Extensive and Severe Oropharyngeal Ulcerations under Sublingual Immunotherapy with a Tablet Allergenic Extract of Phleum pratense

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We report a case of extensive and severe oropharyngeal ulcerations under sublingual immunotherapy (SLIT) with Grazax® (ALK-Abelló France). Grazax® was recently approved in Europe as sublingual self-administered grass pollen immunotherapy: standardized allergen of Phleum pratense, fish gelatine, mannitol and hydroxyde of sodium [1–3].

A SLIT for hay fever (positive prick tests and specific IgE to Phleum >100 Ku/l Immunocap Phadia) with Staloral® 5 grass pollen 8 puffs 300 IR/ml per day (Stallergenes France) was discontinued after 2 months (19/12/07) in a 23-year-old nonsmoking patient. SLIT was continued (23/12/07) in a phase IV clinical trial with Grazax. After the 18th tablet of Grazax the treatment was discontinued for ‘local intolerance’ appearing acutely (09/01/08). On examination, he had a painful ‘superficial ulceration’ of 2 cm in diameter of the floor of the buccal cavity. Immunotherapy was stopped and local corticosteroid therapy was prescribed. Two days later the patient visited an emergency clinic with fever of 39°C, asthenia, dysphagia and very painful buccal ulceration with some tender cervical lymphadenopathies. The peripheral blood count was normal and there was no inflammatory syndrome. The treatment included spiramycin – metronidazole and paracetamol – tramadol.

An aggravation of the symptomatology and of the oral lesions led to an ENT evaluation (14/01/08):

− distressed and pale patient in poor condition with fever, weight loss, complete and painful aphagia, headache;
− large and very painful ulceration surrounded by an erythematous halo and coated with adhesive white patches like a giant aphtous lesion involving the whole floor of the buccal cavity from tooth 36 to tooth 46 and the ventral surface of the mobile tongue extending to the lateral borders of the tongue and several less extensive ulcerations of the anterior tonsil pillars (4–6 mm in diameter);
− massive edema of the uvula sparing the soft palate;
− no other ulcers of the pharyngolaryngeal mucosa, the lips or cheeks and no associated cutaneous, genital or anal lesions and no other detectable health problems.

Later the results of the investigations were:

− chest X ray normal;
− investigations for infectious mononucleosis, HIV, Mycoplasma pneumoniae and Chlamydia infection negative;
− buccal smear culture (11/01/08): Staphylococcus aureus, Streptococcus sp., Neisseria sp.;
− no significant hyperneutrophilia, ESR = 32 mm, CRP 18.4 = mg/l, no other biological abnormalities and no immune deficiency evidenced.

The patient refused any form of hospitalization and was thus treated with prednisolone (60 mg per day) and amoxicillin-acid clavulanic per os and iodized povidone locally. He recovered progressively with disappearance of fever and dysphagia within 3 days and with progressive and complete healing of the oropharyngeal ulcerations within 3 weeks (fig. 1). The patient remained well 15 months later without recurrence of the oropharyngeal ulcerations and without symptoms of any other illness.

SLIT with Grazax® is in general well tolerated despite small buccal ulcers in some cases [2, 3 and SmPC: Summary of Product Characteristics of Grazax®]. For Dahl et al. [2] ‘the majority of the most frequently reported adverse events were application site related, indicating drug relationship’.

For the differential diagnosis we have eliminated the other etiologies and potential cofactors of oral aphthos. The pathophysiological mechanisms involved in these oropharyngeal ulcerations are still unknown, but the clinical aspect and the evolution were highly suggestive of direct mucosal causticity [4–7].

According to the severity of the initial clinical presentation and the patient’s refusal, we have not performed other investigations like biopsies needing general anesthetic or oral provocation test with Grazax®. As for other buccal ulcers [4], biopsies of oral reactions (not erosive or ulcerative lesions) to SLIT [8] gave no evidence for immunological mechanisms or for other well-delineated pathophysiological mechanisms.

Despite the absence of other respiratory, food (including fish) or drug allergies and of other etiological factors of aphthosis, the chronology of the different events, the topography of the ulcerations of the mucosa in contact with the tablets of Grazax and the lack of other associated and distant lesions, the high prevalence (43–67%) of mild or moderate application-site-related adverse reactions (not erosive or ulcerative lesions) to SLIT indicated drug relationship’.

events with SLIT [1–3, 8], the progressive and complete healing after discontinuing SLIT and treatment with corticosteroids and antibiotics and the absence of previous oral aphthosis and of recurrence within 15 months suggest that these oropharyngeal ulcerations were linked to SLIT with Grazax®. They appear as an unreported but very impressive and painful adverse event of clinical relevance. The interest of this case, which is very probably an irritative contact lesion, lies in the wide extension of the lesion and the nature of the irritative agent. This event remains exceedingly rare among 17,000 treatment years of exposure without any severe adverse event in the wait for further surveys of Grazax® clinical trials.

References

Fig. 1. Progressive healing of the mucosal ulceration (D Twelve).