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Tzu Chi Medical Journal

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Case Report

Toxic Epidermal Necrolysis Due to Lamotrigine Monotherapy for Bipolar Disorder

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Article info

Article history:
Received: April 11, 2008
Revised: June 2, 2008
Accepted: August 1, 2008

Keywords:
Anticonvulsants
Lamotrigine
Toxic epidermal necrolysis

Abstract

Toxic epidermal necrolysis (TEN) is a life-threatening mucocutaneous reaction to drugs. Lamotrigine is an antiepileptic agent not chemically related to the aromatic anticonvulsants that is also prescribed for mood disorder. Although adverse reaction from lamotrigine have been reported after a low initial dosage, the risk of developing TEN during lamotrigine therapy is rare when recommended guidelines for the dosing schedule are carefully followed. We present a 35-year-old woman with a mood disorder who developed TEN after about 10 days of lamotrigine (50 mg daily) monotherapy. She developed generalized maculopapular eruptions that progressed until more than 90% of her body surface area was involved, with extensive epidermal detachment. The lesions affected her conjunctival, oral, nasopharyngeal, genital, and vaginal mucosa. Lamotrigine was immediately discontinued. After receiving systemic antihistamine and corticosteroid treatment, the patient had a complete recovery. (*Tzu Chi Med J* 2009; 21(2):165–168)

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1. Introduction

Lamotrigine is an antiepileptic agent that has been increasingly prescribed as a mood stabilizer in bipolar disorders. Like other anticonvulsant agents, lamotrigine can cause adverse drug reactions, including life-threatening Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (1–6). This anticonvulsant hypersensitivity syndrome clinically includes severe maculopapular exanthema, fever, and lymphadenopathy. It can also damage internal organs such as the liver, kidneys and lungs, and cause hematologic or pulmonary impairment (4,7). When an adverse drug eruption involves an extensive portion of the body surface area and several mucosal areas, and is then followed by widespread loss of skin, a diagnosis of SJS-TEN should be considered. SJS-TEN syndromes are caused by adverse drug reactions with an overlapping spectrum of severity that can be distinguished by the percentage of body surface area involved and mucosal involvement, rapidly followed by epidermal detachment (8).

We report a 35-year-old woman who developed SJS after taking lamotrigine at a dosage of 50 mg daily for

about 10 days for bipolar disorder. Her initial skin rash progressed to TEN.

2. Case report

A 35-year-old woman came to our dermatology clinic with the chief complaints of acute onset of a generalized skin rash, lip and oral mucosa ulcers, sore throat, and fever over the past 2–3 days. Physical examination showed crusted swollen lips with ulcers, oral ulcers, and cervical lymphadenopathy. Examination of her skin showed a generalized erythematous maculopapular rash with occasional large confluent patches and atypical targetoid lesions on the trunk (Fig. 1) and all four extremities. Her entire face was erythematous (Fig. 2). She was admitted with the diagnosis of toxicoderma from a suspected drug eruption. However, the patient denied taking any medication, herbal medicine, traditional Chinese medicine, or health supplements before the present illness. She also denied any other chemical exposure or recent infections.

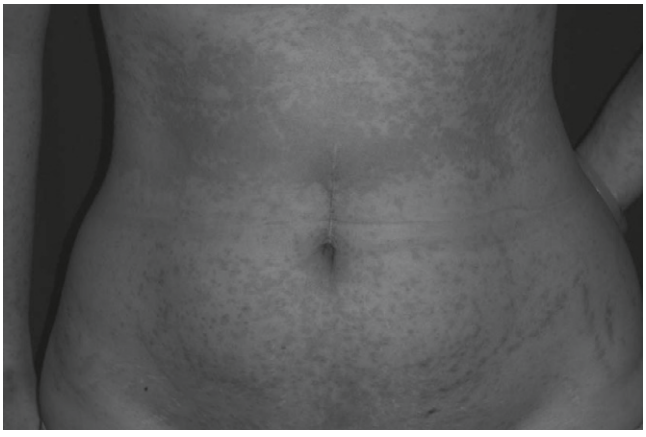

Fig. 1 — Initial stage of generalized erythematous maculopapular eruption on the first day of hospitalization.

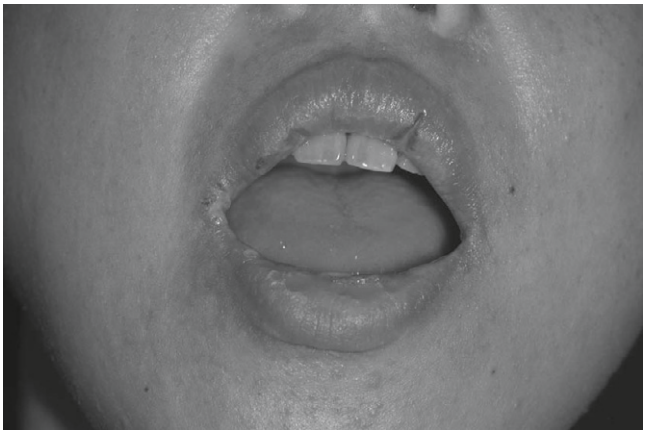

Fig. 2 — Crusted erosions or ulcerations on the lips are almost always present in SJS-TEN, as in this patient.

