

Ibuprofen-Induced Bullous Leukocytoclastic Vasculitis

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GOAL

To discuss a case of ibuprofen-induced bullous leukocytoclastic vasculitis (LCV)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. List the drugs implicated as causative agents of bullous eruptions.
2. Discuss the diagnosis of suspected drug-related bullous eruptions.
3. Describe the distinguishing characteristics that separate bullous LCV from other bullous eruptions.

CME Test on page 308.

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A dramatic case of ibuprofen-induced bullous leukocytoclastic vasculitis (LCV) is described in a patient with a history of prior sensitization to ibuprofen, a common household nonsteroidal anti-inflammatory drug (NSAID) that has few reported adverse skin reactions. Bullous LCV is a relatively rare clinical presentation of LCV, which requires differentiation from other blistering diseases,

including bullous erythema multiforme, bullous fixed drug eruption, linear IgA bullous dermatosis, and bullous pemphigoid. The distinctive histopathologic changes of leukocytoclastic vasculitis readily distinguish this bullous eruption from the others.

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Leukocytoclastic vasculitis (LCV) has many different clinical manifestations, including macules, papules, nodules, vesicles, bullae, and ulcers.¹ The etiology of LCV is just as protean, which includes various infections, cryoglobulinemia, connective tissue diseases, and drugs.² Bullae are a relatively rare clinical presentation of LCV, which requires differentiation from other blistering diseases, including drug-induced blistering eruptions. A dramatic case of ibuprofen-induced bullous LCV is



Figure 1. Multiple bullae with surrounding purpura on the thigh.

described in a patient with a history of prior sensitization to ibuprofen, a common household non-steroidal anti-inflammatory drug (NSAID) with few reported adverse skin reactions.

Case Report

A 65-year-old African American woman presented to the emergency department with a 5-day history of a progressively worsening blistering eruption on the legs and arms bilaterally without systemic symptoms. The patient had diabetes mellitus and hypertension, for which she was on insulin, furosemide, amlodipine, enalapril, and potassium for the past several years. The only new medication she reported was Advil®, which she ingested 2 days prior to the eruption, despite her history of an allergic rash to ibuprofen in the past. The patient was unaware that Advil contained ibuprofen. On physical examination, she had multiple tense hemorrhagic bullae with surrounding purpura on the lower extremities and forearms bilaterally (Figures 1 and 2). There were few flaccid bullae, vesicles, and erosions on the extremities. There was no mucosal involvement. The patient was afebrile, and her overwhelming complaint was pain. The laboratory studies were remarkable for elevated sedimentation rate and positive antibody titer for hepatitis A but not B and C. Serial urinalysis results showed no evidence of hema-



Figure 2. Close-up view of the bullae.

turia. Complete blood count, blood urea nitrogen level, creatinine level, and liver function test results were all within normal limits.

A punch biopsy revealed an intraepidermal blistering process (Figure 3) with a superficial and mid-dermal perivascular and interstitial infiltrate composed of neutrophils and their nuclear dust. There were extravasated red blood cells and fibrin deposition around some of the vessels (Figure 4). Direct immunofluorescence revealed deposits of IgM and IgA within the vessel walls consistent with immune-complex-mediated vasculitis. A diagnosis of ibuprofen-induced bullous LCV was made based on the history and the temporal association with presence of no other etiology of LCV. The hepatitis A titer was assumed to be convalescent, as the patient had no current or recent symptoms of hepatitis. The patient was treated with oral prednisone starting at 60 mg a day and tapering over the subsequent 3 weeks. The eruption cleared within that period. Some of the bullae healed with mild scarring.

Comment

Diverse heterogeneous bullous eruptions can be induced by drugs, which include bullous erythema multiforme (EM), toxic epidermal necrolysis (TEN), bullous fixed drug eruption, pseudoporphyria, bullous lichen planus, and bullous LCV, as well as autoimmune bullous diseases such as linear IgA bullous dermatosis, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, and epidermolysis bullosa acquisita. A wide variety of drugs have been implicated as the causative agents for these diverse group of bullous eruptions (Table), but some drugs have been more frequently associated with specific eruptions (eg, vancomycin and linear IgA bullous dermatosis,

