



Letter

Cutaneous leukocytoclastic vasculitis due to amoxicillin hypersensitivity

The vasculitides are a large group of immunologic diseases characterized by inflammation and necrosis of blood vessels of different diameter. Symptoms usually depend on the organ damaged by ischemia, with the skin being the most frequently affected.¹ Cutaneous small-vessel vasculitis is defined as a skin-isolated form of leukocytoclastic vasculitis (LCV).

Vasculitis may be idiopathic or caused by other underlying diseases (infections, drugs, malignant neoplasms, or systemic inflammatory diseases). Among drugs, β -lactams are a well-known cause of LCV. However, to the best of our knowledge, we are not aware of any previous cases reported in the literature in which a standardized allergy study was performed with positive results. We report 2 cases of aminopenicillin-associated hypersensitivity vasculitis confirmed by allergy testing.

The first patient was a 47-year-old man being treated with amoxicillin, metamizole, ibuprofen, and acetaminophen for a dental infection. After 5 days of treatment, he developed itchy, nonblanching, palpable purpuric papules with cutaneous necrosis that affected the chest, abdomen, and lower limbs (Fig 1). The results of blood tests, including hepatic and renal function tests, a coagulation panel, immunologic study (antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins, basal membrane antibodies, and a complete study of the complement pathways), urinalysis, and chest radiography were normal. Biopsy of the lesions revealed polymorphonuclear inflammatory infiltrate in small vessels, fibrinoid wall necrosis, and extravasation of red blood cells. Vessel walls were strongly positive for fibrinogen on direct immunofluorescence analysis.

The patient was hospitalized and exhibited clear improvement of lesions after a 7-day course of treatment with intravenous prednisone (1 mg/kg per day), followed by 30 mg of oral prednisone for at least 15 to 20 days. On the basis of Naranjo's algorithm score for adverse drug reactions,² the final score was 9 (definitive). He was diagnosed as having probable drug-induced vasculitis.

A month later, 1 day after discontinuing corticosteroid therapy, the patient developed a second, similar episode 6 hours after taking amoxicillin again. At this time, proteinuria and haematuria were also present. The patient was diagnosed as having immunoallergic interstitial nephritis and amoxicillin-related LCV.

A comprehensive allergy study was performed, including intradermal skin tests with benzylpenicilloyl poly-L-lysine at a concentration of 0.04 mg/mL as the major determinant and a minor determinant mixture that consisted of benzylpenicillin sodium, benzylpenicilloic acid, and sodium benzylpenicilloate (0.5 mg/mL),

benzylpenicillin (10,000 IU/mL), amoxicillin (20 and 25 mg/mL), cefuroxime (2 mg/mL), and meropenem (2 mg/mL), with immediate and delayed reading at 24 hours. All yielded negative results.

A patch test was then performed with amoxicillin 20% in dimethyl sulfoxide, 10% paracetamol in petrolatum, 5% ibuprofen in petrolatum, and 1% metamizole in petrolatum; readings were done at day 2 (D2) and day 4 (D4). We observed positive (++++) reactions to amoxicillin alone at D2 and D4. Five healthy controls tested negative for amoxicillin.

Finally, we performed an oral open-challenge test with penicillin, meropenem, cefuroxime, and ceftriaxone to assess cross-reactivity with other β -lactams; all results were negative. The results of an open-challenge test with the other potential culprit drugs (acetaminophen, metamizole, and ibuprofen) were also negative.

