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CASE REPORT

An urticarial vasculitis case induced by glatiramer acetate

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Abstract

Urticarial vasculitis (UV) is a disease characterized clinically by urticarial skin lesions and histologically by leukocytoclastic vasculitis caused by immunocomplex accumulation in post-capillary venules. Cases induced by various drugs such as cimetidine, diltiazem, potassium iodide, fluoxetine, and non-steroid inflammatory drugs have been reported in the literature. A 48-year-old female who developed pruritus and rash on her body 3 months after starting glatiramer acetate (GA) treatment for multiple sclerosis was diagnosed with UV after clinical and histopathological examination. This report presents the first case in the literature of UV induced by GA.

Key words: Drug eruption, glatiramer acetate, urticarial vasculitis

Introduction

Urticarial vasculitis (UV) was first defined by McDuffie et al. in 1973 (1). The incidence of the disease in middle-aged (30–50 years) women is three times that in men (2). Although its etiology is not known for sure, connective tissue diseases such as Sjögren's syndrome, systemic lupus erythematosus (SLE), viral infections such as hepatitis B and C, serum diseases, malignancies and drugs are held responsible. Generally, it has no underlying cause, and is therefore defined as an idiopathic disease (1–5).

Glatiramer acetate (GA) is used in the treatment of multiple sclerosis as an immunomodulator. It is a synthetic drug also known as copolymer-1 and formed from four amino acids, namely L-alanine, L-lysine, L-glutamic acid and L-thyrosine. Only two drug eruption cases were reported due to the drug, whose exact efficiency mechanism is unknown (6).

Case report

A 48-year-old female patient, who was monitored in the neurology clinic upon multiple sclerosis diagnosis and who had started GA treatment 3 months previously, presented at our clinic complaining of itching and rash on the body, as well as abdominal and articular pain. Dermatological and systemic

examination was normal, and showed urticaria-like plaques on the body, face and extremities (Figures 1 and 2).

Laboratory analyses found the following values – leukocytes: 11.980/mm³ (3.8–10.3 mm³); C-reactive protein (CRP): 20.4 mg/l (0–6 mg/l); serum C3 level: 0.8 g/l (0.9–1.8 g/l); and serum C4 level: 0.2 g/l (0.1–0.4 g/l). Other laboratory analyses of the patient did not show any abnormality. Histopathological examination of the material taken from the lesion on the patient's right arm by punch biopsy demonstrated hyperkeratosis epidermis and occasional vacuolar degeneration in basal cells. There was inflammatory cell infiltration composed predominantly of neutrophils, occasional eosinophils and lymphocytes in perivascular areas, and there was also nuclear dust, as well as fibrin accumulation on vessel walls and a resulting thickening of dermis.

Swelling in endothelial cells and a certain amount of degeneration was noted. A leukocytoclastic vasculitis presentation was observed where mixed type inflammatory cell infiltration formed from lymphocytes, neutrophils and eosinophils also influenced the vessel walls (Figure 3).

The patient was clinically and histopathologically diagnosed with UV and 1 mg/kg per day of systemic corticosteroid treatment was started. All the lesions abated on the third day of treatment. The drugs used



Figure 1. Urticaria-like lesions on the body of the patient.



Figure 2. Urticaria-like lesions on the upper extremities of the patient.

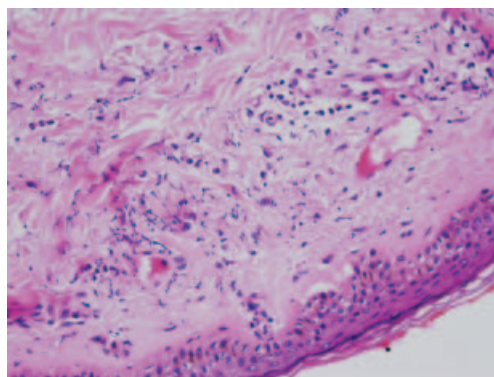


Figure 3. Perivascular inflammatory cell infiltration and fibrin accumulation on vessel walls and mixed type cell infiltration formed from neutrophils, eosinophils and leukocytes, and nuclear crumbs (HE $\times$ 400).

by the patient as part of her treatment were held responsible for the disease etiology, and all drugs were discontinued. Forty-five days after the treatment the patient presented at our clinic due to a recurrence of her symptoms. The patient's anamnesis revealed that GA treatment had been resumed 14 days previously. The patient was started on 1 mg/kg per day of systemic corticosteroid treatment and the lesions improved in a short time.