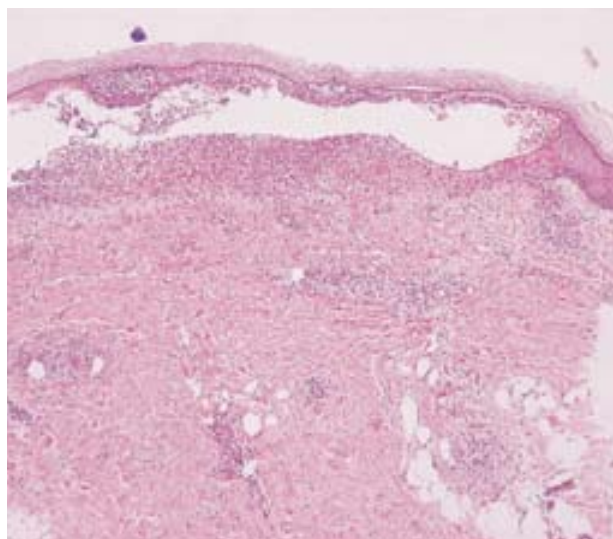


Figure 3. Biopsy specimen showing an intraepidermal blister (H&E, original magnification $\times 50$).

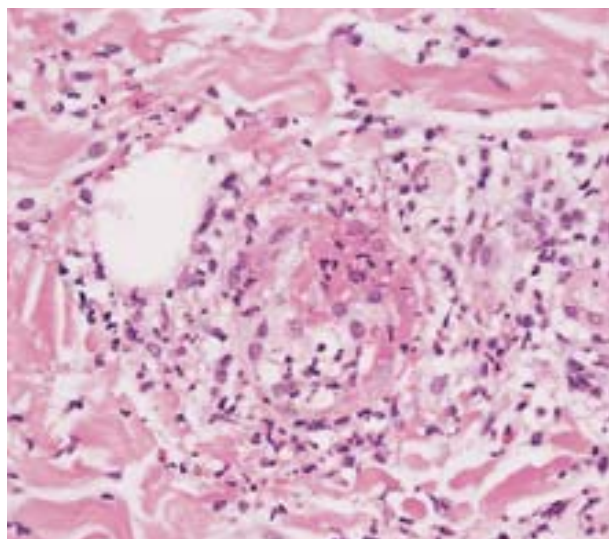


Figure 4. Fibrin deposition within a vessel with neutrophils and eosinophils present around the vessel (H&E, original magnification $\times 400$).

sulfonamides and TEN, penicillamine and pemphigus vulgaris). There are no specific tests that may pinpoint a drug as the culprit. Therefore, most reported drug-induced eruptions are based on circumstantial evidence in which there is usually a history of ingestion of the suspected drug with resolution of the eruption when the suspected drug is withdrawn. The patch tests and *in vitro* tests, such as the lymphocyte transformation test, macrophage migration inhibition, and mast cell degranulation test, may support the association between the eruption and the suspected drug,^{3,7} but they do not provide definitive evidence of the connection. A positive rechallenge test with the suspected drug provides more definitive evidence that the drug is the culprit. The potential detrimental outcome to the patient, however, limits the use of the rechallenge test.

The clinical, histopathologic, and, in cases of autoimmune bullous diseases, direct and indirect immunofluorescent characteristics can distinguish the different types of drug-induced bullous eruptions. Clinically, at times, however, the eruptions are difficult to distinguish from one another, especially among widespread bullous EM, fixed drug eruption, TEN, linear IgA bullous dermatosis, and bullous pemphigoid.⁸⁻¹⁰ Lyell demonstrated this difficulty in his landmark reports on TEN in which he erroneously included a widespread bullous fixed drug eruption.^{11,12} Widespread bullous fixed drug eruption and bullous EM may be particularly difficult to differentiate because both may have similar clinical and histopathologic features.¹³⁻¹⁵ Histopathologically, both show an interface vacuolar alteration at the dermo-epidermal junction with variable necrosis of the epidermis. A

fixed drug eruption is usually associated with a mixed-cell infiltrate of inflammatory cells (ie, with neutrophils and eosinophils), while EM is usually associated with lymphocytes and rarely with eosinophils or neutrophils. In bullous EM, however, the confluent necrosis of the epidermis is chemotactic for neutrophils, and, thus adding to the difficulty in distinguishing it from bullous fixed drug eruption.

