

CASE REPORT

Sibutramine (Reductil[®])-Induced Cutaneous Leukocytoclastic Vasculitis: A Case Report

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A 24-year old woman presented with hemorrhagic vesicles on her legs. She had taken sibutramine (Reductil[®], Abbott Labs., Seoul, South Korea) for 3 months and developed skin lesions the week before. A skin biopsy showed leukocytoclastic vasculitis with conspicuous eosinophilic infiltration of the tissue. These lesions showed improvement after discontinuation of sibutramine. However, 3 months later the skin lesions recurred on other sites on the lower extremities when the patient was rechallenged with the same drug for 2 weeks. Herein, we report the first case of necrotizing vasculitis induced by sibutramine. (*Ann Dermatol* 23(4) 544 ~ 547, 2011)

-Keywords-

Cutaneous leukocytoclastic vasculitis, Drug induced vasculitis, Sibutramine

INTRODUCTION

Sibutramine (Reductil[®]) is a selective monoamine reuptake inhibitor¹. It is an orally administered, centrally acting, weight-management agent devoid of amphetamine-like abuse potential. Its amine metabolites are pharmacologically active and are thought to induce the natural pro-

cesses leading to enhanced satiety and thermogenesis by inhibiting serotonin and noradrenaline reuptake². Several clinical studies assessing the effectiveness and safety of sibutramine have shown that the drug is a safe and well-tolerated agent¹. Common side effects include dry mouth, constipation, nausea, and headache¹. The drug has been associated with increases in blood pressure and pulse rate². Cutaneous side effects such as urticaria, petechiae, mild skin eruption, and allergic hypersensitivity reaction have been rarely reported². Furthermore, a case report is available on an unusual adverse reaction of erythema multiform-like bullous drug eruption caused by sibutramine³.

Drug-induced vasculitis represents approximately 10% of acute cutaneous vasculitis cases⁴ and is difficult to diagnose. Diagnosis and assessment of an underlying cause of a drug includes an analysis of features such as timing of drug exposure, onset, course of reaction, and nature of a recurrent eruption on rechallenge⁵.

Herein, we first report an interesting case of a patient with recurrent episodes of necrotizing vasculitis induced by sibutramine.

CASE REPORT

A 24-year old woman presented with hemorrhagic vesicles on her legs. The skin lesions had appeared the week before. She had been taking 10 mg sibutramine once daily for 3 months, which had been prescribed at an adequate dose and appropriate manner. She had tolerated the drug before the development of skin lesions. She was a student, and had no relevant medical history or any viral infection history. She had no travel or trauma history.

On physical examination, the patient had two overlying hemorrhagic vesicles on purple red patches on the right thigh and left calf (Fig. 1). She did not have any mucosal

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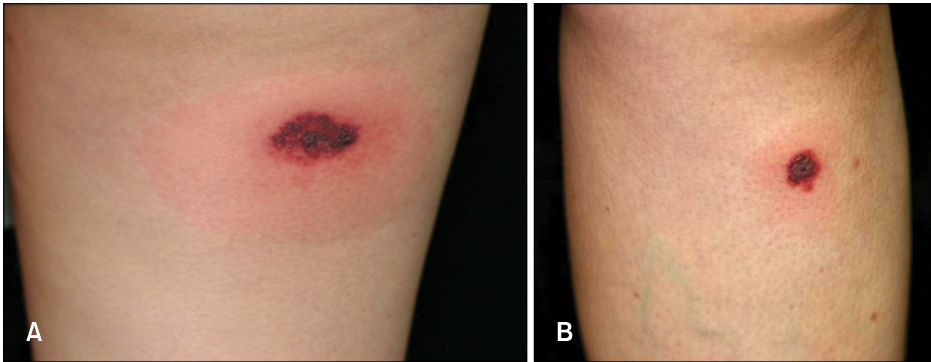


Fig. 1. (A) Overlying hemorrhagic vesicles on a wheal-like patch of the right thigh. (B) A hemorrhagic vesicle on the left calf.