Discussion

GA is a new molecule drug used in the treatment of multiple sclerosis. The literature includes a case report where the drug caused a severe cutaneous reaction defined as Nicolau's syndrome (7). This syndrome arises when coincidental intra-arterial injection leads to an acute vascular spasm, causing vascular necrosis. The drug injection is followed by acute severe pain and cyanotic patches. Development of Nicolau's syndrome was reported to be associated with the intramuscular injection of hydroxyzine, diphtheria-tetanus-pertussis vaccine and non-steroidal anti-inflammatory drugs (7–10). Additionally, a case who developed livedo-like dermatitis following a GA injection was reported (11). Ours is the first case who was found to have UV associated with GA.

Skin lesions observed in UV are urticaria-like itchy or aching, erythematous and edematous plaques. Eruptions appear in the form of temporary attacks, predominantly involve the extremities, recover in more than 24 hours, and leave yellow-green hyperpigmentation after recovery. It is rarely accompanied by angioedema. Less common cutaneous signs of the disease include morbilliform erythema, bullae, livedo and erythema multiforme-like lesions (1,2,12). Our case also had erythematous and edematous aching plaques of an annular type localized predominantly in the extremities, the lesions persist more than 24 hours and left hyperpigmentation when they disappeared.

UV may be accompanied by systemic symptoms such as fever, arthralgia, myalgia, and abdominal and chest pain. Laboratory analyses may show leukocytosis and eosinophilia, and urine analysis may reveal microhematuria and proteinuria, an increase in sedimentation, hypocomplementemia, circulating immunocomplexes, anti-nuclear antibody (ANA) and a positive rheumatoid factor (RF). In addition, there may be symptoms of systemic involvement such as glomerulonephritis, conjunctivitis, uveitis, episcleritis, lymphadenopathy, hepatosplenomegaly, and obstructive pulmonary disease (1,2,12).

The precise mechanism of action of GA is not fully understood yet. The mechanisms discussed include competition with myelin peptides, especially myelin basic protein on antigen presenting cells, antagonism at the T-cell receptor of myelin-specific T cells and induction of GA-specific suppressive/regulatory T cells secreting potentially anti-inflammatory cytokines upon activation. There is increasing evidence for the immunomodulating effects of GA on CD8+ T cells but also on B cells and antigen presenting cells. Its proposed mechanisms of action include competition with myelin antigens for binding to antigen presenting cells, antagonism at specific T-cell receptors, induction of GA-specific regulatory CD4+ and CD8+ T cells which downregulate inflammation by secretion of

anti-inflammatory cytokines and cause bystander suppression of proinflammatory TH1 cells in the central nervous system (13–15). Probably the B cells stimulated by GA-specific T cells converse to plasma cells that synthesize GA-specific Ig. Type 3 hypersensitivity reaction causing complement activation of immunocomplexes that accumulated in venules and resulting in vascular injury has been accused in the pathogenesis of the disease (1,2).

Histopathological evaluation has diagnostic value. Histopathology shows leukocyte dust and fibrinoid accumulation on the walls of post-capillary venules, which is called leukocytoclastic vasculitis, as well as interstitial neutrophils, mononuclear cells, a high number of eosinophils and mild to moderate erythrocyte extravasation of dermis (16). Furthermore, histopathological examination of UV associated with drugs demonstrates mixed type inflammatory cell infiltration formed from lymphocytes, neutrophils and eosinophils (17). A biopsy examination of this case included these signs.

