Leukocytoclastic Vasculitis Induced by Use of Glyburide: A Case of Possible Cross-Reaction of a Sulfonamide and a Sulfonylurea

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Drug-induced leukocytoclastic vasculitis (LCV) may present as the result of a single offending agent or more uncommonly, from a cross-reaction with a related medication. We describe a patient with sulfonamide allergy who developed LCV after exposure to a sulfonylurea. Sulfur-containing drugs may cross-react to induce LCV in susceptible individuals.

Leukocytoclastic vasculitis (LCV) is a common clinicopathologic entity characterized by palpable purpura, especially on the lower extremities, secondary to the deposition of circulating immune complexes in postcapillary venules. Extracutaneous involvement, which occurs in up to 50% of patients, commonly affects the kidneys, joints, nervous system, gastrointestinal tract, lungs, and heart. Numerous etiologies—including medications, autoimmune disorders, infections, inflammatory bowel disease, and malignancies—have been proposed for LCV. In this article, we describe a case of LCV secondary to use of a sulfonylurea in a patient with a history of allergic reaction to a sulfonamide antibiotic. We suggest the possibility that a cross-reaction of these 2 structurally related medications may have led to the development of LCV.

Case Report

A 33-year-old white man presented to the emergency department with the primary complaints of gross hematuria and eyelid swelling. The patient had a history of hypertension, coronary artery disease, morbid obesity, anemia, and a long-term indwelling Foley catheter for an obstructive uropathy. Previously, he had had an allergic reaction to trimethoprim-sulfamethoxazole (TMX); this reaction had been described as a generalized cutaneous eruption associated with mucosal swelling. The patient's medications included furosemide (a sulfur-containing loop diuretic), iron sulfate, pyridoxine, sertraline, atorvastatin, omeprazole, terazosin, diphenhydramine, ibuprofen, doxycycline, hydrocodone, and loratidine. Two days after starting glyburide for newly diagnosed hyperglycemia, the patient developed cutaneous lesions on the lower legs. Over the next 2 days, these lesions spread centripetally to involve the buttocks and trunk, at which point glyburide was stopped. The patient presented to the emergency department on day 7.

The patient was afebrile and had multiple erythematous palpable nonblanching papules and plaques on the trunk (Figure 1) and extremities and small tense blisters over the right posterior shoulder. Laboratory results at the time of presentation included a urine blood level of 3+ and erythrocyte sedimentation rate of 30 mm/h (reference range, 0–20 mm/h). The patient was started on ciprofloxacin for a presumed urinary tract infection and was admitted to the hospital. Results of several blood tests were normal or negative: antineutrophil cytoplasmic antibodies (p-ANCA, c-ANCA), complete blood cell count, electrolytes, urine cultures, antinuclear antibody, and extractable nuclear antigens Ro (SS-A), La (SS-B), C3, C4, and CH50. The patient denied any arthralgia, acute shortness of breath, headaches, or gastrointestinal symptoms. A skin biopsy was performed, and histopathologic results indicated LCV (Figure 2).