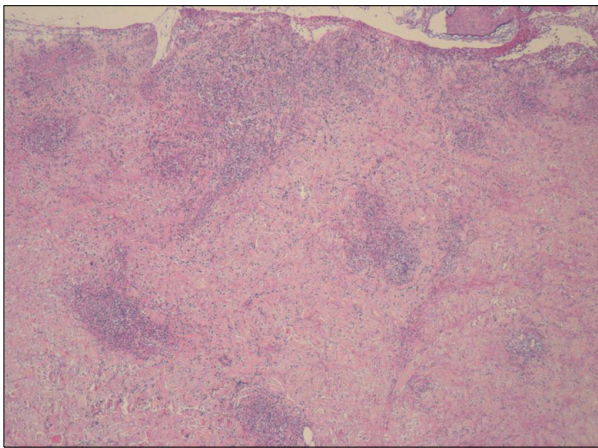


Fig. 2. Epidermal detachment with dense infiltrate in the upper dermis and patchy cellular infiltration around the dermal blood vessels (H&E, $\times 40$).

lesions. She was otherwise healthy, and had no history of fever, abdominal pain, or joint pain.

Kidney and liver function tests were within the normal range. C3 level was normal, and antinuclear and antineutrophil antibodies were absent. A urinalysis with microscopy showed microscopic hematuria. Kidney ultrasonography revealed a small urinary stone but otherwise normal function.

A skin biopsy from the purpuric vesicular patch revealed perivascular cellular infiltration (Fig. 2). Dense perivascular lymphohistiocytic infiltration with fibrinoid deposition in the vascular wall, red blood cell extravasation, nuclear dust, and endothelial swelling were observed revealing leukocytoclastic vasculitis (Fig. 3A). Conspicuous eosinophils were evident in the dermis (Fig. 3B). The lesions showed obvious improvement after discontinuing the sibutramine followed by the administration of 10 mg prednisolone daily for 2 weeks.

Three months later, she visited our clinic again with a recurrence of similar skin lesions on other sites of the

lower extremities (Fig. 4). A history revealed that she had taken sibutramine 2 weeks before lesion recurrence. Again, the patient was told to discontinue the sibutramine, and she improved substantially within 4 days.

DISCUSSION

Vasculitis is a diverse group of segmental inflammatory disorders and blood vessel necroses. Leukocytoclastic vasculitis involves mainly small vessels in the skin and generally manifests as palpable purpura on the lower extremities⁶. Other features include hemorrhagic bullae, ulcers, nodules, and occasional digital necrosis⁶. In our case, hemorrhagic vesicles and palpable purpura were found.

Diverse histological findings are noticeable, based on the inflammation period, Red blood cell extravasation, nuclear dust, and endothelial swelling are suggestive findings of vasculitis⁴. At least two histological components must occur to diagnose vasculitis: a perivascular inflammatory cell infiltrate and evidence of vascular injury⁴. Necrosis of the vessel wall with deposition of fibrinoid material is a pathognomonic finding of vasculitis⁴. This patient had all vasculitis findings such as red blood cell extravasation, nuclear dust, endothelial cell swelling, perivascular cellular infiltration, and fibrinoid deposition.

When cutaneous vasculitis is demonstrated histologically, every effort should be made to define the causative agent. If visceral diseases such as renal, pulmonary, or intestinal diseases are associated, an antineutrophil antibody study should be conducted to rule out Wegener's granulomatosis, microscopic polyangiitis, and Churg Strauss syndrome. If antinuclear antibody or rheumatoid factors are present and dry eye or arthritis develops, then connective tissue disease vasculitis should be considered. If urticarial lesions are found clinically, urticarial vasculitis should be diagnosed. If a high fever or other infection signs are present, then infection-related vasculitis or septic

