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CASE REPORT

Oral lichenoid drug reaction by lithium in a patient with bipolar disorder

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Bipolar disorder (BD) is a psychiatric disease characterized by recurrent and alternated episodes of depression and mania. For the treatment of BD, anticonvulsants drugs as lithium, carbamazepine and oxcarbazepine can be used. These drugs can be associated with potential adverse effects: weight gain, tremors, thyroid abnormalities, and cognitive, gastrointestinal, cardiac or dermatological problems. We describe a case of BD with oral lichenoid drug reaction probably because of the mood stabilizers.
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A 51-year-old Caucasian man had complained about diffuse oral burning symptoms associated to a painful buccal mucosa. These symptoms had been accented by irritating foods and had been lasting for 17 months.

The oral examination showed the presence of atrophic-erosive lesions on alveolar mucosa, and vesicular, bullous lesions bilaterally on buccal mucosa (Fig. 1).

Patient reported no tobacco, no alcohol or super alcohol assumption; he was not allergic to any drug or food. He declared to be affected by bipolar disorder (BD), psychiatric disease characterized from rapid cycling, cyclothymia, and affective instability of borderline personality. The patient had assumed in the last 2 years Carbolithium 300 (Lithium Carbonate, twice a day) and Tolep 600 (Oxcarbazepine, twice a day); and he had never noted any oral mucosal lesions before starting treatment for BD.

An incisional biopsy on buccal mucosa was performed. Histological picture showed acanthosis and hyperkeratosis with thickened granular layer. Formation of sub epithelial bullae was associated to degenerative processes of keratinocytes (Fig. 2a). The papillary dermis underneath showed a dense inflammatory band-like infiltrate rich in lymphocytes (Fig. 2b). Immunohistochemical staining performed with MoAb CD3 showed that most of inflammatory cells were T-lymphocytes (Fig. 2c). In contrast, immunostaining performed with CD20 showed very few B-lymphocytes (Fig. 2d). Furthermore, immunohistochemical staining was performed with the following primary antibodies: antinuclear antibodies (ANA), antibodies to extractable nuclear antigens (ENA), anti-smooth muscle antibodies (ASMA), anti-skin antibodies, anti-basal membrane antibodies and anti-intercellular substance antibodies; all of the reactions resulted negative. Histological diagnosis was vescicular-bollous disease compatible with diagnosis of lichenoid drug reaction. Finally, oculist and othorino-laryngological specialist visits were performed but with negative result.

Topical formulation of clobetasol (emulgel 0.025%) applied directly to the oral lesions was not useful; hence, psychiatric-dentistry team decided to use in exacerbation periods systemic corticosteroids (prednisone in a single morning dose from 50 mg/day up to 15 days tapered to 25, 10 and 5 mg/day for 1 week, for each dosage), in association with topical clobetasol (emulgel 0.025%) on the lesions (once a day); periodically, the patient was monitored for the most common side effects of corticosteroid (e.g. oral candidosis, glycaemia, azotemia) as well as BD treatment (e.g. hypocalcaemia by Oxcarbazepine).

As the patient had suffered from bruxism and cheek biting has been described in several BD cases, a resin bite was also carried out to avoid oral mucosal crunching. The patient showed phases of remission unpredictably alternated to phases of disease reactivation. The psychiatric team did not recommend the interruption or substitution of the therapeutic protocol for BD. Our treatment scheme improved oral lesions and cheek biting, and currently prophylactic therapy with topical corticosteroids has been able to limit recurrence of bullous lesions and pain (Fig. 3), although the persistence of white keratotic patches.

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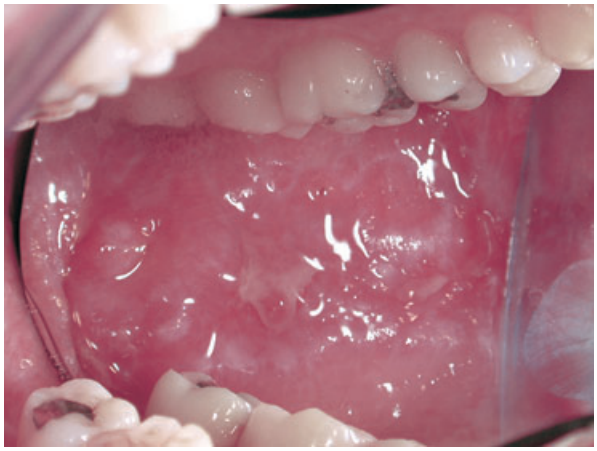

Figure 1 The oral examination showed the presence of vesicular, bullous lesions bilaterally on buccal mucosa.

Comments

Bipolar disorder (including manic-depressive disorder) is a psychiatric illness affecting approximately 1–2% of the general population, with no difference in prevalence among men and women (1).

