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Valproic acid-induced DRESS syndrome with acute liver failure

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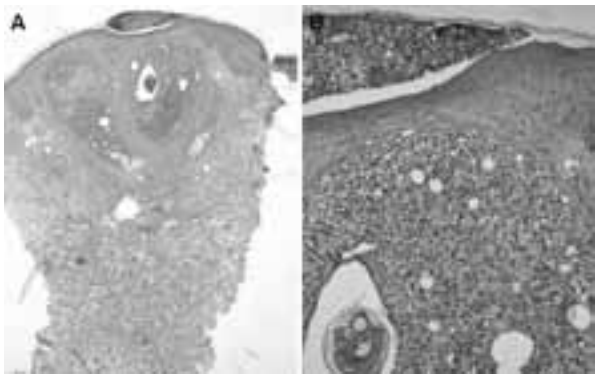
Dear Editor,

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening multisystem adverse drug reaction that must be recognised promptly to withdraw the causative drug. It is most commonly induced by aromatic anticonvulsants and antibiotics. In contrast, non-aromatic anticonvulsants are rare causes of DRESS. Therefore, we wish to add a case of valproic acid as the culprit drug inducing DRESS.

A 26-year-old man presented with acute liver failure with fever, a rash and lymphadenopathy. He had had an intracerebral bleed 5 months and an epileptic insult 1.5 months before presentation after which valproic acid 500 mg twice daily was prescribed. His remaining medication was: baclofen 500 mg three times daily, clemastine 2 mg twice daily and acetaminophen 1 g four times daily. He had not been abroad and had no history of animal/insect bites. As a child he had been vaccinated according to the national vaccination schedule for the Netherlands. He denied alcohol and intravenous drug use and unprotected sexual activities. His skin showed generalised papular-pustular exanthema, partly confluent to plaques on his chest, face and ears. Furthermore, he had facial oedema, yellow sclerae, erosions of his oral mucosa, petechial haemorrhages and lymphadenopathy at multiple sites. An enlarged liver without stigmata of chronic liver disease was observed. Laboratory results were compatible with severe liver dysfunction (prothrombin time 21.6 sec and albumin 27.6 mg/dl; aspartate aminotransferase 1219 IU/l, alanine aminotransferase 2800 IU/l, lactate dehydrogenase 763 IU/l, gamma glutamyl transaminase 216 IU/l, alkaline phosphatase 456 IU/l, and total and conjugated bilirubin 180 and 115 µmol/l). Acetaminophen and valproic acid levels were <2 mg/l (undetectable) and 47 mg/l (sub-therapeutic), respectively. Serological and microbiological assays did not yield an underlying cause for the liver failure. Ultrasonography revealed hepatosplenomegaly with hilar lymphadenopathy. A skin biopsy of a pustule demonstrated extensive superficial and deep infiltrates with eosinophils and lymphocytes and folliculitis (*figure 1A and B*). Valproic acid was replaced by levetiracetam and acetaminophen was stopped. Prednisone was started and within two days the cutaneous symptoms improved substantially and the PT shortened. After six weeks all symptoms had completely resolved, laboratory tests were normal and the prednisone was discontinued after 15 weeks.

This case report describes valproic acid-induced DRESS syndrome with fulminant liver failure. Valproic acid, a non-aromatic anticonvulsant, has not been described before as the culprit drug in DRESS. Furthermore, this report stresses the importance of a complete drug history and the need for clinicians to be aware of the delayed onset and the association between DRESS syndrome and liver failure.

Figure 1. *Histological images of a skin biopsy of a pustule*



Detail of epidermis showing extensive subcorneal en perifollicular infiltration of eosinophils and lymphocytes. Haematoxylin and eosin stain. Original magnification x 2 (A) and x 10 (B).