

## Erythema Nodosum Associated with Valproate

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Dear Editor:

Erythema nodosum is considered to be a cutaneous hypersensitivity reaction to various initiating factors, including infection, medications, rheumatologic diseases, autoimmune disorders, and malignancies<sup>1</sup>. Clinically, it presents with bilateral, multiple, tender, erythematous nodules over the anterior aspect of the leg.

A 55-year-old Korean woman presented with a 2-day history of painful, bilateral, multiple erythematous to violaceous subcutaneous nodules on the upper and lower extremities (Fig. 1A, B). She also complained of headache, fatigue, polyarthralgia, and abdominal discomfort. She had undergone left pterional craniotomy and aneurysmal neck clipping for left anterior choroidal unruptured aneurysm 2 weeks previously. Her past medical history was unremarkable. Since then, the patient had started the administration of valproate (Orfil long retard cap<sup>®</sup>; Bukwang Pharmaceutical, Seoul, Korea) 15 mg/kg to prevent post-operative seizure. The routine laboratory findings were within the reference ranges, except for the elevated levels of C-reactive protein (6.34 mg/dl; reference: 0~0.05 mg/dl), pancreatic amylase (201 U/L; reference: 13~53 U/L), lipase (239 IU/L; reference: 6~52 IU/L), and alanine aminotransferase (90 IU/L; reference: 1~34 IU/L). Computed tomography of the abdomen was performed for the suspicion of acute pancreatitis; however, no evidence of any abnormality was found in the pancreas. Histopathologic examination of the skin lesions revealed inflammatory infiltrates arranged interstitially between the thickened septa in the subcutaneous layer, and there were no signs of vasculitis or fat necrosis (Fig. 1C, D). A diagnosis of erythema nodosum was made. As valproate was suspected to be the possible etiologic factor of erythema

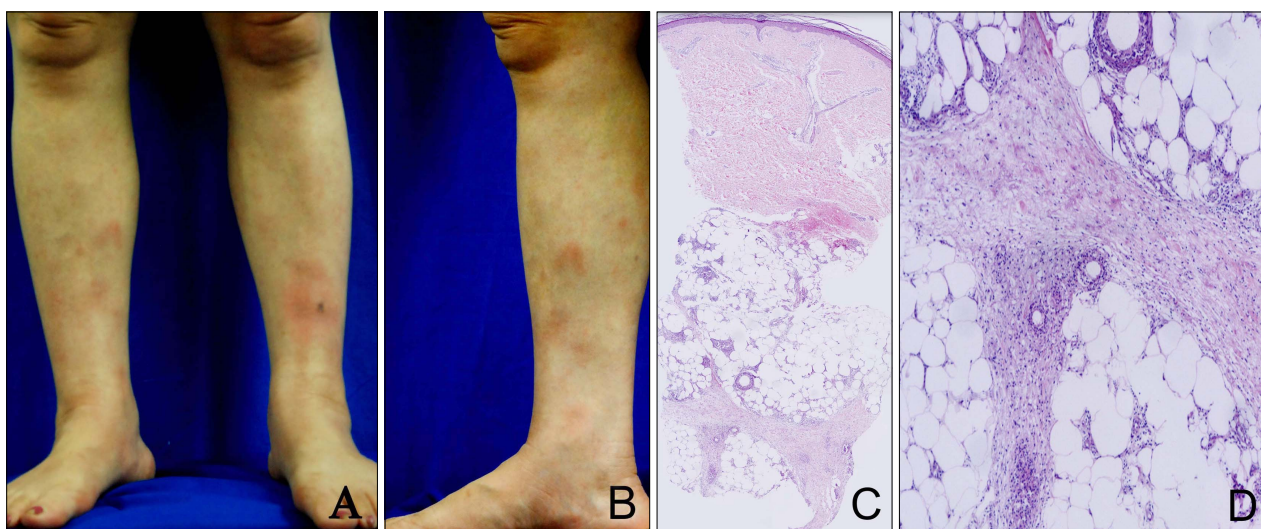
nodosum, this drug was discontinued. Instead, 10 mg/kg levetiracetam (Keppra; UCB SA, Brussels, Belgium) was introduced to the patient. After the discontinuation of valproate, her skin lesions and symptoms started to resolve within 2 days and all of the abnormal laboratory findings returned to the reference ranges within 1 week. She was followed for 3 months without any residual skin lesions and any sign of recurrence.

Valproate is a widely used anticonvulsant approved for the treatment of a variety of disorders such as epilepsy, migraine, trigeminal neuralgia, and bipolar disorder<sup>2</sup>. The well-known adverse effects of valproate are nausea, vomiting, ataxia, tremor, hepatotoxicity, encephalopathy, coagulation disorder, and pancreatitis<sup>3</sup>. The common dermatologic adverse effects of valproate are erythema multiforme, transient alopecia, petechiae, pruritus, and hypersensitivity syndrome<sup>4</sup>. However, there has been no report on valproate-induced erythema nodosum. Although rechallenge with valproate was impossible in this case because the patient rejected the test, given the fact that she had started to take valproate recently and the improvements of her signs and symptoms were observed soon after discontinuing valproate, along with the normalized laboratory parameters, we could assume that valproate was the causative drug of erythema nodosum in this case. Therefore, we herein report the first case of erythema nodosum associated with valproate. Although further studies are needed, we suspect that immune complex-mediated hypersensitivity reaction due to valproate, or, as valproate is known to exert an effect on fatty acid<sup>5</sup>, valproate-induced impaired fatty acid metabolism might consequently lead to local inflammation of subcutaneous fat. The proper recognition of adverse cutaneous reactions to anti-

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**Fig. 1.** (A, B) Tender, bilateral, multiple, erythematous to violaceous subcutaneous indurated nodules and plaques on the anterior aspect of the lower extremities. (C) Inflammatory infiltrate is mainly present in the thickened septa of the subcutaneous layer (H&E,  $\times 40$ ). (D) Higher magnification showed lymphocytes arranged interstitially between thickened septa and extended to the periseptal areas in the subcutaneous layer ( $\times 100$ ).

convulsant medications is important because it may affect the subsequent treatment options, like in this case, and can prevent further fatal reactions<sup>4</sup>. Our observation emphasizes that valproate should be considered as a possible etiologic factor of erythema nodosum.

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