

## Anticonvulsant Hypersensitivity Syndrome Secondary to Lamotrigine Mimicking a Septic Episode

### Dear Editor,

Anticonvulsant hypersensitivity syndrome consists of the hallmark features of fever, rash, and lymphadenopathy and multiorgan involvement. We report a case of lamotrigine hypersensitivity that was difficult to diagnose because of comorbid systemic lupus erythematosus (SLE), and the presence of clinical features mimicking sepsis due to a zoonosis. The syndrome resolved with the discontinuation of the medication. Timely recognition of this rare but potentially fatal drug reaction is important.

### Case Report

A 49-year-old Australian woman presented with fever of 5 days duration associated with backache, abdominal pain and headache. One week before admission, she visited her family near a cattle farm. She denied any direct exposure to birds, cattle or any animal carcasses. Two days before admission, she also noted rashes around her back, arms, and legs. Two weeks earlier, she had been started on lamotrigine for back pain. She was diagnosed to have SLE in 1998 when she had presented with arthralgia and rashes. She defaulted follow-up after that but was asymptomatic ever since.

On presentation, her temperature was 39°C, blood pressure 80/60 mmHg, respirations 18 breaths per minute, and a pulse of 120 beats per minute. The rash predominated on her extremities and torso and were macular papular. There was no oral mucosal involvement or hepatosplenomegaly. Cardiovascular and lung examination was normal initially.

Initial laboratory findings: Hb: 10 g/dl; white cell count:  $4.8 \times 10^9/L$ , neutrophils:  $4 \times 10^9/L$ , lymphocytes:  $0.3 \times 10^9/L$ , eosinophils:  $0.1 \times 10^9/L$ , platelets:  $156 \times 10^9/L$ , prothrombin time 15 seconds (range, 11 to 15 seconds), activated partial thromboplastin time (APPT) 40 seconds (range, 25 to 35 seconds). Liver function test and renal profile was normal. Blood and urine cultures were negative. Erythrocyte sedimentation rate (ESR) was 24 mm/h and C-reactive protein (CRP) was 88 mg/dl ( $<10$  mg/L). Chest x-ray, computed tomography (CT) brain and lumbar puncture were normal.

Based on the initial findings, a form of zoonoses and a SLE reactivation were entertained. Anticonvulsant hypersensitivity syndrome secondary to lamotrigine was also considered. Lamotrigine was immediately discontinued. Initial treatment included aggressive fluid resuscitation and

antibiotics (ceftriaxone and doxycycline) was started.

However, the patient complained of worsening diffuse abdominal discomfort and headaches. The patient's respiratory status and liver enzymes worsened. She also developed thrombocytopenia on day 2 of hospital admission (platelets:  $91 \times 10^9/L$ ). On day 5 of admission, her hepatitis worsened; [(alanine aminotransferase (ALT): 196, aspartate aminotransferase (AST): 300, gamma glutamyl transferase (GGT): 406 and alkaline phosphatase (ALP): 420 (U/L)]. Antibiotics were discontinued on day 5 due to worsening hepatitis. CT thorax and abdomen done on day 5 of admission revealed bilateral pleural effusions with free fluid in the abdomen and lymph nodes in the axilla, superior mediastinum and retroperitoneum area. Transthoracic echo showed normal systolic function.

Connective tissue results were as follows: C3 and C4 complements normal, antinuclear antibody (ANA) (1:320) speckled, extractable nuclear antigens positive for Sjogren's Syndrome A (SSA), ds-DNA, anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor and beta 2 glycoprotein I antibody were all negative. Serology results were all negative for hepatitis B and C, cytomegalovirus, Epstein-Barr virus, leptospira, rickettsia, brucella, syphilis and HIV.

She was treated symptomatically with pain killers. On day 10 of admission, the abdominal pain, headache and shortness of breath improved. The rashes also disappeared. CRP, chest x-ray, liver function test and thrombocytopenia normalised.

### Discussion

Anticonvulsant hypersensitivity syndrome (AHS) is an unpredictable and potentially severe reaction with an incidence ranging between 1 in 1000 and 1 in 10,000 exposures. It typically presents with fever, rash and lymphadenopathy accompanied by serological alterations including elevated liver enzymes, haematological abnormalities and multiorgan involvement.<sup>1</sup> Diagnosis of AHS is difficult because the syndrome occurs 1 to 12 weeks after exposure and mimics several infectious, vasculitic and neoplastic conditions.<sup>2</sup> Several cases have been reported with lamotrigine, with features comparable to those observed in patients exposed to aromatic anticonvulsants, apart from a somewhat higher incidence of severe skin rashes and a lower

frequency of eosinophilia (46%) and lymphadenopathy.<sup>3</sup> Just like in this case, a lack of eosinophilia does not mean this is not a drug hypersensitivity reaction.

The initial diagnosis was difficult as the suspicion of a zoonotic infection was high on the list in view of the recent visit to the cattle farm. However, all cultures and microbial serologies were negative and she was given antibiotics for only 4 days. Reactivation of SLE was less likely as ESR was only 24 mm/hr, ds-DNA was negative, complements were normal and she improved without corticosteroid treatment.

The overall rate of rashes for patients taking lamotrigine is 13% and of serious rashes, 0.1%. They typically occur between day 5 and week 8 after the start of therapy. Internal organ involvement usually develops between 1 and 2 weeks after the cutaneous eruption.<sup>4</sup>

Although the lymphocyte toxicity assay is a diagnostic tool for AHS, it cannot be performed during the acute phase because the lymphocyte yield is suboptimal due to death of lymphocytes in vivo and this can lead to increased chances of a false-negative result.<sup>5</sup> Also, the test is conducted in few research laboratories which limits its accessibility to physicians. Therefore, the diagnosis is usually made based on time of onset, clinical and laboratory examination and resolution with cessation of the anticonvulsant drug.

## Conclusion

In this case, we have highlighted the difficulty in diagnosing a case of lamotrigine hypersensitivity due to comorbidity of SLE and clinical features mimicking sepsis due to zoonosis.

With proper recognition, the risk of morbidity and mortality of this rare condition can be reduced.

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