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Case Presentation

A case of glyburide-induced leukocytoclastic vasculitis

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Abstract

Introduction: Medication-induced leukocytoclastic vasculitis is a small-vessel vasculitis that most commonly manifests with palpable purpuric lesions on gravity dependent areas. Development of the vasculitis occurs within weeks after the initial administration of the medication, with clearance upon withdrawal of the medication. Glyburide, a sulfonylurea medication, is used to treat non-insulin dependent diabetes mellitus. We report a rare case of glyburide-associated leukocytoclastic vasculitis.

Observation: We report a 71-year-old man with type 2 diabetes mellitus who presented with palpable purpura on the lower extremities. Cutaneous biopsy revealed superficial small vessel vasculitis with IgA perivascular deposits. Further questioning revealed three prior episodes of palpable purpura after restarting the glyburide medication, with clearance upon discontinuation. We diagnosed drug-induced vasculitis related to the glyburide.

Conclusions: This case highlights a rarely reported cutaneous adverse reaction to the commonly used diabetic medication, glyburide. Physicians should consider cutaneous vasculitis as a potential side effect of glyburide.

Abbreviations: LCV (Leukocytoclastic vasculitis), c-ANCA (centrally accentuated anti-neutrophilic cytoplasmic antibody), p-ANCA (Perinuclear anti-neutrophilic cytoplasmic antibody), anti-TNF-alpha (anti-tumor necrosis factor alpha)

Keywords: Leukocytoclastic vasculitis, Glyburide, Drug-induced leukocytoclastic vasculitis

Introduction

Leukocytoclastic vasculitis (LCV), also known as hypersensitivity vasculitis, is a small-vessel vasculitis caused by vascular immune-complex deposits. Subsequent activation of the complement system produces vascular injury and extravasation of erythrocytes. LCV has many etiologies, including collagen vascular diseases, infections, malignancies, and medications.

Cutaneous manifestations include confluent non-blanchable, palpable purpura on gravity dependent areas such as the lower extremities and buttocks.

Medication	Dose	Frequency
Glyburide	5mg	One tablet twice daily
Losartan	100mg	One tablet daily
Metformin	1,000mg	One tablet twice daily
Simvastatin	40mg	One tablet at bedtime
Aspirin	81mg	One tablet daily

Table 1. Patient's Medication Regimen

Case synopsis

A 73 year-old white male with a history of chronic type 2 diabetes mellitus presented to the dermatology clinic with recurrent palpable purpura across the lower extremities. His initial eruption commenced two weeks after beginning oral glyburide, 5mg twice daily. The patient described a remitting-relapsing course with flares of purpura lasting two to four weeks, with complete clearance of the lesions in between. Table 1 provides a list of the patient's current medications at the time of presentation (Table 1). The patient had no family history of any rheumatologic or immunologic diseases. He did not have any preceding infections or illnesses. The patient had no other systemic manifestations, with notable absence of arthralgias, hematuria, melena, or abdominal pain. Initial examination revealed symmetric palpable purpura across the dorsal feet that extended up the lower extremities to his thighs bilaterally. Initial laboratory studies revealed a platelet count within normal limits.

Cutaneous biopsy obtained from an outside dermatologist and pathology laboratory of the left anterior thigh demonstrated superficial perivascular granulocytic inflammation with extravasated erythrocytes, karyorrhexis, and vascular mural fibrin deposits. Upon outside chart review, glyburide-induced LCV was suspected and the patient was advised to discontinue glyburide therapy. Despite medical advice, the patient inadvertently restarted glyburide three times throughout the following year owing to his concerns about progression of his diabetes. Within three weeks of restarting his medication, he developed the palpable purpura across the lower extremities. The lesions completely resolved within four weeks of discontinuation of glyburide. With each outbreak of cutaneous manifestations there were no other concurrent systemic signs or symptoms.

Following his initial presentation, the patient was referred to the rheumatology clinic for further evaluation where he underwent an extensive laboratory workup for various autoimmune, neoplastic, and infectious conditions. The patient had the purpuric lesions on the lower extremities at the time of his laboratory work-up and had a platelet count of 242,000. Additional findings included a negative antinuclear antibody, c-ANCA, p-ANCA, serum protein electrophoresis, hepatitis screen, urinalysis, anti-double-stranded DNA antibody, anti-smith antibody, and normal levels of thyroid stimulating hormone and free thyroxine. The patient was once again referred to the dermatology clinic.



