Telmisartan induced urticarial vasculitis

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Introduction

Among several angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blocker (ARB) drugs, telmisartan + hydrochlorothiazide combination is a frequently prescribed antihypertensive in patients who do not achieve the desired effect after monotherapy. Henoch-Schönlein purpura, atypical lymphoid cutaneous infiltration, purpuric rash with vasculitis or acute nephritis, and polycyclic rash with systemic illness, and urticaria with or without angioedema are infrequently reported cutaneous adverse effects with ARBs. Similarly, phototoxic dermatitis, subacute cutaneous lupus erythematosus, erythema annulare centrifugum and acute eczematous dermatitis, and morbilliform and leukocytoclastic vasculitis may be induced by hydrochlorothiazides. There is also an instance of symmetrical drug-related intertriginous and flexural exanthema being attributed to this combination itself. Although losartan and candesartan from ARBs have been implicated for vasculitis, telmisartan is not a described cause of vasculitis. Here, we describe a case of urticarial vasculitis following ingestion of telmisartan, a commonly prescribed antihypertensive drug.

Case Report

A 53-year-old man was hospitalized with deep dusky red lesions over trunk and extremities for 5 days. The lesions were persistent and had intense pruritus and burning. He was hypertensive and taking telmisartan + hydrochlorothiazide (40 + 12.5 mg/day) regularly for 2 weeks and infrequently for the past 16 months. He was afebrile and had no other systemic symptoms. Coalescing, dusky red and ecchymotic lesions of urticarial vasculitis having variable size and shape were widespread over abdomen, flanks, groins, buttocks, and extremities [Figure 1]. Hemogram showed mild leukocytosis (total leukocyte count - 12,800/cmm, normal - 4000–11000/cmm) and neutrophilia (N82%, L14%, E1%, M3%). C-reactive protein was positive. Other laboratory investigations, including serum biochemistry, throat swab culture, Widals test, antistreptolysin-O titer, serum cryoglobulins and complements (C3, C4), antibodies for hepatitis A, B, and C, antinuclear antibodies, rheumatoid factor, prostate-specific antigen, venereal disease research laboratory, human immunodeficiency virus (HIV) serology, G6PD estimation, chest X-rays, abdominal ultrasonography, and urinalysis, were normal. Skin biopsy showed unremarkable epidermis, mild dermal edema and perivascular inflammatory cell infiltrate comprising lymphohistiocytes, neutrophils, and occasional eosinophils in papillary and upper dermis, focal vascular endothelial swelling, and extravasation of erythrocytes suggestive of urticarial vasculitis [Figure 2]. With the possibility of drug-induced urticarial vasculitis, telmisartan + hydrochlorothiazide combination was switched...
with amlodipine 5 mg/day. He improved symptomatically after 10 days’ treatment with cetirizine (10 mg/day) and prednisolone (40 mg/day). Blood counts were normalized and prednisolone was tapered off over next 3 weeks with advice to strictly avoid telmisartan + hydrochlorothiazide and continue amlodipine only. He was re-hospitalized for recurrence within a week after stopping prednisolone. He revealed that he had continued taking telmisartan + hydrochlorothiazide. The drugs were withdrawn immediately, and he was managed with systemic prednisolone as earlier. Two weeks after stopping prednisolone, with informed consent, a drug re-challenge test was performed as per previously described methodology.\textsuperscript{15} Briefly, he was administered a half dose of the hydrochlorothiazide under direct supervision on day 1 followed by full dose next day when it did not elicit any cutaneous rash. On day 3, he was administered telmisartan in a similar manner. Lesions of urticarial vasculitis of less intensity were elicited with 40 mg of telmisartan but not with 20 mg. He was advised to strictly avoid ARBs/ACE inhibitors in the future.