The second patient was a 73-year-old man with diabetes mellitus and no known allergies who was receiving amoxicillin for a respiratory infection. The patient was also prescribed a fixed-dose combination of acetaminophen, vitamin C, and codeine (Algidol) and metamizole for symptomatic relief. On the ninth day of treatment, he was referred to the emergency department for onset of palpable, nonblanching purpuric papules in both legs and the gluteal region, with no other systemic symptoms. After 3 days of hospitalization and treatment with systemic steroids, he developed a new vesicular rash with purpuric papules on the foot. A skin biopsy performed in that area revealed a dense, largely perivascular, neutrophilic inflammatory infiltrate, with fibrinoid necrosis of the vessel wall, leukocytoclasia, and extravasation of red blood cells. Superficial oedema and spongiosis were also observed, as well as an intraepidermal pustule. The results of immunofluorescence testing (IgG, IgM, IgA, C3, and fibrinogen) were negative. The patient was then referred to our service for further investigation. The results of an intradermal skin test with poly-L-lysine (0.04 mg/mL), benzylpenicillin sodium, benzylpenicilloic acid, and sodium benzylpenicilloate (0.5 mg/mL), benzylpenicillin (10,000 IU/mL), amoxicillin (20 and 25 mg/mL), cefuroxime (2 mg/mL), and meropenem (2 mg/mL), with immediate and delayed reading at 24 hours, were uniformly negative. The results of a patch test performed with 20% amoxicillin (dimethyl sulfoxide), 10% acetaminophen in petrolatum, 1% metamizole in petrolatum, and 1% codeine in petrolatum, with readings at D2 and D4, were weakly positive (+) for amoxicillin at D2 and negative for all other sensitizers. The results of an open-challenge test with penicillin, meropenem, cefuroxime, and the other potential culprit drugs (acetaminophen, metamizole, and codeine) were also negative.

The patient was diagnosed as having cutaneous LCV attributable to amoxicillin hypersensitivity, with tolerance to penicillin, meropenem, and cefuroxime.

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Figure 1. Purpura papules with cutaneous necrosis after 5 days of treatment with amoxicillin.

Cutaneous vasculitis may occur because of multiple disorders and causes, but drug hypersensitivity, especially to β -lactams, is one of the most frequent. Clinical findings are widely varied, and a skin biopsy is necessary to confirm the diagnosis.¹ Typical histologic characteristics include polymorphonuclear leukocyte infiltration, erythrocyte extravasation, fibrinoid necrosis, and leukocytoclasia. Vasculitis may be accompanied by other systemic manifestations, including renal and pulmonary involvement, as in our second case, and is sometimes life-threatening.

Because of this potential complication, in patients with delayed reaction to a β -lactam antibiotic, the entire class of β -lactams is usually forbidden.³ We have found several cases of LCV in the literature^{4,5} in which the suspected culprit drug was a β -lactam, but no allergy study was performed to confirm the diagnosis or assess tolerance to alternative drugs in the same class. Koutkia et al⁶ reported a case of LCV associated with oxacillin, but no allergy study was performed.

In the 2 cases described herein, patch testing confirmed a type IV hypersensitivity mechanism. In both patients, intradermal testing with delayed reading at 24 hours was noncontributory. We stress the importance of performing a correct allergy study to

confirm the pathophysiologic mechanism of the reaction, establish the most accurate etiologic diagnosis possible, and rule out cross-reactivity with other β -lactams. Moreover, we provide additional evidence for the well-known fact^{7,8} that patients with such hypersensitivity, even those with severe delayed reactions, such as vasculitis, can be selectively allergic to aminopenicillins alone, with good tolerance to other β -lactams that contain different side chains in their chemical structure.

Mercedes Sáenz de Santa María García, MD^{*,†}

Cristina Morales-Cabeza, MD^{*,†}

Blanca Noguerado-Mellado, MD^{*,†}

Patricia Rojas-Pérez-Ezquerro, MD^{*,†}

Jose M. Zubeldia, MD, PhD^{*,†,‡}

^{*}Allergy Service

Hospital General Universitario Gregorio Marañón

Madrid, Spain

[†]Gregorio Marañón Health Research Institute (IISGM)

Madrid, Spain

[‡]Biomedical Research Network and Rare Diseases (CIBERER) – U761

Madrid, Spain

mercedessaenzgarcia@gmail.com

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