Bullous LCV also may be difficult to distinguish clinically from the aforementioned eruptions,¹⁶ but the histopathologic features readily distinguish bullous LCV from the other eruptions. Bullous LCV is a type III hypersensitivity reaction in which immune complex deposition in postcapillary venules results in a destructive inflammatory vasculitis. The endothelial injury caused by immune-complex deposition results in activation of the complement cascade, resulting in an influx of inflammatory cells, including eosinophils and neutrophils, which release proteolytic enzymes that damage the vessel walls.^{17,18} As the process progresses, leukocytoclasia, fibrinoid necrosis, and fibrin deposition within and around the affected vessels eventuate. Rarely, either an intraepidermal or a subepidermal blister may form, the former due to spongiosis and/or ballooning (intracellular edema) of the epidermis, and the latter due to pronounced edema in the superficial dermis.¹⁹ A subepidermal blister is more commonly encountered in cases of bullous LCV.²⁰ It is relatively a rare manifestation of LCV with no consistent specific causes or associations attributed to it.

The causes of LCV include various infections, connective tissue diseases, cryoglobulinemia, malignancies, and drugs. In more than half of the cases, a

Bullous Diseases and Some of the Drugs That Have Been Reported to Induce Them*	
Bullous Diseases	Drugs That Have Been Reported to Induce Them
Bullous fixed drug eruption	Mefenamic acid, paclitaxel, paracetamol (acetaminophen), phenylbutazone, piroxicam, sulfonamides, vinburnine
Bullous lichen planus	Radiocontrast dye
Bullous pemphigoid	Chloroquine, furosemide, penicillamine, penicillins
Cicatricial pemphigoid	Indomethacin, oral practolol, penicillamine, topical pilocarpine
Epidermolysis bullosa acquisita	Furosemide, penicillamine, sulfonamides
Erythema multiforme (bullous and nonbullous)	Furosemide, nonsteroidal anti-inflammatory drugs, penicillins, phenothiazines, phenytoin, sulfonamides, benzothiazides
Leukocytoclastic vasculitis (bullous and nonbullous)	Allopurinol, food additives, naproxen, penicillin, propylthiouracil, phenylbutazone, sulfonamides, benzothiazides
Linear IgA bullous dermatosis	Captopril, diclofenac, lithium, vancomycin
Pemphigus foliaceus	Captopril, nifedipine, penicillamine, rifampin
Pemphigus vulgaris	Captopril, cephalixin, enalapril, penicillamine, penicillin, rifampin
Pseudoporphyria	Furosemide, nalidixic acid, naproxen, piroxicam, tetracycline
Toxic epidermal necrolysis	Allopurinol, aminopenicillins, phenobarbital, phenylbutazone, phenytoin, sulfonamides

*For further information, consult *Clinic Dermatol.* 1993;11(4).

cause cannot be established.² Although NSAIDs have been reported as one of the classes of drugs to cause LCV, the more common adverse skin reactions to NSAIDs are pruritus, morbilliform erythematous eruption, urticaria, and photosensitivity.^{21,22} More serious adverse reactions, such as Stevens-Johnson syndrome and TEN, are very rare, but they have been documented, especially with phenylbutazone, piroxicam olamine, sulindac, tolmetin, and zomepirac sodium.^{23,24} Among the NSAIDs, aspirin, phenylbutazone, piroxicam olamine, sulindac, and zomepirac sodium are more commonly involved in adverse skin reactions.²⁵ Ibuprofen, on the other hand, has the second lowest incidence of causing adverse skin reactions among the NSAIDs after indomethacin.²⁶

Believed to be a safe and reliable drug, ibuprofen is one of the most frequently used NSAIDs for pain and inflammatory diseases.²⁵ Similar to other NSAIDs, the more common adverse skin reactions that occur with ibuprofen use are morbilliform eruption, angioedema/urticaria, and photosensitivity, with rare reports of fixed drug eruption, and TEN.^{25,26} In addition, a bullous eruption resembling bullous pemphigoid has been reported.²⁷ Vasculitis, specifically LCV due to ibuprofen, is rare with only 7 known cases worldwide.²⁸ Inadvertent ingestion of ibuprofen in this patient, who had a history of prior sensitization, resulted in a dramatic eruption of bullous LCV. Despite widespread involvement of the skin, there was no clinical evidence of visceral organ involvement

in this patient. Oral steroid resulted in a prompt resolution of the eruption and symptoms. Prior sensitization may have accounted for the acute accelerated blistering eruption in this patient.

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