It is a multiple phases illness characterized by a symptoms picture that varies considerably among patients, with a range of behaviours from extreme elation (mania) to depression. These cycles are often unpredictable and of variable duration. Rapid switching of mood is the central event in BD phenomena, it was reported by 44% of interviews and was associated with early age at onset of BD, with a higher risk of anxiety and substance abuse or dependence co-morbidity, suicide attempts, antidepressant drug use, and a rapid switching of mood. The pathogenesis of BD is still unclear, although studies on families, twins and linkage have been shown implications of genetic factors.

Regards to the therapy, nowadays drugs indicated for BD treatment can be different: lithium, valproate, lamotrigine, carbamazepine and oxcarbazepine (1). Lithium and valproate provide greater benefits for the prevention of manic relapses and the control of manic symptomatology more than for the control of depression. Lamotrigine appears effective in delaying relapse

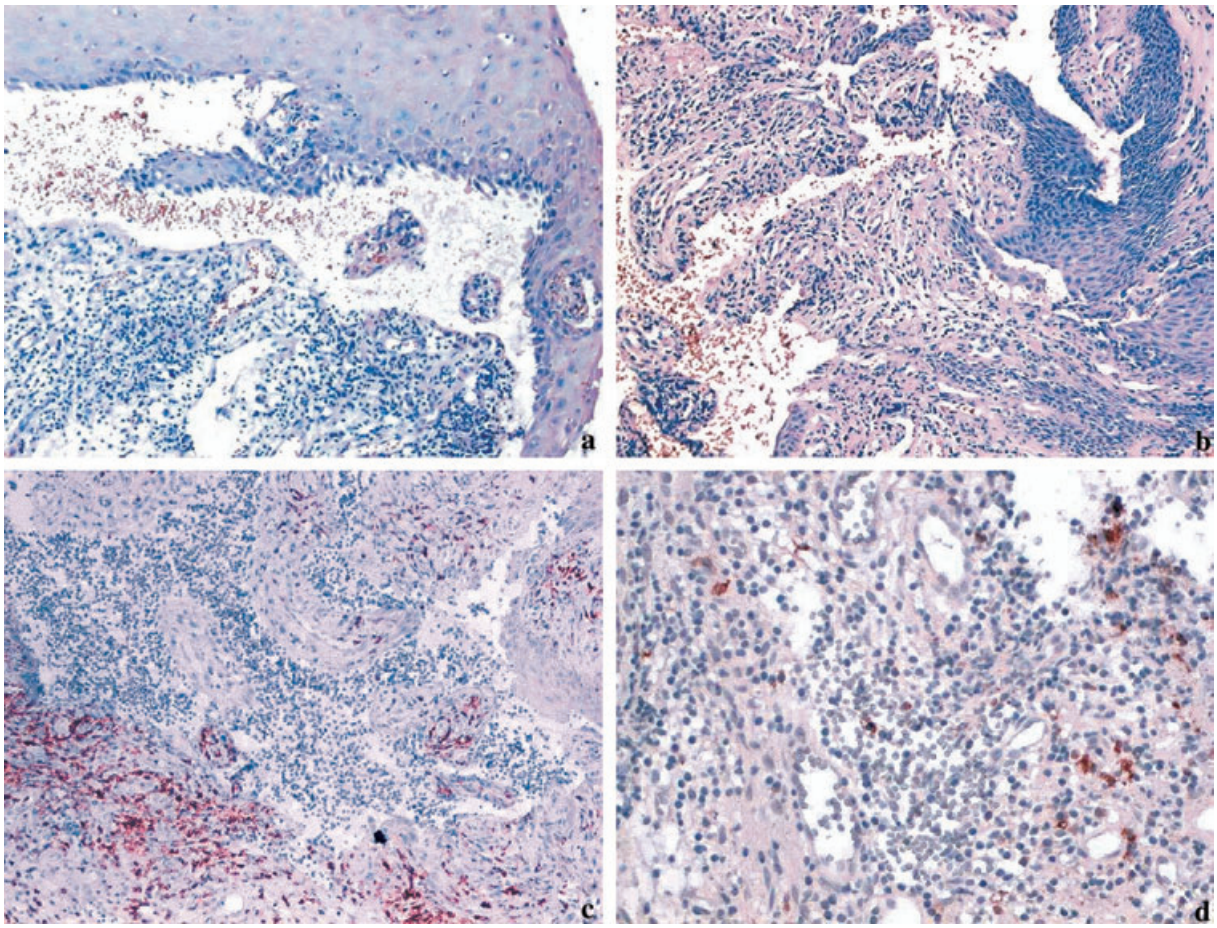

Figure 2 (a) At low magnification, sub-epidermal cleavage with formation of a bulla is visible. The papillary dermis underneath shows a dense inflammatory infiltrate, which is sharply delimitated. Histologically there is lack of atypia and presence of acanthosis (H&E, ×100). (b) A more detailed picture of the infiltrate shows that it is mainly composed of lymphocytes and plasma cells (H&E, ×250). (c) At low magnification, an immunohistochemical staining performed with MoAb CD3, shows that most of inflammatory cells are T-lymphocytes (StreptABC, CD3 ×100). (d) In contrast, the staining for B-lymphocytes, shows very few positive cells (StreptABC, CD20 ×250).

