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Henoch-Schönlein Purpura during Isotretinoin Therapy

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Dear Editor:

Henoch-Schönlein purpura (HSP) is a leucocytoclastic vasculitis that typically presents with a palpable purpuric rash. The disease primarily affects children and has rarely been seen in adults (3.4 to 14.3 cases per million)[1]. Hereby, we present a 20-year-old patient with HSP that developed during isotretinoin treatment for his acne.

A 20-year-old man presented at our outpatient clinic with palpable purpuric lesions developed after the fourth week of isotreinoin (30 mg/day) treatment for severe inflammatory acne. Examination revealed multiple palpable purpura on the legs, 1 mm to 15 mm in diameter (Fig. 1). Furthermore, the patient had arthralgia in both ankles and knees. Complete blood count, liver and kidney function tests, coagulation test, routine biochemistry panel, and lung posterior/anterior graphy were normal. All of the following tests were negative: antinuclear antibodies, anti-neutrophil cytoplasmic antibody, cryoglobulins, hepatitis B surface antigen, anti-human immunodeficiency virus and anti-hepatitis C virus antibodies were. The patient's serum anti-streptolizin O, rheumatoid factor, immunoglobulin A (IgA), and complement levels (C3～C4) were normal. C-reactive protein level was 16 mg/L (reference range 0～6 mg/L). Erythrocyte sedimentation rate was 35 mm/h (Westergren method). He had no abdominal complaints like pain or rectal bleeding; fecal occult blood test was negative. Urinary sediment analysis was normal. During the taking of his medical history, the patient denied recent upper respiratory, gastrointestinal or genitourinary tract infections and he did not have any physical evidence of infection. The patient also denied any vaccination or drug use other than isotretinoin over the last 2 months. A skin biopsy of from one of the lower limb lesions showed leukocytoclastic vasculitis with IgA and C3 deposition

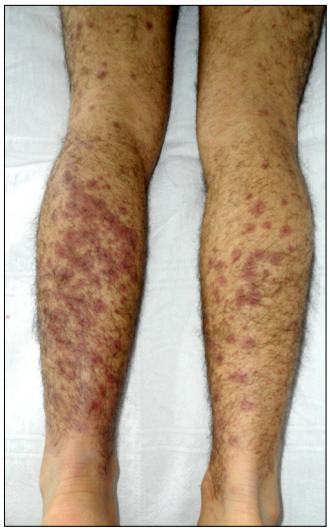

Fig. 1. Palpable purpuric lesions on the lower limbs.

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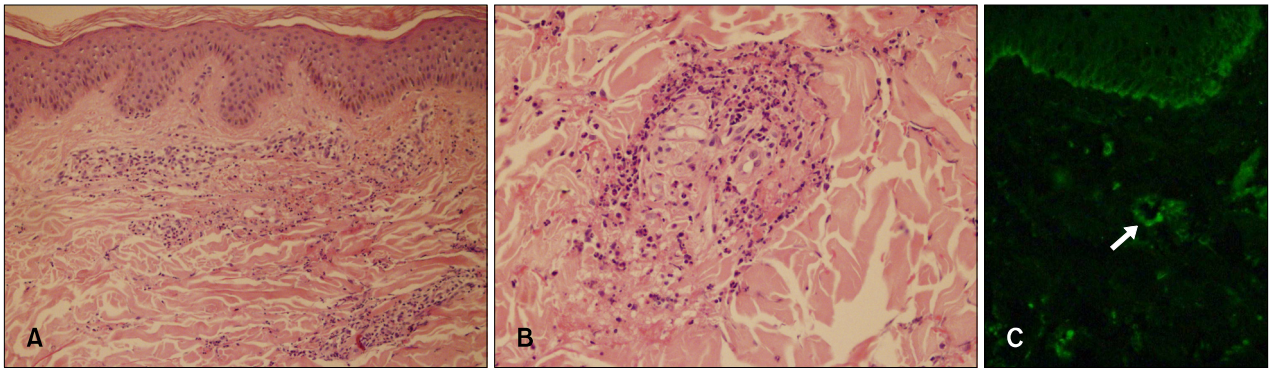

Fig. 2. (A) Dermal perivascular inflammatory infiltration (H&E ×40). (B) High power view of perivascular inflammatory infiltration including neutrophils with quite a few eosinophils and fibrinoid necrosis (H&E ×200). (C) Perivascular Immunoglobulin A deposition in immunofluorescence microscopy as shown by arrow.

(Fig. 2). On histopathological examination, in support of the relationship between vasculitis and the drug, quite a few eosinophilic infiltration in addition to perivascular neutrophilic infiltration was observed (Fig. 2B). According to these clinical and histopathological findings, the patient was diagnosed with having HSP. Isotretinoin treatment was discontinued; low-dose steroid therapy (fluocortolon 20 mg/day) was initiated and continued 3 weeks. All lesions disappeared by 2 weeks and the disease did not relapse during the 2 months' follow-up.

