


Eruptive Keratoacanthomas Associated With Leflunomide

The keratoacanthoma (KA) is a rapidly growing, well-differentiated epidermal neoplasm that may be locally invasive or may spontaneously resolve. Most often, KA presents as a solitary lesion; however, multiple KAs can be seen in various syndromes, including Muir-Torre syndrome, the autosomal dominant Ferguson-Smith syndrome, and Grzybowski-type eruptive KAs.1

Several medications have been temporally associated with eruptive KAs. Recently in the literature there has been a report of eruptive KAs following treatment with leflunomide.2 The KAs resolved after stopping treatment with the medication. Herein, we report another case of multiple KAs in a patient under treatment with leflunomide.

Report of Case | A woman in her 50s presented for evaluation of skin lesions located on the arms, trunk, and legs. She had similar lesions for the past 2 years, but they had recently increased in number.

Her medical history included the following diagnoses: systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis. She had undergone recent abdominal surgery to remove a carcinoid tumor. Her medications at the time of presentation included intermittent infusions of rituximab, oral leflunomide, insulin, benazepril hydrochloride, cyclobenzaprine hydrochloride, hydromorphone hydrochloride, morphine sulfate, esomeprazole magnesium, potassium chloride, rosuvastatin calcium, and duloxetine hydrochloride.

The patient reported developing keratotic papules a few months after initiation of leflunomide therapy, approximately 2 years prior to her presentation. Several other dermatologists treated the patient with clobetasol propionate ointment and hydroxyzine hydrochloride for a presumed diagnosis of prurigo nodularis. She was sent to general surgery for removal of several larger lesions on her legs, which were interpreted as multiple, well-differentiated proliferative squamous lesions with hyperkeratosis and underlying mixed inflammation.

Physical examination at presentation revealed numerous 2- to 4-mm keratotic papules on her arms and legs (Figure 1A) in addition to multiple ulcerations on the legs secondary to prior excisions. Two biopsies performed on arm papules found verrucous and crateriform squamoproliferative lesions associated with squamous epithelial protrusions containing keratotic material, inflammatory debris, and elastic fibers associated with focal pustule formation (Figure 2). A diagnosis of eruptive keratoacanthomas was made.

The patient was started on a regimen of oral isotretinoin, 40 mg/d, and her leflunomide treatment was discontinued.

Figure 1. Leflunomide-Associated Eruptive Keratoacanthomas

A, Multiple keratotic papules consistent with eruptive keratoacanthomas seen at presentation. B, Resolving eruptive keratoacanthomas 2 months after beginning oral isotretinoin treatment and stopping leflunomide treatment.

Figure 2. Punch Biopsy Specimen From Eruptive Keratoacanthoma Papule on the Arm

An endophytic cystic squamoproliferative lesion shows accumulation of keratin and basophilic inflammatory debris within the cyst cavities, consistent with keratoacanthoma (hematoxylin-eosin, original magnification ×40).
At 1-month follow-up, the skin lesions had partially resolved, and resolution was greater by 2 months (Figure 1B). Initiation of isotretinoin therapy and discontinuation of leflunomide treatment resulted in complete lesional resolution by 3-month follow-up. The leg ulcers healed with continued conservative wound management. At 3 months, her isotretinoin dose was decreased to 20 mg/d without recurrence of additional lesions.

Discussion | Leflunomide is an immunosuppressant drug that inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, thus preventing the synthesis of pyridines. It is used in the treatment of rheumatoid arthritis.

We have noted 1 other report of eruptive KAs following treatment with leflunomide in the literature. Several drugs have been associated with eruptive KAs, including sorafenib, imiquimod, cycloporsine, and vemurafenib.

Treatment for eruptive KAs is challenging. Oral retinoids have become the preferred treatment option for eruptive KAs. Systemic methotrexate and cyclophosphamide have also been reported as effective treatments.

The link between immunosuppression and squamous cell carcinoma has been well established. There is a much less reported link between KAs and various medications in the literature. Keratoacanthomas are thought to arise secondary to long-standing solar damage, chemical carcinogens, viruses, and genetic predispositions. The more darkly pigmented skin type of the present patient makes it less likely that solar damage highly contributed to the pathogenesis of her KAs.

This report adds another entity to the growing list of medications that have been associated with the development of eruptive KAs. This case also highlights the possible effectiveness of isotretinoin in treating patients with multiple KAs.

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