J Oral Pathol Med (2005) 34: 56–8

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CASE REPORT

Acquired macroglossia due to lopinavir/ritonavir treatment

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A HIV-positive patient, 3 months after the treatment initiation with lopinavir-/ritonavir (LPV/r) acquired macroglossia. The tongue biopsy revealed mature adipose tissue accumulated into submucosa. The drug was discontinued and the patient showed a significant improvement. This case is the first case in the medical literature of acquired macroglossia because of LPV/r, a drug causing changes in body fat composition.
J Oral Pathol Med (2005) **34**: 56–8

Keywords: acquired immunodeficiency syndrome; human immunodeficiency virus-infection; Kaletra; lopinavir; LPV/r; macroglossia; protease inhibitor; ritonavir; side-effects of LPV/r

A female patient, 65-years-old, with HIV-infection (C2, CDC 1993), diagnosed in 2000, was referred to the Specific Infectious Disease Unit of 'AHEPA' General Hospital of Thessaloniki (Greece) for investigation and management of macroglossia complaining of mild dysphagia and dysarthria. The patient had initially commenced the treatment (for the HIV-infection) with sanquinavir soft gel (1600 mg twice daily), didanosine (400 mg once a day), stavudine (40 mg twice daily) and ritonavir (100 mg twice daily). However, as a consequence of development of intolerance to sanquinavir, this was changed to lopinavir/ritonavir (LPV/r; 400 mg/100 mg twice daily) with lamivudine (150 mg twice daily) and zidovudine (300 mg twice daily) in March 2002. Three months following commencement of this anti-HIV regime, the patient developed macroglossia. Physical oral examination revealed a tongue painless and diffusely enlarged (Fig. 1a,b). Furthermore, the patient suffered from diffuse pseudomembranous candidiasis. Palpation showed no lymph node enlargement. The radiographic study of the maxillofacial area did not show any abnormality. At that time, the patient did not present any other oral or extra-oral manifestation. Also the blood examination showed that CD_4^+ cell count was $210/mm^3$ and the plasma HIV-1-RNA level was 109 copies/ml.

Oral candidiasis was treated with fluconasole (100 mg/day for 15 days) and a biopsy of the dorsum of the tongue was performed. Microscopic examination of the specimen revealed mature adipocytes of different size, accumulated into submucosa (Fig. 2a,b). LPV/r was discontinued as a consequence of the macroglossia, being charged to tenofovir (250 mg once a day). Five months after cessation of LPV/r treatment, significant improvement was observed.

Other causes for acquired macroglossia as acromegaly (HGH, 0.7 ng/ml; cranial radiographic study, normal), amyloidosis (rectal; subcutaneous tissue and tongue biopsy, negative for amyloid deposits with haematoxylin-eosin and Congo red stains) allergy-related oedema, Melkersson–Rosenthal syndrome, tumours and vascular malformations were excluded.

In July 2003, a letter was sent to Abbott Laboratories presenting the case and asking whether a similar case had already been reported. A negative answer was received.

Comments

Lopinavir is a novel protease inhibitor (PI) developed from ritonavir, with a high specificity for HIV-1 protease. The subtherapeutic dose of ritonavir inhibits the metabolism of lopinavir, resulting in higher lopinavir concentrations than when lopinavir is administered alone.

Co-formulated LPV/r (under the brand name Kaletra®, Abbott Laboratories, Chicago, IL, USA) was developed for easy of administration and to ensure that both drugs are taken simultaneously as part of a combination therapy with other antiretroviral agents.

The most common side-effects of LPV/r, are diarrhoea, nausea, asthenia, abdominal pain, vomiting, headache and skin rash. Recently was described inflammatory oedema of the legs as a new side-effect of lopinavir (1).

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Accepted for publication March 10, 2004