Figure 1. A 73-year-old man presents with well-circumscribed palpable purpuric lesions distributed on the left leg.

On presentation to the dermatology clinic for the second time, the patient had restarted the glyburide two weeks prior to his appointment. Physical examination revealed multiple well demarcated, 2-4 mm purpuric papules distributed circumferentially on the forearms, lower extremities, and the dorsum of the feet, bilaterally (Figure 1). The lesions were mildly tender but did not blanch upon palpation and application of pressure.

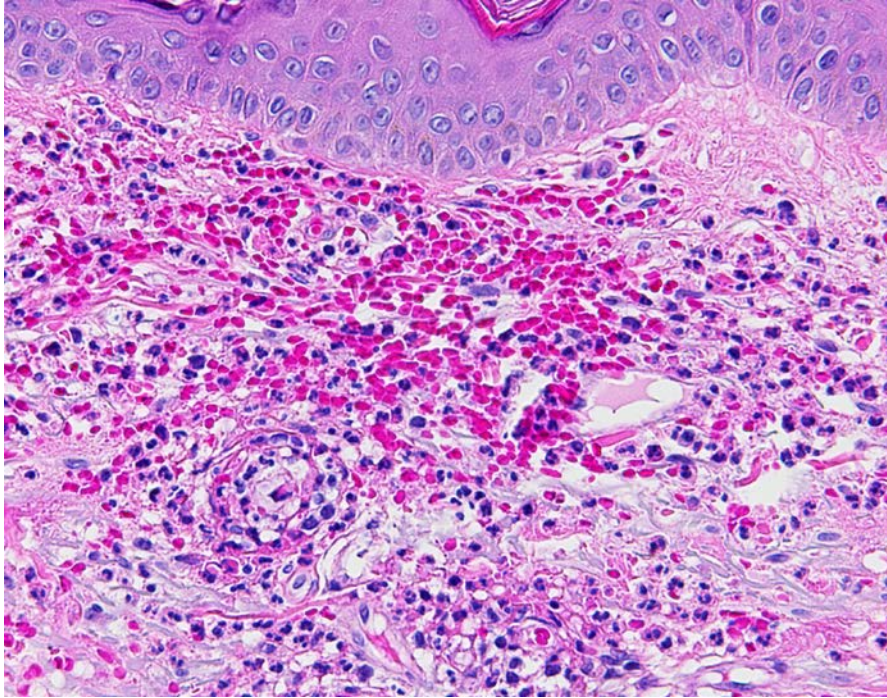


Figure 2. A punch biopsy specimen of the right forearm demonstrates red-blood cell extravasation, infiltration of neutrophils and eosinophils, and fibrinoid necrosis. (hematoxylin-eosin, original magnification x400).

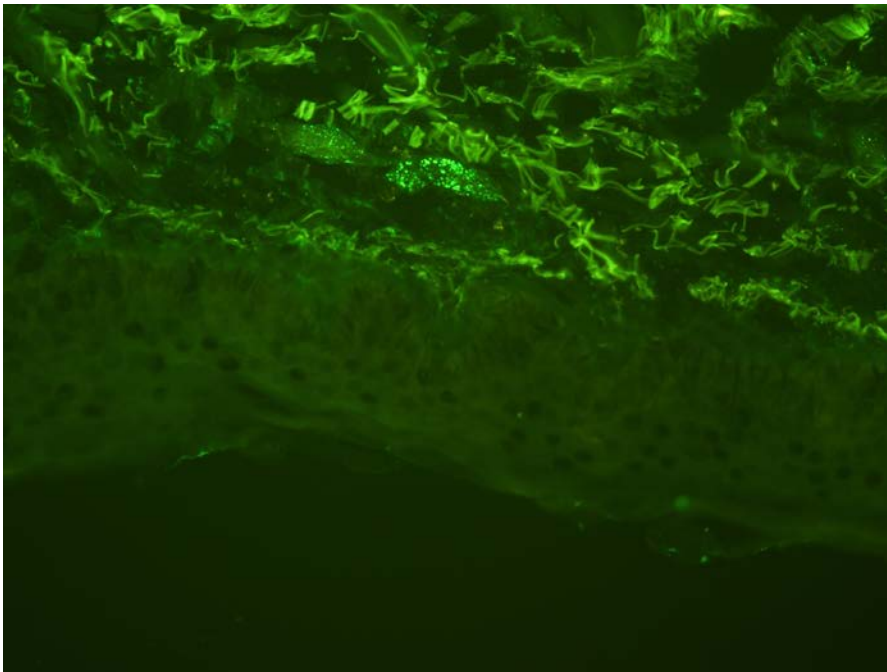


Figure 3. A punch biopsy of the right forearm demonstrates IgA perivascular deposits in the papillary dermis. (Direct Immunofluorescence, original magnification x400).

