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Lamotrigine-Induced Steven-Johnson Syndrome: A Case Report

SUMMARY

Steven-Johnson syndrome (SJS) or erythema multiforme major is recognized as a severe form of erythema multiforme that predominantly involves the mucous membranes. Drugs are clearly the main causative factor and only few cases appear to be linked to infections or other factors. Prodromal systemic illness such as fever, cough, weakness, malaise, sore throat, arthralgia, myalgias and diarrhea usually precedes the appearance of bullae and erosion on the mucosal membranes.

SJS can be a mild-to-life-threatening process after exposure to many antiepileptic drugs. The increased use of antiepileptic drugs for treatment of bipolar disorder and neurologic disorders has extended the risk of exfoliative disorder to this population of patients, and these patients and their health care providers may not be familiar with the risks involved with these drugs. Lamotrigine (LTG) is a novel antiepileptic drug effective in partial and generalized seizures. Recently, this drug has started being used for mood stabilization in psychiatric patients.

This report presents the diagnosis and management of Lamotrigine-induced severe oral lesions of a 76-years-old woman with bipolar disorder.

Keywords: Lamotrigine; Steven-Johnson Syndrome; Oral Lesions

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Introduction

Steven-Johnson syndrome (SJS) or erythema multiforme major is recognized as severe form of erythema multiforme that predominantly involves the mucous membranes. Drugs are clearly the main causative factor and only few cases appear to be linked to infections or other factors. Prodromal systemic illness such as fever, cough, weakness, malaise, sore throat, arthralgia, myalgia and diarrhea usually precedes the appearance of bullae and erosions on the mucous membranes[1].

The oral mucosa is invariably involved, with extensive formation of the bullae, followed by extremely painful erosions covered by greyish-white or hemorrhagic pseudo-membranes. The lips usually show characteristic bloody crusting. Erosions may extend to pharynx, larynx, oesophagus and respiratory system. The ocular lesions consist of conjunctivitis, but corneal ulceration, anterior uveitis or panophthalmitis are not rare and sometimes may lead to symblepharon, corneal opacity or even blindness. The genital lesions consist of balanitis or vulvovaginitis. The skin lesions are variable in extent. They may be the typical macula-papular eruption of erythema multiforme, but more commonly are bullous or ulcerative[1].

Lamotrigine (LTG) is a new antiepileptic drug, effective in partial and generalized tonic-clonic seizures[2]. In 2003, the Food and Drug Administration (FDA) approved LTG for the maintenance treatment of bipolar I disorder to delay the time to occurence of mood episodes such as depression, mania, hypomania and mixed episodes, in adult patients treated for acute mood episodes with standard therapy[3,4]. Side effects are mostly related to the central nervous system and include headache, nausea, vomiting, dizziness, diplopia and ataxia[5]. Cutaneous side effects are seen in 3% to 10% of patients[5,6]. These

are mostly maculopapular eruptions beginning within 2 weeks of the therapy. In some patients, rash subsequently disappears, despite the continuation of therapy. However, in some patients, these side effects may be very severe, requiring drug discontinuation, or may even end up with the death of the patient[6].

We describe a case of 76-years-old woman with bipolar disorder treated with LTG, after poor responses to other drug regimens. Painful, erythematous, erosive, lesions on buccal and labial mucosa and erosive, bloody crusts on lips and nose had developed, after she had started treatment with LTG. The diagnosis and management of SJS with LTG-induced severe oral adverse reactions were presented.

Case Report

A 76-years-old woman applied to Istanbul University, Faculty of Dentistry, Department of Oral Medicine and Surgery with the complaint of severe oral mucosal reactions. The medical history revealed that she was under regular review in psychiatric clinic for 7 years and treated with Lithium carbonate (Lithuril 300 mg), Ketiapin (Seroquel), Propranolol HCI (Dideral) for 4 years. Because of the poor control of symptoms, Lamotrigine chewing tablets (Lamictal Chewable Dispersible Tablets) was added to the treatment with the dose of 25mg/day. 4 days after the treatment onset, an angioedema developed around the mouth and eyes and after one dose of systemic corticosteroid therapy (40 mg prednisolon IM), complaints regressed. But on the following day, extremely painful erosions covered by greyish-white and hemorrhagic pseudo-membranes on oral mucosa and erosive, bloody crusts on lips and nose were developed. She immediately discontinued the LTG therapy and came to our clinic.

On physical examination, she had a temperature of 39.5^{0}C and a general body weakness. There were no skin eruptions throughout the body except nose, oral and perioral area. Extraoral examination revealed perioral oedema, erythematous, erosive, painful, bloody crusts on the lips and erosive lesions on the nose (Figs. 1 and 2). Intraoral examination revealed bullae, extremely painful erosions covered by greyish-white and hemorrhagic pseudo-membranes, both on buccal and labial oral mucosa. Opening of the mouth was limited and it was very difficult to examine the oral cavity; anyway, a punch biopsy from the labial mucosa of the lower lip was hardly performed under local anaesthesia (Fig. 3).

