Extensive Lichenoid Drug Eruption Due to Glyburide: A Case Report and Review of the Literature

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GOAL

To understand lichenoid drug reactions to better manage patients with the condition

OBJECTIVES

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

1. Describe the various presentations of lichenoid drug reactions.
2. List the various drugs that have caused lichenoid reactions.
3. Discuss the temporal relationship between drug administration and lichenoid reactions.

CME Test on page 36.

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Lichenoid reactions to sulfonylurea drugs have been reported, albeit infrequently.[1] To our knowledge, this is the first case of a generalized lichenoid dermatitis likely induced by the third-generation sulfonylurea hypoglycemic drug glyburide.

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Lichenoid reactions to sulfonylurea hypoglycemic drugs[1-4] and sulfonamides[1,5-7] have been reported, albeit infrequently. A review of the indexed literature revealed prior publication of lichenoid drug reactions to the sulfonylureas chlorpropamide,[1,2,8-10] tolazamide,[1,2,8] and tolbutamide[1,11]; a single report of a reaction to glimepiride[4];

and no report of reactions to glipizide or glyburide. To our knowledge, this is the first case of a generalized lichenoid reaction likely induced by the third-generation sulfonylurea glyburide.

Case Report

A 46-year-old white man presented for evaluation of a widespread skin eruption. He had diabetes for approximately 15 years that was initially treated with diet, then diet plus metformin. Seven months prior to presentation, the patient's primary care physician switched the patient's medication from metformin to glyburide. The patient denied receiving prior sulfonylurea therapy for his diabetes. Within 2 months of starting oral glyburide 2.5 mg/d, the patient noted the onset of a mildly pruritic, scaly eruption that started on the dorsa of his feet. It progressed to involve his hands, including the palms. The patient attributed the rash to his outdoor activities and thus did not seek medical care. During the next several months, the eruption progressed to involve the remainder of the upper and lower extremities and the trunk, sparing the head, neck, genitalia, nails, and mouth. The patient then sought medical advice from his primary care physician.

Figure 1. Abundant, violaceous, polymorphic lichenoid papules on the right calf.

During the next several months, various topical therapies (pimecrolimus 1% cream, mometasone 0.1% cream, and triple antibiotic ointment) were tried, with no notable improvement. During this period, there were no other changes in the patient's long-term therapeutic regimen, which included atorvastatin, pioglitazone, gabapentin, lisinopril, aspirin, and omeprazole. This regimen had been stable for several years prior to the medication change. At no time did the patient experience constitutional symptoms.

The patient stated he was meticulous about using sun precautions (long sleeves, hat, covered golf cart, and sunscreen), both before his eruption began and during the time it evolved. He was married and monogamous by history. His diabetes at the time of presentation was well controlled. Prior to onset of the eruption, the patient had no personal or family history of significant dermatologic disease. There was no significant occupational chemical exposure.

The results of a physical examination revealed the patient had a widespread, violaceous, polymorphic papulosquamous eruption, with lesions varying in size from several millimeters to confluent plaques and in character of the scale from none to collarette to thick and adherent (Figures 1–3). The head, neck, genitalia, nails, and mouth were not involved. Biopsy specimens were obtained, the glyburide was stopped, and a 2-week prednisone taper was initiated.

At the 2-week follow-up, the patient had complete resolution of symptoms and marked clearing of his eruption. After an additional 2 weeks with no corticosteroids, no new papules or plaques had formed. A few residual lichenoid papules remained around the ankles, and there were diffuse residual asymptomatic postinflammatory skin changes in the areas of prior involvement.

The biopsy specimens showed a lichenoid tissue reaction; specifically, irregular epidermal hyperplasia,

focal hydropic change at the base of the epidermis with underlying bandlike infiltrate of lymphocytes, some evidence of dyskeratotic cells in the epidermis, and very little evidence of spongiosis (Figure 4). No eosinophils were present within the inflammatory infiltrate.

Figure 2. Extensive violaceous lichenoid plaque formation on the right forearm.

Figure 3. Lichenoid papules and plaques on the right foot.