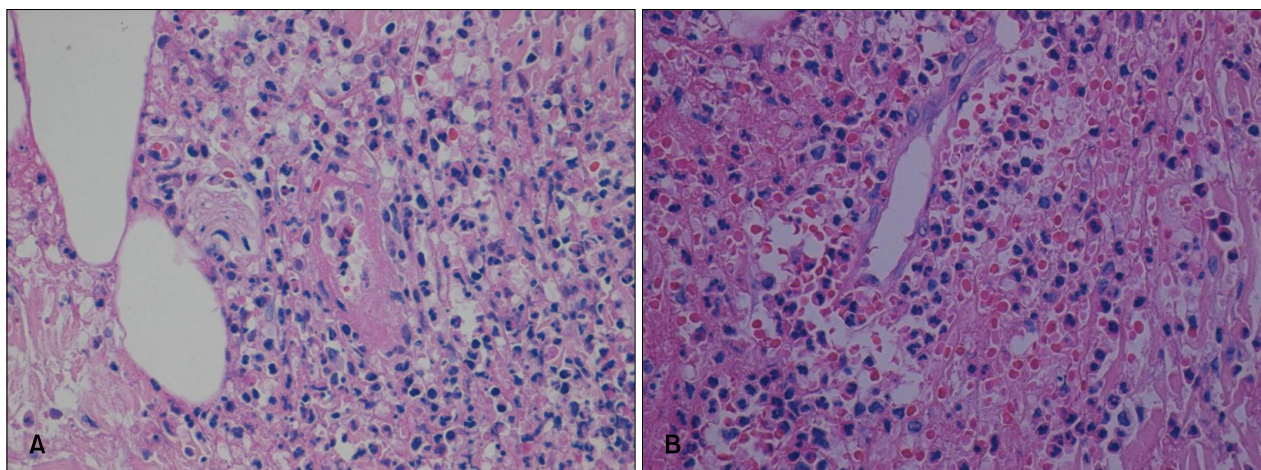


Fig. 3. (A) Fibrinoid deposition in the vascular wall, perivascular lymphoid cellular infiltration, red blood cell (RBC) extravasation, and nuclear dust (H&E, ×400). (B) Conspicuous eosinophils, RBC extravasation, and endothelial cell swelling (H&E, ×400).



Fig. 4. A purpuric vesicular patch recurred on the right calf after rechallenging the patient with sibutramine 3 months later.

vasculitis should be considered. Paraneoplastic vasculitis should be suspected if hematological abnormalities or abnormal masses are found on imaging studies, and the lesions do not improve with corticosteroids. If there is a history of drug intake, drug-induced vasculitis should be considered.

Drug-induced vasculitis represents approximately 10% of acute cutaneous vasculitis cases⁵. It can be difficult to diagnose and is often a diagnosis of exclusion⁶. Other causes for cutaneous vasculitis, such as infection or autoimmune disease, must be excluded. Diagnosis and assessment of an underlying drug etiology consists of analyzing features such as timing of drug exposure, reaction onset, course of reaction with drug withdrawal or continuation, timing and nature of a recurrent eruption on rechallenge, and previous reports of similar reactions to

the same medication⁶. A skin biopsy should be considered for patients with potentially severe reactions, such as those with erythroderma, blistering, skin tenderness, purpura, or pustulation⁶. Tissue eosinophilia may be an indicator of drug etiology in patients with cutaneous small vessel vasculitis⁷. The therapeutic approach can be divided into antigen removal and treatment of the cutaneous vasculitis⁸. Withdrawal of the precipitating medication is mandatory. Treatment for cutaneous vasculitis consists of preventing the deposition of immune complexes, and suppressing the inflammatory response⁸. H1 antihistamines are used to alleviate lesional symptoms and to reduce tissue deposition of circulating immune complexes. Nonsteroidal anti-inflammatory agents are combined with an H1 antihistamine, and colchicine or hydroxychloroquine sulfate can be added to or substituted for these agents⁸. If there is still no therapeutic response, systemic glucocorticoids or other immunosuppressants (azathioprine, methotrexate, cyclophosphamide, cyclosporine) should be considered⁸.

In our case, as similar skin lesions recurred after a rechallenge with sibutramine, the offending drug was sibutramine. Moreover, conspicuous eosinophilic infiltration of the tissue on histological examination suggested a drug etiology.

Sibutramine has been increasingly used since obesity has become a social issue. It is a selective monoamine reuptake inhibitor, primarily of serotonin and noradrenaline¹. It is a centrally acting weight-management drug, devoid of amphetamine-like abuse potential². Overall, selective serotonin reuptake inhibitors are safe, and adverse effects are mainly associated with gastrointestinal tract symptoms such as nausea, vomiting, or diarrhea.

Previous studies of vasculitic reactions associated with selective serotonin reuptake inhibitor therapy have been reported. Case reports of urticarial vasculitis secondary to fluoxetine⁹ and paroxetine¹⁰ have also been documented. Leukocytoclastic vasculitis after administering citalopram for 2 months has been reported¹¹. A patient who developed cutaneous vasculitis while taking paroxetine for 4 months has also been reported¹².

Serotonin plays a role in blood clotting, evokes smooth muscle contraction, and narrows blood vessels.

Therefore, manipulating serotonin levels may result in abnormal cutaneous or visceral manifestation¹³. The ability of serotonin to induce and augment platelet aggregation following vascular inflammation may explain the vasculitic reaction. Further studies are needed to identify the exact mechanism of the induction of vasculitis by selective serotonin reuptake inhibitors.

No reports are available on drug-induced vasculitis associated with sibutramine. Thus, this is the first reported case of cutaneous leukocytoclastic vasculitis caused by sibutramine.

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