Cutaneous punch biopsies demonstrated small vessel vasculitis consisting of extravasated erythrocytes, neutrophils, eosinophils, fibrinoid necrosis (Figure 2), and sparse perivascular IgA deposits (Figure 3). Given the clinical and pathological correlation as well as the aforementioned history of glyburide medication use with the development of each purpuric episode, a diagnosis of glyburide associated LCV was made.

Discussion

An accurate diagnosis of medication-induced LCV depends upon conducting a thorough history including chronological association of initiation of medication and development of LCV. Comprehensive examination, exclusion of other potential etiologies, and supportive histopathology are essential. Drug-induced LCV may present with non-specific signs and symptoms such as arthralgias, myalgias, fever, weight loss, lymphadenopathy, and palpable purpura in the absence of associated major organ involvement [1,2,6,9]. Such systemic manifestations are usually seen in other etiologies of LCV including systemic vasculitis, Henoch-Schonlein Purpura, or ANCA associated vasculitides. Dermatologic manifestations of drug-induced vasculitis include palpable purpura, papules, and bullae [5]. Palpable purpura may occur from hours to weeks following exposure to the offending drug; it most often develops on gravity dependent areas, such as the lower extremities and buttocks [5,9].

Certain drugs such as propylthiouracil or anti-TNF alpha agents have a well-known association with leukocytoclastic vasculitis. To the best of our knowledge, there has been only been one previous case of glyburide induced LCV [1,6,15]. The patient presented similarly with violaceous papules and plaques dispersed on the lower extremities and buttocks two days after beginning glyburide therapy [15]. Other medications in the class of sulfonylureas have rarely been associated with similar conditions. There were single case reports of drug-induced leukocytoclastic vasculitis secondary to the related sulfonylureas, glipizide [13] and glimepiride [14].

Distinguishing a drug-related cause versus other etiologies of LCV can be challenging. However, the pattern of development and resolution of the lesions with continuation or discontinuation of the medication can aid in the diagnosis [1]. The exact pathogenesis of associated cutaneous vasculitis is unclear, but current studies suggest the offending drug may act as a hapten, which then stimulates antibody production and immune-complex formation [8,9,10]. The immune-complexes are likely then deposited in the post-capillary venules leading to complement activation and vascular damage. Two other proposed mechanisms include (1) the medication's ability to bind to components of the complement cascade that hinders the clearance of immune complexes and (2) the drug's ability to alter nucleosomes of cells in the body leading to autoantibody development [7,8,10,11].

There are no accepted serologic or laboratory studies for the diagnosis of drug-induced LCV. Several laboratory values have been evaluated and reported in the literature when investigating drug-induced etiologies. Elevated antibodies to multiple neutrophilic antigens, most commonly myeloperoxidase, but also human leukocyte elastase, cathepsin G, and lactoferrin are reported [1,2,3,4,5,6]. In addition, there can be slight elevations in antiphospholipid antibodies, such as IgM anticardiolipin antibody without known associated thrombosis [2,5,6]. Additionally, there can be elevation of the acute phase reactants, the erythrocyte sedimentation rate (ESR) or c-Reactive Protein (CRP) [2,5,6]. Our patient had a negative or normal c-ANCA and p-ANCA and low values of anti-myeloperoxidase and serine protease-3 antibodies. Cutaneous biopsies are essential and demonstrate prominent granulocytic inflammation with leukocyte nuclear fragments, extravasated erythrocytes, and vascular mural fibrin deposits [9]. It is important to rule out infectious and neoplastic causes of vasculitis by conducting a full history and laboratory work-up [1]. Our patient's infectious work-up, including a full hepatitis screen, was negative.

Discontinuing the offending medication usually leads to complete resolution of the vasculitis, as it did in our patient. The treatment for the cutaneous manifestations is typically supportive with topical corticosteroids, nonsteroidal anti-inflammatories, and antihistamines [9]. Depending on the extent of cutaneous and organ involvement, more intensified treatment options can be considered such as systemic corticosteroids [1,9]. Chronic low-dose or a tapering course of corticosteroids may need to be used in the months following discontinuation of the medication to prevent recurrence of symptoms, depending on the severity of the initial outbreak [12].

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