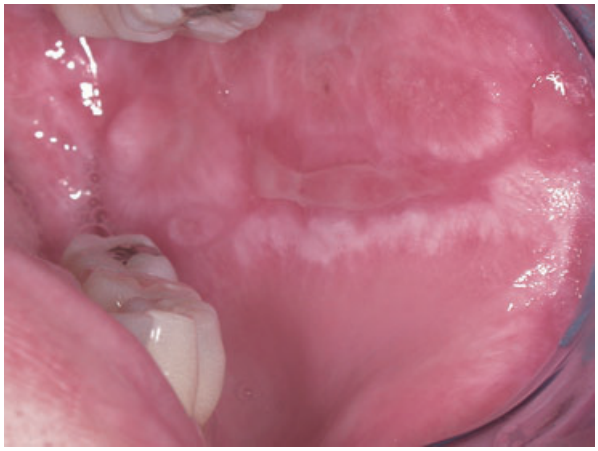

Figure 3 Currently prophylactic therapy with topical corticosteroids is useful to limit recurrence.

into a new episode, with most benefits limited to delaying time to depression.

Nevertheless the molecular basis for mood stabilizer action is still unknown, several studies have suggested that lithium could directly inhibit two evolutionarily conserved signal transduction pathways: the protein kinase glycogen synthase kinase-3 (GSK-3) and inositol signalling.

Recently, a new drug, Oxcarbazepine, a 10-keto analogue of carbamazepine, has been introduced in clinical practice for its anticonvulsant activity (2). Oxcarbazepine therapy is as effective as phenytoin and valproic acid in reducing both generalized tonic-clonic crisis and partial, refractory seizure frequency (2).

At the same time, lithium, valproate, lamotrigine, carbamazepine and oxcarbazepine could be responsible for several adverse reactions, especially on the skin and in oral cavity. Specifically, in lithium carbonate therapy, some patients reported oral lichenoid drug reaction (3–7), some reported non-specific stomatitis (8), others reported a metallic taste sensation (3). Some anticonvulsants may also cause aplastic anaemia and fulminant liver failure, kidney stones, and psychiatric syndromes. Lamotrigine is prone to cause skin rash, and oxcarbazepine may cause symptomatic hyponatraemia. The switching to oxcarbazepine therapy from carbamazepine, could cause allergic or skin reactions (rashes, pruritus, eczema) or a combination of malaise, dizziness and headache (2).

In the present case, burning sensation, painful, atrophic-erosive lesions and vesicular, bullous lesions could represent oral lichenoid drug reactions in a patient treated for BD. Oral lichenoid drug reactions are generally characterized by hyperkeratotic striae, plaques, erosive or ulcerative lesions; milder cases are clinically indistinguishable from oral lichen planus (OLP), while severe reactions include extensive ulceration, especially on the palate or dorsum of the tongue. In this context, we should take into account the controversies between pathologists (intra- and inter-observers) and clinicians on the criteria for the definitive diagnosis of OLP vs. oral lichenoid lesions.

In fact, histological and immunohistochemical procedures from bioptic specimens are the main laboratory investigation required in cases such as these; but, the histological pictures and immunohistochemical reactions could overlap with OLP, and eosinophil infiltration is not always useful to differentiate lichenoid drug reactions from OLP (9). Furthermore, deep perivascular infiltrates and lymphoid follicle formation are more frequent than in OLP. Finally, the finding of oral mucosal lesions as starting subsequently to a drug chronic treatment regimen can help in the definitive diagnosis.

Among the several adverse reactions to lithium carbonate reported in literature, oral lichenoid reactions have been not frequently reported, and they are probably because of a change in immunoregulation determined by the drug (5, 6). Furthermore, in patients affected by BD, it is also possible to observe episodes of cheek biting or oral mucosal abrasion, along with teeth wearing by crunching or vigorous and repetitive teeth brushing, especially during manic phase (3, 10).

In conclusion, taking into account the compulsory and chronic nature of the BD treatment, our protocol (drug therapy and resin bite) for oral lesions in BD disorder could be considered adequate and efficacious for the maintaining of a good oral and dental status in this kind of diseases.

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