Committee for Research with Humans at the Federal University of Rio Grande do Norte (CAAE: 29834320.4.0000.5292) under protocol number 3.994.915. The patient gave his voluntary participation by signing the Informed Consent Form.

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CASE REPORT

A 56-year-old man, 86 kg, admitted to treat pericardial abscess and infection of the right foot stump (amputated), coming from another hospital institution at the patient's request due to a history of coronary revascularization in our institution 12 years before. The patient sought hospital care five days before admission with complaints of pain in the left flank region with irradiation to the chest and left upper limb. He came in a regular general state, hemodynamically stable, afebrile, in ambient air, referring only to mild dyspnea, with decreased pulmonary auscultation to the left and distended and hypertimpanic abdomen, without other symptoms or clinical problems.

Initially treated with meropenem and vancomycin, on admission, this regimen was replaced by oxacillin (2 g, intravenous, 4/4 hours) as recommended by the infectologist. A bacterioscopy of the abscess secretion showed the presence of gram-positive cocci and a blood culture result, collected on admission, revealed the presence of oxacillin-sensitive *Staphylococcus aureus* three days later. New blood cultures were collected two weeks later but showed no growth of new microorganisms. Besides antibiotic therapy, the prescription also included subcutaneous heparin, dipyrone, tramadol, pantoprazole, and furosemide, all intravenously, and NPH insulin. Amitriptyline, quetiapine, gabapentin, acetylsalicylic acid, rosuvastatin, trimetazidine, bisoprolol, isosorbide, simethicone, folic acid, and B complex were prescribed orally.

At the beginning of the third day of hospitalization, during the oxacillin infusion, the patient complained of intense urticaria all over his body and was medicated with 180 mg fexofenadine and 20 mg prednisone, both orally, with remission of the urticarial reaction after medication. However, a few hours after the pruritic symptoms, the patient evolved with widespread petechiae formation all over the body, an episode that the patient himself associated with the use of oxacillin. On the following day, the use of this antimicrobial was discontinued and replaced by vancomycin (1 g, intravenously, 12/12 hours) after medical evaluation. However, the petechiae persisted and evolved to palpable purpuric lesions, especially on the dorsum of the hands and feet, and a rheumatologist evaluation was requested.

In the clinical evaluation, the rheumatologist described the existence of diffuse purpuric lesions throughout the body with predominance on the dorsum of the upper and lower limbs (Figure 1), but without involvement of the mucous membranes, face, and palmar and plantar areas. He also reported no clinical and laboratory evidence of extracutaneous involvement, and there was no synovitis. At no time during the course of the vasculitis did the patient complain of arthralgia, abdominal pain, paresthesia, fever, chills, or other clinical complaints that might indicate involvement of other organs.

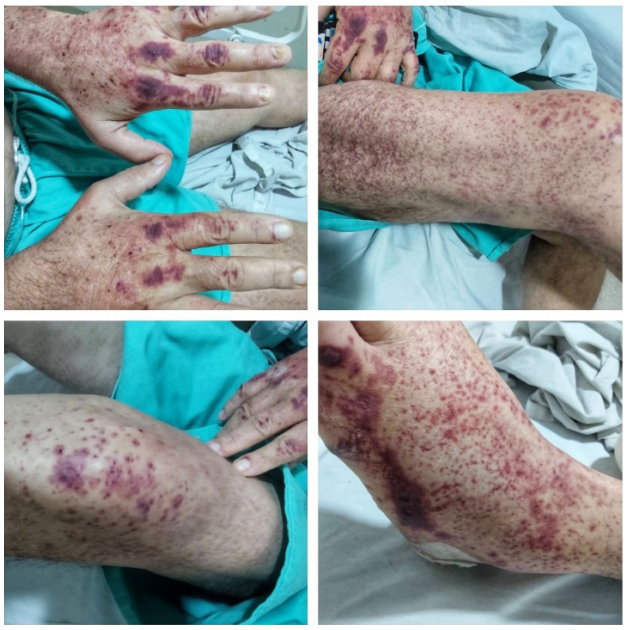

Figure 1: Multiple palpable purpuric lesions in the lower and upper limbs.

Some laboratory tests were required for further investigation of the case, but the results were normal for Antinuclear Antibodies (ANAs), rheumatoid factor (11 UI/mL; *Reference*: <14 UI/mL), complement C3 (115 mg/dL; *Reference*: 87-200 mg/dL) and C4 (45 mg/dL; *Reference*: 19-52 mg/dL), CH50 (258.6 U/CAE; *Reference*: 60-265 U/CAE), anti-cardiolipin IgG (<9.4 GPL; *Reference*: <15.0 GPL) and IgM (<9.4 MPL; *Reference*: <12.5 MPL), anti-HCV test and anti-ANCA test unreactive. The

only change detected was the VDRL, which was reactive up to 1:4. Due to this result, the hypothesis of syphilitic lesions was initially considered; however, later, this possibility was excluded based on the results of the FTA-abs IgG (reagent) and IgM (non-reactive) tests, which showed that it was only a serological scar.