According to EULAR/PRES/PRINTO (European League Against Rheumatism / Paediatric Rheumatology European Society / Paediatric Rheumatology International Trials Organisation), the criterion of palpable purpura or of petechia with lower limb predominance is mandatory criterion for the diagnosis of HSP. Furthermore, at least one of the following criteria must be present: diffuse abdominal pain, IgA deposition in any biopsy, arthritis/arthralgia, and renal involvement[2]. The most common causes of HSP are infections of respiratory, gastrointestinal, and genitourinary tracts. Other well-known triggering factors of the disease are hepatic infections, inflammatory bowel disease, autoimmune rheumatic diseases, hematological and solid organ malignancies, vaccinations and adverse drug reactions to diverse drugs. Use of isotretinoin was the sole suspected cause of HSP in our case.

Isotretinoin induced vasculitis is very rare in the literature. Dwyer et al.[3] reviewed 11 isolated vasculitis cases, which could have been associated with isotretinoin and were gathered by manufacturer of isotretinoin. In the manufacturer's judgment, 5 of the 11 patients the leucocytoclastic vasculitis was associated with the use of systemic isotretinoin. There were no other factors other than retinoid use that may have caused vasculitis in these patients except for 1 patient who had streptococcal infection.

Reynolds et al.[4] reported a case of disseminated vasculitis, which developed 6 weeks after completion of isotretinoin treatment. However, some authors argued that this cause was controversial considering a serum half-life of isotretinoin[5]. Epstein et al.[6] described 2 patients who developed severe vasculitis in whom one patient with Wegener's granulomatosis and the other patient with small-vessel angiitis, while receiving isotretinoin for severe cystic acne. Chochrad et al.[7] reported a case of 'polyarteritis-like vasculitis' associated with isotretinoin.

It is interesting that despite these early reports of vasculitis associated with isotretinoin, in a PubMed search we could not detect any other reports after 1997. The reason may be associated with a rare occurrence of cases, alternatively further cases may have not been reported. In addition, it is not possible to make a definitive diagnosis. Instead, the diagnosis of drug induced vasculitis is based on a temporal relationship between exposure to the agent and the development of vasculitis and the exclusion of other factors.

In our case, we couldn't find any causal factor other than treatment with isotretinoin. Although rare, the clinicians should remember retinoid medications as a possible cause of vasculitis.

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Eosinophilic Pustular Folliculitis Involving Labial Mucosa, Which Improved with Naproxen

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Dear Editor:

Eosinophilic pustular folliculitis (EPF) is a sterile eosinophilic infiltration of hair follicles. There are three variants, including the classic, immunosuppression-associated, and infantile type[1]. Although they are histologically indistinguishable from each other, some propose that the three types be regarded as different disease entities due to their different responses to treatment.

Histologically, the most diagnostic feature of EPF is the infiltration of eosinophils in hair follicles and perifollicular areas[1]. However, the term 'folliculitis' is being challenged[2], on account of the fact that approximately 20% of patients with classic EPF have the disease on palms and soles[1].

Here, we report a case of EPF involving the labial mucosa, which improved with naproxen. An 11 year-old girl presented with itching erythematous plaques and clustering pustules on the lateral side of the nose and perioral area, with erosive lesions on the external lips (Fig. 1A). A biopsy was taken from the lateral side of the nose at a district hospital. The lesion at nose showed the same feature and connected with labial lesion. It demonstrated follicular and perifollicular infiltration by eosinophils and other inflammatory cells (Fig. 2). The diagnosis of classic EPF was made at the hospital, and she was treated with systemic prednisolone, cyclosporine, dapsone, and/or topical corticosteroid, pimecrolimus. However, her symptoms waxed and waned over 6 months and showed improvement only with the systemic prednisolone. Routine blood test was within normal limits without eosinophilia. Because pruritus was the prominent symptom rather than pain and tenderness, infectious condition was less suspected. Suspecting EPF, we started her on naproxen, 250 mg twice a day; and after three months, her symptoms greatly improved (Fig. 1B).

The etiology and pathogenesis of EPF have still yet to be fully elucidated, and there are multiple treatment options. The utilization and efficacy of therapies seem to depend on the type of EPF[2]. Topical corticosteroids tend to be the first choice in all EPF variants[1]. In children, topical calcineurin inhibitors and oral antihistamines are also usually effective and are viewed as the first-line agents[3]. However, our case was recalcitrant to various treatments, including topical corticosteroids and topical calcineurin inhibitor. Only the naproxen had a remarkable effect.

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