After the first examinations in our clinic, the patient was referred to dermatology department for consultation. Laboratory examinations, including complete blood count, liver and kidney functional tests, electrolytes, erythrocyte sedimentation rate, urine analysis and chest radiograph were all in normal limits. Urine, throat cultures and indirect immunofluorescence blood analysis were negative. The histopathological examination confirmed the SJS.

After the diagnosis of LTG-induced SJS was established, the patient was hospitalized in dermatology clinic and oral prednisolone 60 mg per day and intravenous fluids were given initially. Topical steroid gel (Triamsinolone asetonate) and viscous lidocaine were applied to patients lips and oral mucosa. On the fourth day of hospitalization prednisolone was started to decrease gradually and a mouthwash consisting of diphenhydramine, viscous lidocaine and sodium bicarbonate was prescribed. The immediate withdrawal of LTG and treatment with steroids was followed of a slowly favourable course with disappearance of symptoms 8 days later (Figs 4 and 5). On the hospital day 10, the patient improved substantially and after psychiatric consultation, the patient was discharged home.

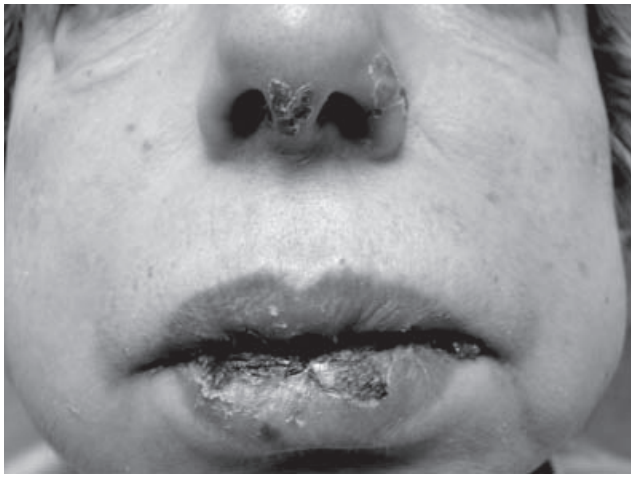

Figure 1. Perioral edema, erythematous, erosive, painful, hemorrhagic crusts on the lips, and erosive lesions on nose

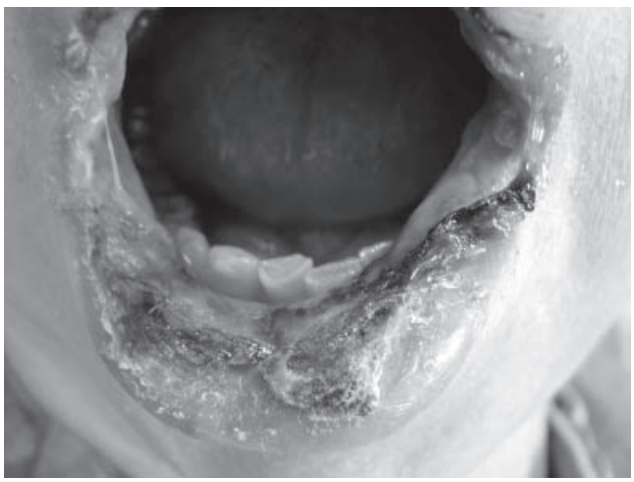

Figure 2. Opening of the mouth was limited and it was very difficult to examine the oral cavity

Figure 3: A punch biopsy from the labial mucosa of the lower lip was hardly performed

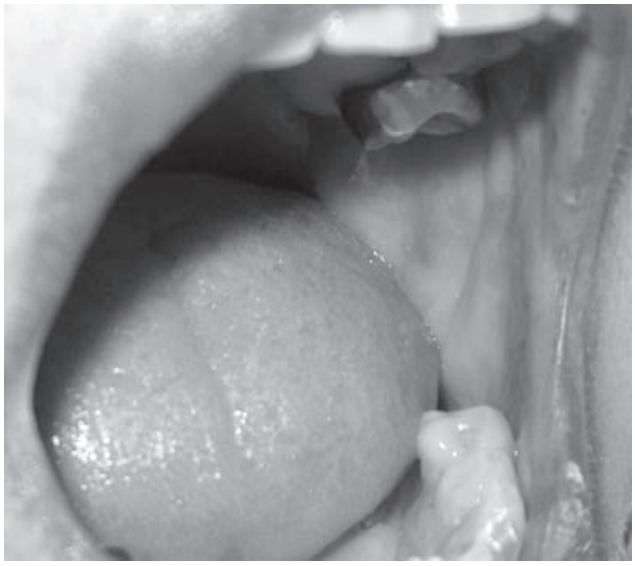

Figure 4. Intraoral view of the left buccal mucosa after corticosteroid treatment