After she was admitted, we found that she had previously visited our psychiatric clinic, and had taken lamotrigine, 50 mg daily, for bipolar disorder. She had already taken lamotrigine for about 9–10 days before the constitutional symptoms of fever (38.5°C), sore throat, and cervical lymphadenopathy appeared. The skin rash developed on the next day. She kept taking lamotrigine because she did not correlate her symptoms with the drug. We discontinued lamotrigine on the second day of hospitalization.

Her skin eruptions progressed for several days after lamotrigine was stopped, and coalesced quickly. Then, a full-blown skin rash developed and spread to more than 90% of her body surface area. Large, widespread confluent erythematous, dark red or purplish patches, with multiple serous papules, vesicles, or bullae were noted. Her epidermis then turned brownish and became necrotic, and finally detached in sheets. Nikolsky's sign, where the top layers of the skin slip away from the lower layers when rubbed slightly, was positive. She also complained of red eyes with discharge, painful crusts in her nose, oral ulcers, swollen crusted lips, and painful genital and vaginal ulcers with a yellowish discharge.

A diagnosis of lamotrigine-related SJS-TEN was established. She received a systemic antihistamine (diphenhydramine, 30 mg three times daily intravenously) and a corticosteroid (betamethasone, 4 mg twice daily intravenously) after admission. She was also given parenteral hydration and nutrition because of her oral lesions and difficulty in swallowing. We gave her supportive treatment with a topical corticosteroid and emollient to relieve her mucosal symptoms.

Her condition improved slowly. The dosage of the systemic corticosteroid was tapered gradually and finally stopped after 3 weeks. Her skin rash subsided completely and the mucosal lesions healed without scarring.

Laboratory tests included complete blood count with white cell differentiation, erythrocyte sedimentation rate, C-reactive protein, liver studies (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and kidney function test, electrolytes, plasma protein, antinuclear antibody, total IgA, IgG, IgM, IgE, and urine and stool analyses. Serum antibodies against antistreptolysin O and antibodies to *Mycoplasma pneumoniae* were also surveyed and both were negative. The lab results on the first hospital day showed a slight elevation in C-reactive protein of 2.437 mg/dL (normal range, 0–0.5 mg/dL), AST of 79 IU/L (normal range, 10–38 IU/L), and ALT of 59 IU/L (normal range, 3–41 IU/L).

On the fourth hospital day, the following data were noted: AST 46 IU/L and ALT 90 IU/L. The abnormal

urinalysis results (occult blood, 1+; RBC, 8–10; WBC, 2+; epithelial cells, 2–4) could have been related to the genital ulcers. The other tests were all negative or within normal ranges. Eosinophil count and IgE were also within normal limits. Chest film showed no active lung involvement and her heart size was normal. The mild liver function impairment noted could have resulted from lamotrigine hypersensitivity.

A skin biopsy was performed on the fourth hospital day. Histologically, the skin lesions showed multiple vesicles with full-thickness epidermal necrosis and sparse superficial perivascular lymphocytic infiltration (Fig. 3). This was consistent with toxic epidermal necrolysis.

Antibodies against herpes simplex viruses (HSV) were also investigated. The results were available 1 week after the patient was discharged from hospital. The results included HSV type 1: IgG, high positive, IgM, positive; and type 2: IgG, negative, IgM, positive, ratio >200. These results suggest that the patient might have had a concomitant HSV infection leading to delayed healing of her mucosal ulcers and positive antibodies to HSV.

3. Discussion

Lamotrigine, an antiepileptic drug of the phenyltriazine class, is not chemically related to other antiepileptic drugs. It was first released in Ireland in late 1990 and was approved by the U.S. Food and Drug Administration (FDA) in 1998 as adjunctive therapy or monotherapy for adults or children with partial and generalized tonic-clonic seizures [9].