Comment

Lichenoid reactions to drugs have been reported in a number of classes, including sulfonylureas[1-4] and sulfonamides.[1,5-7] Regarding the sulfonylurea agents, prior reports have implicated chlorpropamide,[1,2,8-10] tolazamide,[1,2,8] tolbutamide,[1,11] and glimepiride.[4] However, we found no prior reports of lichenoid reactions to glipizide or glyburide.

Sulfonylurea agents are often described in the literature as a cause of drug-induced lichen planus (LP); however, in 1994, Thompson and Skaehill[3] concluded there was insufficient primary literature to make a causal link. There has been a similar paucity of primary literature since then to clarify this postulated link. This report adds support for the thesis that sulfonylureas are a cause of lichenoid drug reactions and that glyburide may be included in the list of agents with that potential. In this case, there was a plausible temporal relationship between the start of glyburide therapy and the onset of a lichenoid reaction typical for a lichenoid drug eruption. Specifically, our patient exhibited a widely distributed eruption with polymorphic features.[3] Also, there was a temporal relationship between the cessation of therapy and the clearing of the eruption, though corticosteroid therapy also was started because it was believed to be clinically and ethically inappropriate not to offer this option to the patient.

Prior reports of sulfonylurea reactions have described intraoral reactions without cutaneous involvement,[9,12] cutaneous involvement with no intraoral involvement,[4,8] and involvement of both the mucous membranes and skin. With the latter, onset may be sequential and temporally disparate.[2] Oral involvement in lichenoid drug reactions appears less frequently than in idiopathic LP.[3]

Noakes[4] reported a patient who had a long-standing stable medication regimen to which glimepiride was added. A biopsy-confirmed lichenoid eruption developed 3 months later on the lower extremities. No new lesions developed after drug cessation, and the eruption cleared within several months of discontinuing the drug.[4] To our knowledge, that was the only prior report of a lichenoid reaction to

a third-generation sulfonylurea hypoglycemic drug.

Barnett and Barnett[2] reported a patient who developed oral LP 6 weeks after starting chlorpropamide, which was followed by a lichenoid cutaneous reaction about 1 year later. Similar to our patient, the face, genitalia, and nails were spared. Stopping the medication resulted in complete resolution. Subsequently, the patient was started on tolazamide; 2 months later, the patient experienced a recurrence that again resolved with cessation of medication.[2] This sequence supports the case for a cause-and-effect relationship.

Dinsdale et al[9] reported a patient who developed intraoral LP approximately 6 months after starting chlorpropamide and within 2 months after a dosage increase. By history, the lesions may have started much sooner after initiation of drug therapy. These intraoral lesions resolved within 5 days of stopping the medication. Approximately 2 months later, the patient restarted the medication. Within approximately 4 days, he experienced recurrent oral lesions. Again, the lesions resolved within a few days of discontinuing the medication.[9] Once more, this sequence supports a cause-and-effect relationship between the drug and the eruption.