The presence of internal organ involvement is important in the treatment of the disease. When there are systemic symptoms, systemic steroids, dapsone or colchicine can be administered. In refractory cases who do not respond to these treatments, immunosuppressive drugs such as azathioprine, cyclophosphamide, 6-mercaptopurine and methotrexate can be tried. There may be relapses, when the drugs are discontinued. Antihistamines can be used in cases where the disease is limited to the skin, but these drugs are generally inefficient. Non-steroidal anti-inflammatory drugs may be useful in those with articular involvement (1,2,12). Our patient responded in a short time to 1 mg/kg per day systemic corticosteroid treatment.

In conclusion, we present this case of UV associated with GA, which has not been reported hitherto, hoping that it would contribute to the literature.

References

- Braun-Falco O, Plewing G, Wolff HH, Burgdorf WHC A (eds). Diseases of the blood vessels. In: Dermatology. 2nd edn. Berlin: Springer-Verlag; 2000. p. 881–954.
- Mandell BF, Hoffman GS. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's dermatology in general medicine. 5th ed. New York: McGraw Hill; 1999. p. 2034–44.
- Alexander JL, Kalaaaji AN, Shehan JM, Yokel BK, Pittelkow MR. Plasmapheresis for refractory urticarial vasculitis in a patient with B-cell chronic lymphocytic leukemia. J Drugs Dermatol. 2006;5:534–7.
- Wang CC, Chen MJ, Ho HC, Hong HS. Urticarial vasculitis and dermatomyositis in a patient with nasopharyngeal carcinoma. Cutis. 2003;72:399–402.
- Wilson D, McCluggage WG, Wright GD. Urticarial vasculitis: A paraneoplastic presentation of B-cell non-Hodgkin's lymphoma. Rheumatology. 2002;41:476–7.
- Perumal J, Filippi M, Ford C, Johnson K, Lisak R, Metz L, et al. Glatiramer acetate therapy for multiple sclerosis: A review. Expert Opin Drug Metab Toxicol. 2006;2: 1019–29.
- Bosca I, Bosca M, Belenguer A, Evole M, Hernandez M, Casanova B, et al. Necrotising cutaneous lesions as a side effect of glatiramer acetate. J Neurol. 2006;253: 1370–1.
- Gaudez C, Regnier S, Aractingi S, Heinzlef O. Livedo-like dermatitis (Nicolau's syndrome) after injection of Copolymer-1 (Glatiramer acetate). Rev Neurol. 2003;159:571–3.
- Erkek E, Tuncez F, Sanli C, Duman D, Kurtipek GS, Bagci Y, et al. Nicolau's syndrome in a newborn caused by triple DTP (diphtheria-tetanus-pertussis) vaccination. J Am Acad Dermatol. 2006;54:241–2.
- Cherasse A, Kahn MF, Mistrih R, Maillard H, Strauss J, Tavernier C. Nicolau's syndrome after local glucocorticoid injection. Joint Bone Spine. 2003;70:390–2.
- Gayken J, Westanmo A, Knutsen A, Ahrenholz DH, Mohr WJ, Solem LD. Livedoid dermatitis and severe necrosis (Nicolau's syndrome) after intramuscular hydroxyzine injection. J Burn Care Res. 2006;27:541–4.
- Thomas PH B (ed). Urticaria. In: Clinical dermatology. 3rd ed. Boston: Von Hoffman Press; 1996. p. 122–47.
- Schrempf W, Ziemssen T. Glatiramer acetate: Mechanisms of action in multiple sclerosis. Autoimmun Rev. 2007;6: 469–75.
- Liu J, Johnson TV, Lin J, Ramirez SH, Bronich TK, Caplan S, et al. T cell independent mechanism for copolymer-1-induced neuroprotection. Eur J Immunol. 2007;37: 3143–54.
- Weber MS, Prod'homme T, Youssef S, Dunn SE, Rundle CD, Lee L, et al. Type II monocytes modulate T cell-mediated central nervous system autoimmune disease. Nat Med. 2007;13:935–43.
- Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: A histopathologic and clinical review of 72 cases. J Am Acad Dermatol. 1992;26:441–8.
- Weedon D. Skin pathology. New York: Elsevier; 2003. p. 232–3.