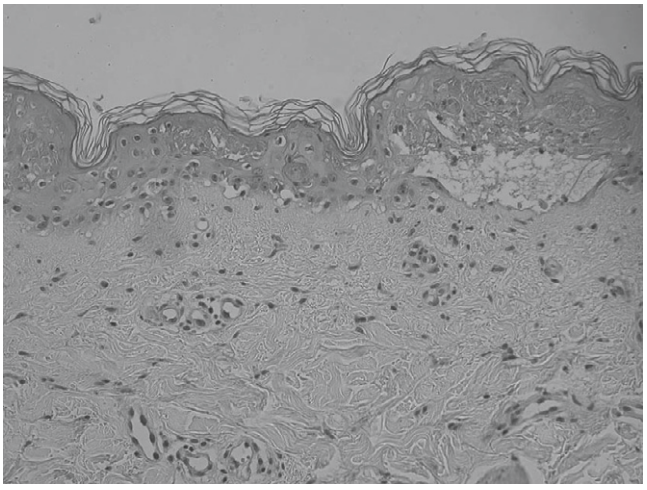

Fig. 3 — Skin biopsy from the trunk shows basal vacuolation, frequent dyskeratosis, and extensive epidermal necrosis with sparse inflammation (hematoxylin & eosin, 100×).

During the development of lamotrigine, the drug was observed to improve mood, alertness, and social interaction in some patients. These early observations in patients with epilepsy stimulated interest in the evaluation of lamotrigine as an antidepressant and mood stabilizer [10]. In 2003, it was approved by the FDA with a new indication: maintenance therapy for bipolar I disorder [9].

Lamotrigine can produce adverse reactions similar to the hypersensitivity syndrome caused by other anticonvulsants. This syndrome consists of a triad of fever, skin rash and multiple internal organ dysfunction that occurs 1–8 weeks after exposure to the causative agent [4–7,11–13]. Aromatic anticonvulsants (phenytoin, phenobarbital and carbamazepine) are the drugs most often involved in this triad. A skin rash appears as localized purpura, angioedema, fixed drug eruption [14], a maculopapular erythematous rash, or a serious life-threatening rash, such as in SJS and TEN. The multiorgan dysfunction can be asymptomatic or symptomatic. The liver is more frequently involved than other organs such as the kidneys, central nervous system, lungs, heart, or thyroid. Disseminated intravascular coagulation has also been reported, but is rare [5,7].

SJS and TEN are both severe, episodic acute mucocutaneous intolerance reactions, characterized by a rapidly expanding erythematous or purplish macular rash, often with atypical (flat, irregular) target lesions on the skin, and prominent involvement of more than one mucosal site. Usually, two or three mucosal sites (oral, conjunctival, and anogenital) are affected. In TEN, the rash usually coalesces to widespread erythema and epidermal necrosis. Constitutional symptoms and severe internal organ involvement frequently occur. Adverse drug reactions are the main causes of TEN and few cases have been reported to be associated with infection, vaccination, graft-versus-host disease, or idiopathic causes [5,8].

In the beginning, most TEN presents as SJS. In fact, TEN is almost identical to SJS and the two syndromes are differentiated by the extent of body surface area involvement. In TEN, more than 30% of the skin area is involved, whereas in SJS, less than 10% of the skin area is affected [8].

The results of serologic studies of HSV in our patient suggested a concomitant acute HSV infection, and erythema multiforme should be considered in the differential diagnosis. The extent of the skin lesions and sparse inflammation in the tissue section favored a diagnosis of SJS-TEN rather than erythema multiforme.

Patients with severe SJS or TEN should be treated in an intensive care unit or burn center. The risk of death is significant and the patient's outcome depends on the severity of the disease and the quality of medical care. A minimum battery of laboratory tests, such as

liver transaminase levels, complete blood count, urinalysis and serum creatinine levels, should be ordered. General supportive treatment should include immediate withdrawal of the offending drug, careful fluid and nutritional support, whole-body skin lesion care with dressings to prevent secondary bacterial infection, and pain control. Systemic corticosteroids should be administered when the patient's adverse reactions are severe. The early use of systemic corticosteroids should be beneficial in treating TEN patients when there is no clinical contraindication to their use [5,8].

Several studies have investigated the risk factors for the development of lamotrigine-associated skin rash, SJS or TEN. The results showed that the incidence of skin rash might be increased in the following conditions: (1) exceeding the recommended initial dosage of lamotrigine, for example, 50 mg daily or above; (2) exceeding and relatively rapid escalation of the recommended dosage for lamotrigine; (3) coadministration of lamotrigine with valproate; (4) use in the pediatric population, age younger than 13 years; (5) a previous history of another anticonvulsant drug-related rash. The last condition could pose the greatest risk [9,13,15–18]. Therefore, the concomitant use of lamotrigine and other drugs for epilepsy or bipolar disorder should be very carefully designed because of the possibility of drug interaction as well as lamotrigine's different dosing schedule [9].

In conclusion, clinicians should be aware that lamotrigine treatment can produce life-threatening adverse reactions, particularly in patients on concurrent dosages of valproate and in pediatric patients.

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