In the absence of physiological causes that could justify the vasculitis episode, the rheumatologist diagnosed the case as an adverse reaction secondary to the use of oxacillin. For treatment of this adverse outcome, corticotherapy with intravenous methylprednisolone (125 mg/day) was prescribed for seven days, which was later replaced by oral prednisone (20 mg/day) for another four days. A satisfactory therapeutic response was observed, with notable improvement of the skin lesions by the fifth day of methylprednisolone administration and near complete remission of the lesions by the end of corticotherapy. Following recovery and completion of other treatments, the patient was discharged without any further complications.

DISCUSSION

Vasculitis are products of the deposition of immunocomplexes and pro-inflammatory mechanisms in the blood vessel walls, manifesting mostly as palpable cutaneous purpura (cutaneous vasculitis) or may affect other organs with potentially significant clinical repercussions. They can occur in small, medium, or large vessels[6]. In the context of small vessel vasculitis, there is leukocytoclastic vasculitis, in which inflammation is triggered by the deposition of neutrophilic immunocomplexes on the blood vessel walls due to the activation of the complement system, the presence of chemotactic factors and adhesion molecules, which stimulate the inflammatory cascade in loco and result in erythrocyte extravasation, fibrinoid necrosis, and leukocytoclasia[4].

The incidence of leukocytoclastic vasculitis in the population is low, and although it manifests mainly on the skin, extracutaneous involvement can also occur, but cases of vasculitis associated with the use of oxacillin are rare, with only three cases reported in the scientific literature[2,4-5]. The etiology of leukocytoclastic vasculitis is most often idiopathic, although, in some situations, it is associated with certain drugs, autoimmune diseases, infections, and others[2,7]. The probable related pathophysiological mechanism is the activation of a type III hypersensitivity reaction[5].

To our knowledge, this is only the fourth report of this reaction associated with this antimicrobial and although we have not performed histopathological analysis for diagnostic confirmation, it is plausible to consider that this is a case of leukocytoclastic vasculitis due to the characteristics of the clinical manifestation to the cases already reported. The temporal relationship between the use of oxacillin and the development of vasculitis, with suspension of the drug associated with the outcome, improvement of the clinical symptoms after corticotherapy, and absence of a new occurrence, even with the treatment of the other drugs prescribed, which had little adjustment during the period, strongly suggest oxacillin as a drug associated with this adverse reaction.

Another factor that supports this hypothesis is the great similarity of our case with the report of Mericlier *et al.*[2], although in our case the leukocytoclastic vasculitis developed within a few days. As for the time of exposure and development of the adverse reaction, our case is similar to that of Arsanios *et al*.[5]. The vasculitis appeared after infusion of oxacillin, and the lesions were predominantly on the dorsum of the upper and lower limbs, presenting characteristics of purpuric, palpable lesions and, in some areas, with a bullous appearance. In addition, adjustments in pharmacotherapy and laboratory test results were very similar to existing reports[2,4-5]. We applied Naranjo algorithm[8] to assess the causality between the use of oxacillin and the development of leukocytoclastic vasculitis, and our case was classified as probable. This is due to previous studies that associated this adverse reaction with the use of oxacillin (+1), the onset of the adverse reaction after administration of the suspected drug (+2), the improvement of the adverse reaction after discontinuation of the antimicrobial (+1), and the absence of other causes that could contribute to the adverse reaction (+2).

All medications prescribed and used by the patient from admission to the time of the pruritic reaction associated with the onset of petechiae were thoroughly evaluated. It was found that there are also reports of leukocytoclastic vasculitis associated

with the use of quetiapine[9], gabapentin[10], acetylsalicylic acid[11], and heparin[12]. However, it is unlikely that these drugs triggered the clinical problem, except for heparin, because all of them were already chronically used at home, with no previous reports of cases like those presented during hospitalization. The use of heparin was maintained until hospital discharge without any clinical complications.

The initial clinical management of vasculitis depends on the severity and extent of the disease, and the use of corticosteroids is widely accepted for the treatment of this problem[13]. In this case, intravenous methylprednisolone was administered for seven days, followed by oral prednisone for 4 days, with satisfactory remission of the skin lesions and we observed no recurrence of vasculitis in subsequent days.

CONCLUSION

A rare case of leukocytoclastic vasculitis associated with the use of oxacillin has been reported. Therapeutic management consisted of discontinuation of the drug associated with the adverse reaction and treatment with intravenous methylprednisolone followed by oral prednisone. Although other drugs are also associated with this reaction, the clinical and laboratory evidence, together with the comparative literature review, supports the hypothesis of an association between oxacillin use and the development of leukocytoclastic vasculitis.

These findings emphasize the necessity for vigilant monitoring of patients undergoing treatment with oxacillin, particularly those with a susceptibility to or a history of vascular adverse reactions. Furthermore, the positive response to the therapeutic approach employed, including oxacillin suspension and corticosteroid use, highlights the efficacy of these interventions in managing leukocytoclastic vasculitis within this clinical context. This clinical information can serve as a valuable resource for medical practitioners, providing guidelines for early diagnosis, appropriate management, and prevention of further complications. Furthermore, considering the damage to health and the increased healthcare costs related to its treatment, additional studies evaluating ways to prevent it are needed.

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