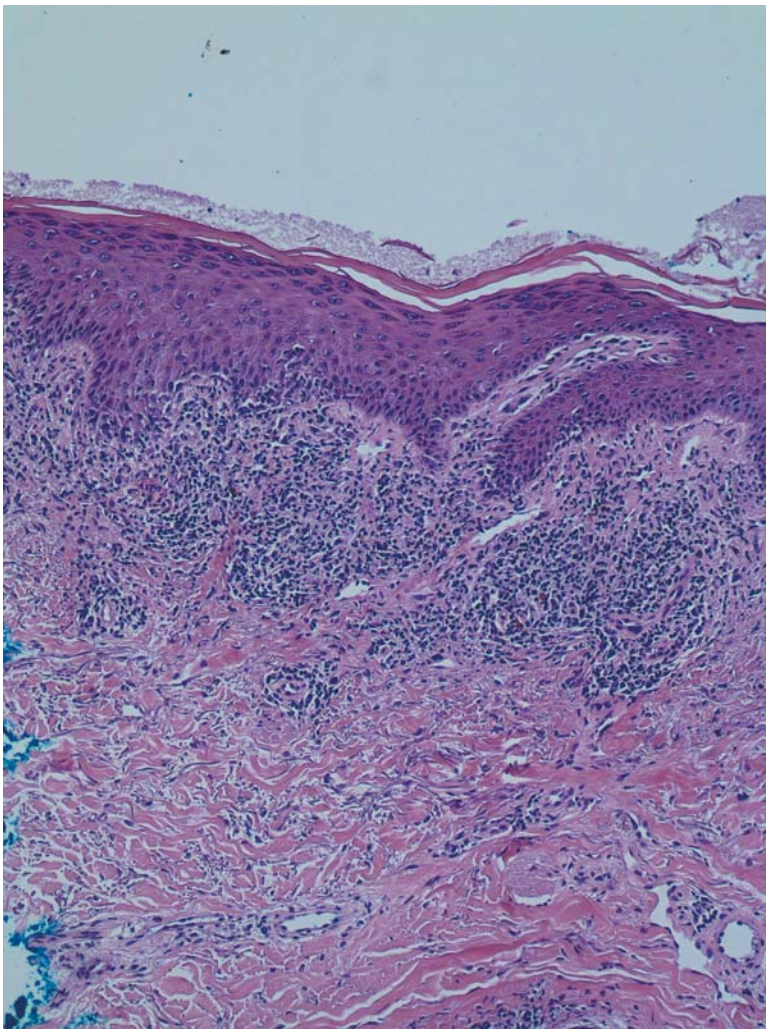

Figure 4. A bandlike infiltrate of lymphocytes with epidermal hyperplasia and focal hydropic change of the basal cell layer (H&E, original magnification ×40).

Franz et al[8] reported a patient who experienced the onset of cutaneous LP 8 months after starting chlorpropamide. The medication was discontinued, after which no new lesions formed; the eruption began to resolve within 3 weeks. Later, the patient was started on tolazamide; within 2 weeks, new lesions appeared. No oral involvement was noted with either drug.[8] This pattern of events also suggests a cause-and-effect relationship between the sulfonylurea and the lichenoid eruption.

Reports of lichenoid dermatitis from chemically related sulfonamide agents strengthen the case for sulfonylurea drugs as a plausible cause of lichenoid reactions. For example, Kaplan et al[5] reported 3 patients who developed cutaneous LP while receiving sulfasalazine therapy. One patient developed LP after 9 months of therapy and, when the patient restarted therapy on her own, her eruption recurred within 1 week. Two other patients developed cutaneous LP—one at 3 months and one at 2 weeks into therapy.[5] Alstead et al[6] reported 2 patients who developed oral and cutaneous LP after sulfasalazine therapy was initiated, which cleared after the sulfasalazine was discontinued. The first patient had a 5-month interval between the start of sulfasalazine and the onset of oral and penile LP. The second patient experienced an interval of 2 years between the start of sulfasalazine and the onset of cutaneous and oral LP.[6]

Reports that detail lichenoid eruptions in association with a drug, then resolution of the eruption with withdrawal of the drug, suggest but do not confirm a cause-and-effect association between the drug and the eruption. When the sequence is repeated in the same patient—specifically, the patient is rechallenged with either the same or a chemically-related moiety, again followed by

recurrence of the eruption, and again followed by resolution of the eruption with discontinuation of the agent (A/B/A/B experimental design)—there is a much stronger case for a cause-and-effect relationship. The tighter the temporal association, the stronger the case for a cause-and-effect relationship. For most drug reactions, the latent period between the beginning of drug therapy and the onset of eruption is days to weeks, allowing a tight temporal association.[4] For lichenoid drug eruptions, the interval tends to be longer—sometimes much longer—making temporal association more difficult and the link less obvious.[4]

Unfortunately, drug-induced and idiopathic LP are clinically and histologically indistinguishable.[3] Drug-induced lichenoid reactions from sulfonylureas are too infrequent to be verified epidemiologically. Therefore, the best evidence about them is likely to come from case reports. The strongest case evidence is likely to come from reports of temporal relationships and instances where patients are reexposed to the same or a chemically-related drug. Under usual circumstances where alternatives exist, intentional rechallenge is ethically questionable.

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