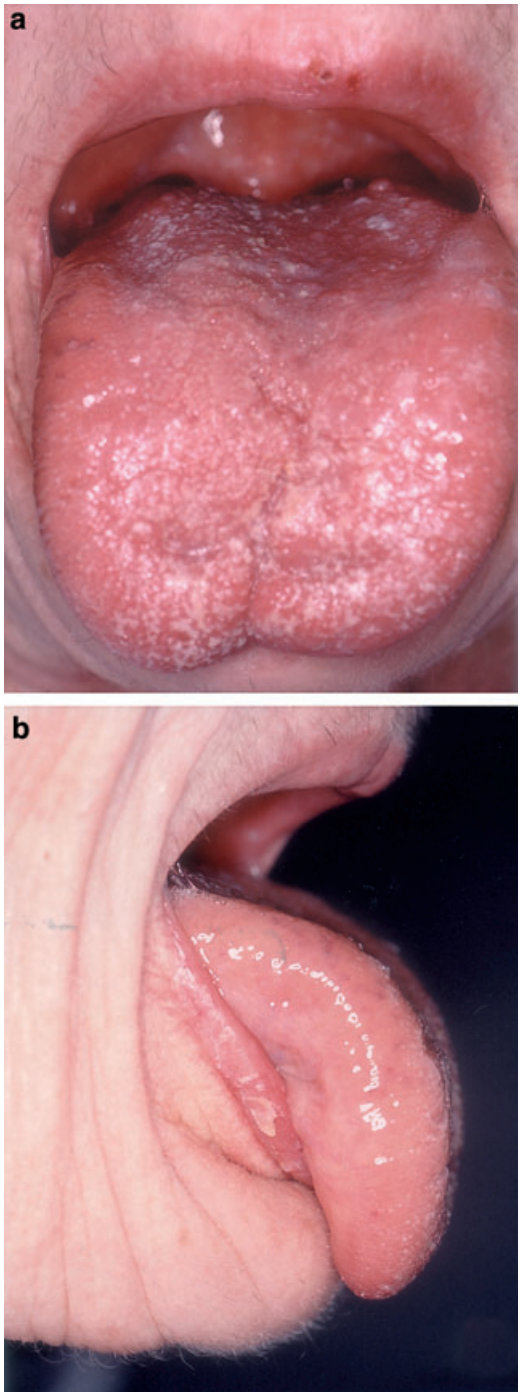

Figure 1 Clinical view of the patient's tongue showed diffuse enlargement.

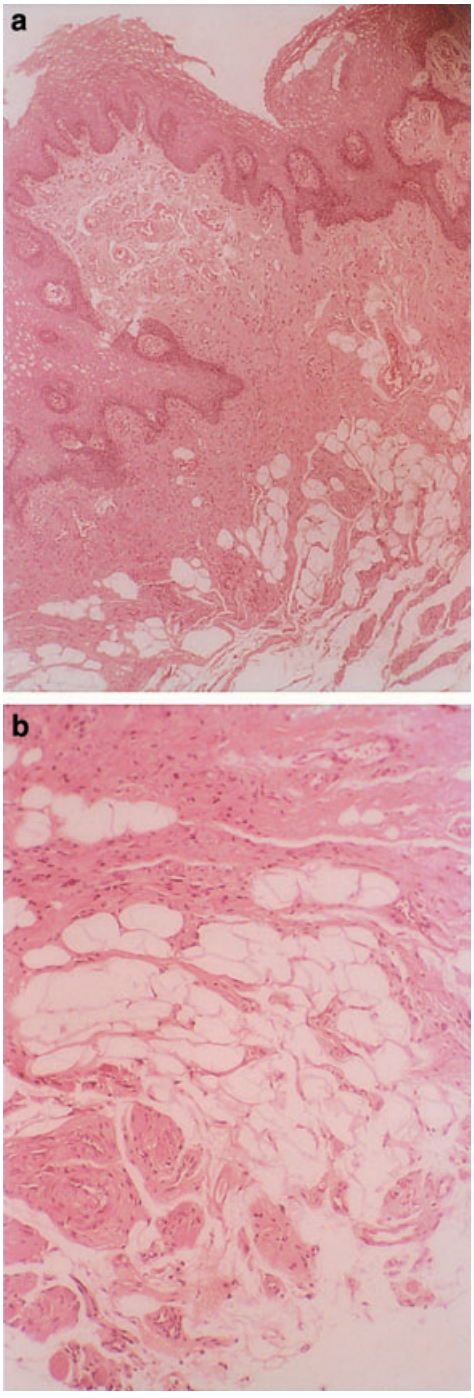

Figure 2 Microscopic examination of the specimen revealed mature adipose tissue accumulated into submucosa [H&E stain, original magnification: (a) ×30, (b) ×120].

Hyperlipidaemia is frequently observed during antiretroviral therapy with PIs (LPV/r included) but clinical adverse events possibly related to the hyperlipidaemia (such as cardiovascular diseases or acute pancreatitis) were not observed during the entire 12 months study period (2). Also, changes in body fat composition occurred in LPV/r-treated patients (3).

International literature lacks objective clinical diagnostic criteria for the indication of macroglossia. The clinical diagnosis of macroglossia is made on the basis of subjective criteria, such as morphology and the protrusion of the tongue, phonation, deglutition, and the respiratory and drooling difficulties (4). The tongue of the patient of the presented case was diffusely enlarged, which was important enough to restrain her from eating and speaking. Also, the tongue biopsy revealed mature adipose tissue accumulated into submucosa.

Macroglossia is a tongue pathology of multiple aetiology, and may be due to idiopathic muscular hypertrophy, to vascular malformations, to endocrine disorders, to allergic reactions, to tumours etc. In extremely rare cases macroglossia originates of drugs (5) or fatty infiltration of the tissues (6). When drugs may cause of macroglossia, the enlargement of the tongue may be due to allergic reactions. In the present case, we excluded the macroglossia originates from allergy-related oedemas. As changes in body fat composition occurred in LPV/r-treated patients (3), as the histopathological examination revealed fat accumulation, and as a significant improvement of macroglossia was observed after cessation of drug, we believe that the cause of macroglossia was the fatty accumulation of the tongue.

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