**Discussion**

Urticarial vasculitis is an uncommon clinicopathological entity that may be hypo-complementemic (low C1q and C4 levels and variably decreased C3 levels), occurs almost exclusively in female patients, or normo-complementemic. Its reported prevalence is about 5–10% in chronic urticaria patients wherein episodes of urticaria are characteristically associated with leukocytoclastic vasculitis. However, lymphocyte-predominant cellular infiltrate with an admixture of eosinophils is observed more frequently than leukocytoclastic vasculitis. It remains idiopathic in most cases or is secondary to connective tissue diseases with a prevalence of 20% in systemic lupus erythematosus and 32% in Sjogren’s syndrome. Serum sickness, neoplasia (leukemias or tumors of breast, pituitary, thyroid, colon, and pancreas), and infections (hepatitis B, hepatitis C, HIV, syphilis, and infectious mononucleosis) are commonly described causes. Clinically, wheals in urticarial vasculitis last for 48–72 h and angioedema involving lips, tongue, eyelids, and hands may occur additionally in 40% cases. The lesions differ from true urticaria in their association with burning, pain or tenderness, purpura, and induration that resolve usually with purpura or hyperpigmentation. Hypo-complementemic variety being severe form may be associated with fever, malaise, myalgia, fatigue, and organopathy (arthralgia, arthritis, serositis, glomerulonephritis, and interstitial nephritis), Raynaud’s phenomenon or conjunctivitis, and episcleritis.\textsuperscript{14} Skin ulcers or multiorgan damage (lungs, eyes, and kidneys) is not uncommon in secondary or hypo-complementemic variety.\textsuperscript{15} Normo-complementemic or idiopathic cases usually respond to antihistamines or nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen and naproxen) while patients with organopathy or severe disease will require systemic corticosteroids or other disease modifying drugs (hydroxychloroquine, colchicine, dapsone, azathioprine, or cyclophosphamide).\textsuperscript{16} Although spontaneous resolution occurs usually in normo-complementemic or idiopathic cases, the overall prognosis depends upon the prognosis of the underlying cause.

Drugs have been implicated in about 10% of vasculitis cases and diltiazem, cimetidine, antibiotics, interferon, NSAIDs, and potassium iodide remain as commonly implicated drugs.\textsuperscript{13} Glatiramer,\textsuperscript{15} glimepiride,\textsuperscript{17} enalapril,\textsuperscript{18} and levetiracetam\textsuperscript{19} too have been reported to elicit urticarial vasculitis. Curiously, the drugs appear to elicit urticarial vasculitis after a variable period irrespective of dose and frequency of drug administration. For instance, a 48-year-old female developed histologically confirmed urticarial vasculitis 3 months after glatiramer acetate administered for multiple sclerosis,\textsuperscript{17} glimepiride induced urticarial vasculitis in a 72-year-old woman occurred 6 weeks after starting the drug,\textsuperscript{17} and urticarial vasculitis appeared 8 days after enalapril therapy.\textsuperscript{18} Similarly, our patient developed urticarial vasculitis only recently despite ingesting the implicated antihypertensive infrequently during >1-year period. Apparently, he developed urticarial vasculitis only when he started taking the drug more frequently. However, the reasons for such a phenomenon remain unelucidated for now.

The diagnosis of drug-induced urticarial vasculitis in most cases is by exclusion of other known causes, temporal correlation between drug intake and onset of skin eruptions, clinicopathological correlation, and improvement of the symptoms after withdrawal of suspected drug (de-challenge), or re-challenge. The described patient was normo-complementemic, recovered after withdrawal of suspected antihypertensive, and re-challenge test imputed his lesions to telmisartan. The causality assessment by World
Health Organization Uppsala Monitoring Centre causality scale was “certain” in view of temporal correlation to drug intake, complete clearance and no recurrence of skin lesions after drug withdrawal (de-challenge), and recurrence after re-challenge. Clinicians need to be aware of this uncommon cutaneous adverse reaction, as more cases may become apparent with the wider use of ARBs than in pre-marketing studies.

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**Conflicts of Interest**
There are no conflicts of interest.

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