Accepted for publication September 27, 2002.
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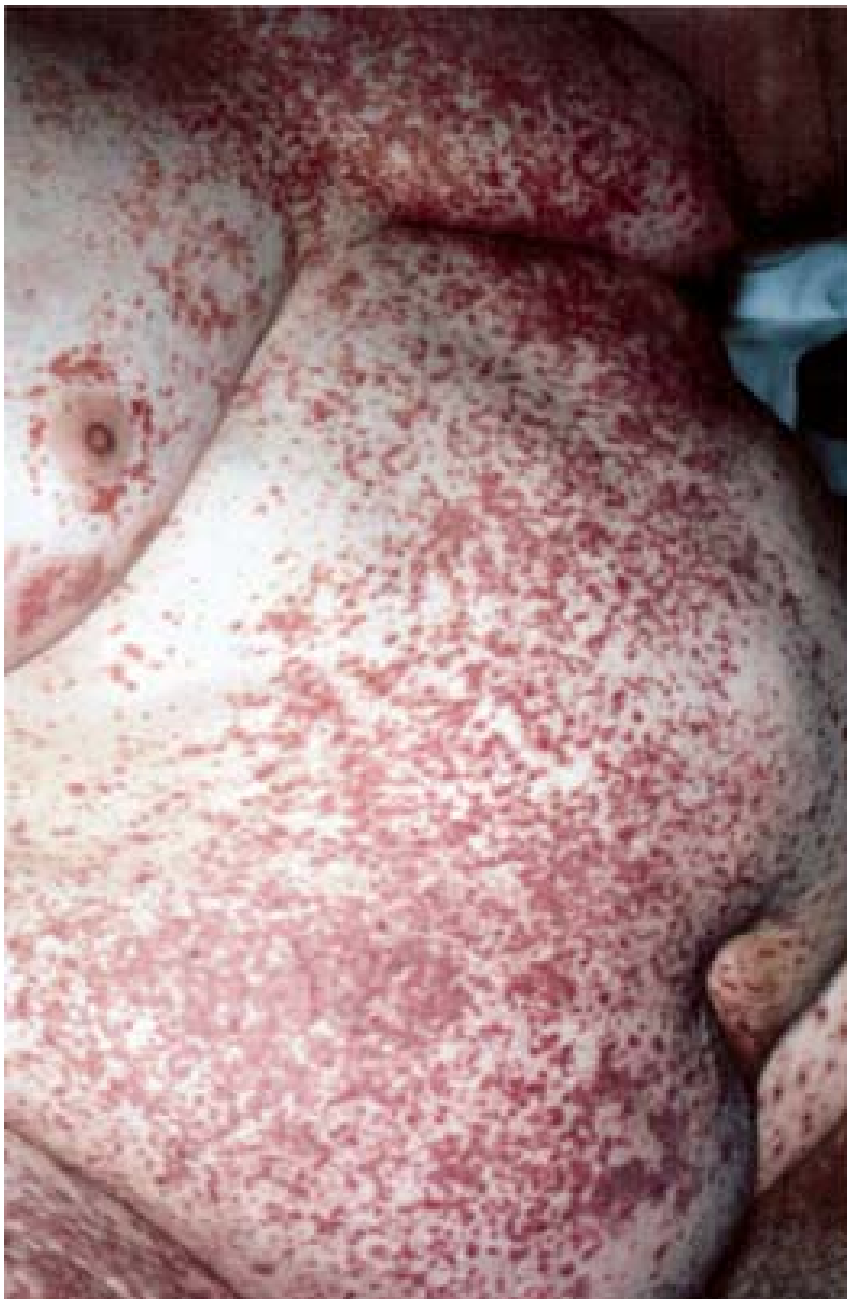

Figure 1. Diffuse palpable purpura on the trunk of a 33-year-old man.

Direct immunofluorescence was positive for fibrin but negative for IgA, IgG, IgM, and C3. The patient's cutaneous eruption and hematuria resolved spontaneously during his 2-week hospital stay.

Comment

Our patient's case involved many of the common clinical features of LCV—development soon after use of an offending medication was initiated (and spontaneous resolution after discontinuation of the same medication), palpable purpura on the lower extremities, angioedema, and renal involvement. Other less common skin lesions may include urticaria, pustules, blisters, necrosis, and livedo reticularis. The purpura usually involves the lower legs or other dependent areas; involvement of the face, palms, soles, and mucosal membranes is uncommon. Hematuria is a common manifestation of kidney involvement by LCV.