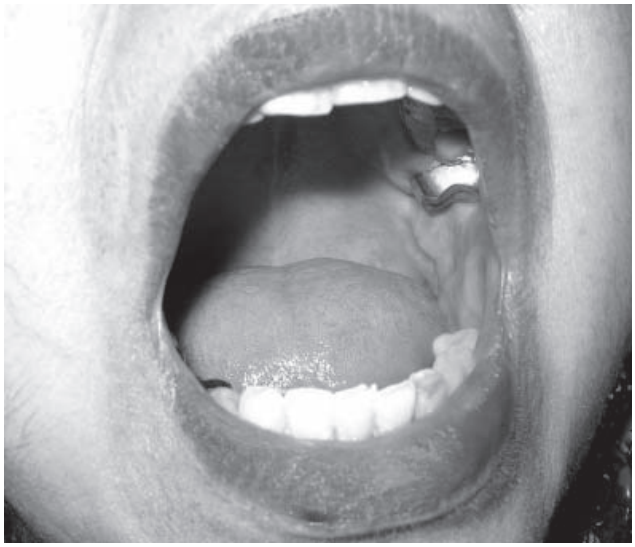

Figure 5. Complete healing of severe lesions

Discussion

SJS is severe, life-threatening reaction that has been associated with more than 100 different medications[7,8]. These reactions are characterized by erythema and tenderness of skin and mucosa, fever, skin blistering or crusting, ulceration of the mucous membranes and subepidermal separation[1,7-9].

LTG, a phenyltriazine, is extensively metabolized, predominantly by *N*-glucuronidation, whereas only minor fractions undergo *N*-oxidation and *N*-methylation[10,11]. It has a wide range of efficacy for partial and generalized seizures and is effective as carbamazepine and phenytoin when used as monotherapy in newly diagnosed epilepsy[12-14]. LTG is being investigated for variety of additional indications, such as bipolar disorders, cocaine abuse, trigeminal neuralgia and postoperative analgesia[15-17].

Most of adverse drug reactions attributed to LTG therapy are related to the central nervous system and include headache, nausea, vomiting, diplopia and ataxia[18,19]. The prescribing information for LTG reports a 1% risk of SJS in paediatric population and 3% in adults[3]. Subsequent to its FDA-approved indication for the treatment of bipolar I disorder, LTG has gained popularity among patients with bipolar and other mood disorders. In clinical trials of LTG effectiveness in the treatment of bipolar and other mood disorders, 0.08% of adults who received LTG as monotherapy developed rash[3]. The rate was 0.13% in patients receiving the drug as adjunctive therapy. The risk of rash increased when valproic acid was co-administered, exceeding the recommended initial dose and the rate of dose adjustments[3,9].

In the series of 57 cases with LTG-induced severe cutaneous adverse reactions (SJS or Toxic Epidermal Necrolysis), Schlienger et al[20] found a significant difference in the age distribution. Patient with SJS were significantly younger and the percentage of patients who were <18 year of age was significantly higher in the SJS group[20]. Our patient was 76 years old and, regarding age, our finding does not correspond with the published data.

The typical interval from beginning of a drug therapy to the onset of reaction in patients with SJS is usually 1-3 weeks[21,22]. In 2 SJS cases from World Health Organization records, the onset was relatively short (2 and 4 days)[20]. In our patient, adverse reaction firstly developed as perioral oedema, but after 1 dose of systemic corticosteroid injection, the symptoms regressed partially; however, severe reactions developed on the fifth day of the LTG treatment. No skin reaction developed on the body in our patient in contrast with other reported cases in the literature; therefore we conclude that application of one dose systemic corticosteroid, after the occurrence of perioral oedema, prevented more severe reactions.

Certain precautions can help to prevent serious rash associated with LTG. Among the most important

preventive measures are appropriate dosage and its adjustment. In adults, the recommended initial dose of LTG alone is peroral 25 mg daily for the first 2 weeks, 50 mg daily during 3 and 4 weeks and then weekly increases of 50-100 mg per day as clinically indicated[3,4,9]. Despite the prescription of recommended initial dose of LTG, severe oral adverse reactions developed in our patient.

In conclusion, severe adverse reactions following LTG treatment can occur even when a low starting dose was given. Therefore, patients who begin the LTG treatment should be observed for the development of both skin and mucosal reactions and if indicated the agent should be withdrawn or replaced, depending on the necessity of the therapy. Serious drug-induced eruptions associated with LTG are rare and although SJS is a potentially life-threatening syndrome, clinicians must weigh the risk benefit of this medication with more common risks associated with untreated bipolar depression. The role of dentists in the diagnosis of the SJS is very important. SJS should be considered in patients having suspicious drug history with intraoral erosions and ulcerations, and also biopsy must be performed for final diagnosis.

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