Non-healing tongue ulcer in a rheumatoid arthritis patient medicated with leflunomide. An adverse drug event?

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Abstract
Leflunomide is a member of the disease modifying anti-rheumatic drugs group used as a treatment modality in active rheumatoid and psoriatic arthritis. “Oral ulcers” are reported in 3-5% of leflunomide medicated rheumatoid arthritis patients with adverse events, but they are not described in detail in the literature. We present a case of an ulcer in the tongue of a rheumatoid arthritis patient managed with leflunomide and contemplate on its pathogenesis.

Key words: Leflunomide, oral ulcer, DHODH.
of the skin to trauma due to alterations caused by prolonged systemic steroid treatment, and adverse effects of DMARDs and non-steroidal anti-inflammatory drugs (1-5). Leflunomide-associated cutaneous ulcers are considered rare, not preceded by trauma and show non-specific inflammation on microscopic examination (5,6). Adverse reactions of leflunomide in the oral cavity include oral candidiasis, herpetic infection (7) and “oral ulcers” (http://products.sanofi.us/arava/arava.html, revised February 2016), although the latter are not described in rheumatoid arthritis patients (8).

We present a case of an ulcer in the tongue of a rheumatoid arthritis patient medicated with leflunomide that microscopically showed severe epithelial dysplasia, and contemplate on its pathogenesis.

**Case Report**

A 59-year-old woman was referred by her dentist for diagnosis and management of an ulcerated lesion on the tongue. According to the patient, the lesion was first noticed approximately 6 months before presentation and showed periods of “exacerbation”, lasting for less than 15 days, and “remission”. She considered it as a “common aphthous ulcer” and tried to manage it with local application of baking soda. Her medical history included rheumatoid arthritis with inflammatory polyarthritis diagnosed approximately 12 years ago and medicated with orally administered prednisolone 7.5 mg/day plus leflunomide (Arava®, Aventis Pharmaceuticals, Bridgewater, NJ) 20mg every day, for the last 6 years. She was also, receiving olmesartan for hypertension and atorvastatin for hypecholisteraimia. She did not smoke or drink alcohol.

Clinical examination revealed an irregularly shaped ulcer covered by fibrinopurulent membrane and partly surrounded by a firmly attached white plaque on the ventral surface of the right side of the tongue (Fig. 1). The ulcer measured approximately 1x0.5cm and was soft and slightly painful on palpation. Small, white epithelial tugs around the lesion were easily removed with gauze, while the rest of the oral mucosa was within normal limits. The lesion was in contact with broken amalgam fillings and decayed teeth’s roots. A provisional diagnosis of traumatic ulcer and/or lichenoid reaction was rendered and complete dental restoration was asked. In addition, oral rinses with a dexamethasone oral drops solution 2mg/ml x10ml and local applications of a chlorhexidine gel were prescribed for 2 weeks.

The patient presented for re-examination six weeks later. The amalgam fillings were replaced by composite resin fillings and the roots were extracted approximately 2 weeks ago, while she was still rinsing her mouth with the dexamethasone solution, but the lesions persisted. A partial biopsy was requested to establish a diagnosis, but she refused to proceed. At that time, on her rheumatologist’s advice he discontinued leflunomide and on re-examination a month later, a <50% healing of the ulcer was evident. Another month later, the ulcer had not fully healed and as reinstitution of leflunomide at a reduced dosing schedule (10mg/day) was necessary due to relapse of rheumatoid arthritis, she consented to the biopsy.

Microscopic examination of formalin-fixed and paraffin-embedded tissue sections showed an ulceration covered by a fibrinopurulent membrane and based by granulation tissue (Fig. 2). It was surrounded by hyperparakeratotic and acanthotic stratified squamous epithelium, showing drop-shaped rete ridges, irregular stratification, loss of polarity of basal cells, increased nuclear to cytoplasmic

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**Fig. 1.** Irregularly shaped ulcer covered by fibrinopurulent membrane and partly surrounded by a firmly attached white plaque on the ventral surface of the right side of the tongue. Notice small, white epithelial shreds around the lesion.

**Fig. 2.** Ulceration covered by a fibrinopurulent membrane is surrounded by hyperparakeratotic and acanthotic stratified squamous epithelium [hematoxylin and eosin stain, original magnification x200].
ratio, cellular pleomorphism, increased nuclear size, increased number and size of nucleoli, dyskeratosis, as well as increased number of mitotic figures (Fig. 3). Those features occupied the full extent and thickness of the epithelium. The underlying connective tissue showed dense inflammatory infiltrates of lymphocytes, plasma cells and polymorphonuclears, mostly in a band-like subepithelial distribution. Atypical cell were not found in the connective tissue. A periodic acid-Schiff (PAS) stain did not reveal candidal hyphae. A histopathologic diagnosis of severe epithelial dysplasia was rendered. Therefore, excision of the residual white lesions on clinically healthy margins was performed, confirming the initial diagnosis. The healing process was uneventful, and six months later the patient is on 20mg/day of leflunomide, while no recurrence or new lesions have developed. The patient gave her informed consent for the use of her data for study.

Discussion
“Oral ulcers” are described in 3-5% of leflunomide-mediated rheumatoid arthritis patients reporting adverse events (http://products.sanofi.us/arava/arava.html, revised February 2016), but this may be a sign of various oral diseases, including oral candidiasis and herpetic infection that may be seen in those patients (7).
of “oral ulcers” in those patients is necessary for documenting that oral ulceration is an adverse event associated with immunomodulatory doses of leflunomide.

References

Conflict of Interest
None declared.