The histopathologic profile of LCV includes fibrinoid necrosis of small blood vessels in the superficial dermis, perivascular infiltrate of polymor-

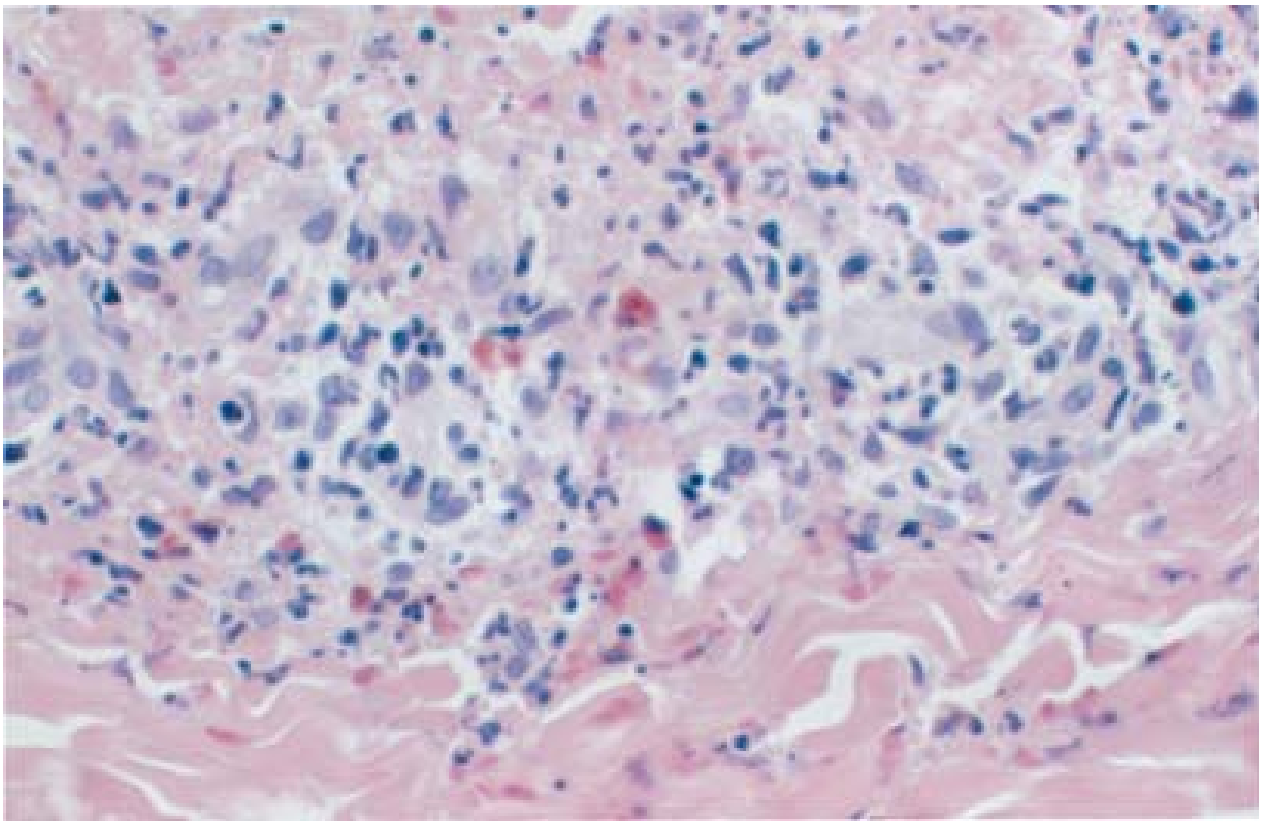

Figure 2. Leukocytoclastic vasculitis with infiltration of vessel walls by neutrophils with fibrinoid necrosis, red blood cell extravasation, and leukocytoclasis. Numerous eosinophils are present (H&E, original magnification ×400).

phonuclear leukocytes, nuclear dust (karyorrhexis), and red blood cell extravasation. Polymorphonuclear leukocytes are frequently identified within small blood vessel walls.[2] Results of direct immunofluorescence are positive (granular deposition of fibrin, IgA, IgG, IgM, and C3 in the blood vessel walls) if the biopsy specimen is taken less than 24 hours after development of a specific lesion. The most common immunoreactants are C3 and IgM; C3 is the most sensitive because of its amplification in the complement cascade.

Medications have been implicated as etiologic agents in up to 13% of LCV cases. The pathogenesis is thought to involve the antibody response to medications—a response that leads to formation of circulating immune complexes. These complexes become lodged in the postcapillary venules, activating the complement cascade, which chemotactically attracts polymorphonuclear leukocytes. Neutrophils phagocytose the immune complexes and release lysosomal enzymes, leading to vascular wall damage. The resultant increased vascular permeability, inflammation, and hemorrhage produce the well-known clinical lesions of LCV.[3]

The literature on the cross-reactivity rates of various sulfur-containing medications (eg, sulfonamides, sulfonylureas, dapsone, sulfur-containing diuretics) is sparse. Holtzer et al[4] evaluated the cross-reactivity of dapsone after encountering hypersensitivity reactions to TMX during prophylaxis for *Pneumocystis carinii* pneumonia in patients with the human immunodeficiency virus (HIV). Defining cross-reactivity on the basis of documented occurrence of a specific hypersensitivity reaction in a patient within 60 days after converting from TMX to dapsone, Holtzer et al[4] found the rate of cross-reactivity to be 22%. Dapsone is a sulfone compound structurally similar to sulfonamides and is one of the second-line agents for *P carinii* pneumonia prophylaxis. Holtzer et al[4] noted that the study group's dapsone hypersensitivity rate of 22% was higher than the 10% to 16% found for patients who had HIV but who were not intolerant of TMX. They questioned whether the higher rate represents a chemical class–specific response or a tendency to react to all medications.

Sulfonamide antibiotics and diuretics (eg, furosemide, thiazides) are among the most common

causes of medication-induced LCV.[5] In the English-language literature, to our knowledge, there are only 2 reports of LCV caused by a sulfonylurea (glyburide in both cases).[6,7] There are no reports of sulfonamide-sulfonylurea cross-reactions. Our patient had a history of allergic reaction to sulfonamides, and he developed LCV on day 2 after starting to use a sulfonylurea (glyburide). Typically, medication-induced LCV occurs 7 to 10 days after medication is started.[8] We suggest that our patient's LCV was induced by a cross-reaction of TMX and glyburide, 2 structurally similar sulfur-containing agents. To the best of our knowledge, the English-language literature includes no reports of cases of such cross-reactions. Physicians should be aware of possible cross-reactivity of various sulfur-containing classes of medications, including sulfonamides, sulfonylureas, dapsone, and certain diuretics.

REFERENCES

1. Braverman IM. Angiitides. In: Braverman IM, ed. *Skin Signs of Systemic Disease*. 3rd ed. Philadelphia, Pa: WB Saunders; 1998:278-334.
2. Gower RG, Sams WM Jr, Thorne EG, et al. Leukocytoclastic vasculitis—sequential appearance of immunoreactants and cellular changes in serial biopsies. *J Invest Dermatol*. 1977;69:477-484.
3. Sanchez NP, Van Hale HM, Su WPD. Clinical and histopathologic spectrum of necrotizing vasculitis. *Arch Dermatol*. 1985;121:220-224.
4. Holtzer CD, Flaherty JF Jr, Coleman RL. Cross-reactivity in HIV-infected patients switched from trimethoprim-sulfamethoxazole to dapsone. *Pharmacotherapy*. 1998;18:831-835.
5. Soter NA. Cutaneous necrotizing vasculitis. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. *Fitzpatrick's Dermatology in General Medicine*. Vol 2. 5th ed. New York, NY: McGraw-Hill; 1999:2044-2053.
6. Dickey W, Handley J. Purpura, leukocytoclastic vasculitis, and glibenclamide. *BMJ*. 1980;293:823-824.
7. Clarke BF, Campbell IW. Generalized hypersensitivity reaction and visceral arteritis with fatal outcome during glibenclamide therapy. *Diabetes*. 1974;23:739-742.
8. Sams MW Jr. Small vessel vasculitis. In: Sams MW Jr, Lynch PJ, eds. *Principles and Practice of Dermatology*. 2nd ed. New York, NY: Churchill Livingstone; 1996:543-552.