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-Torres 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 undergoing 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, cyclosporine, 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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**Published Online:** September 9, 2015. doi:10.1001/jamadermatol.2015.2506.

**Conflict of Interest Disclosures:** None reported.

**Disclaimer:** Dr Callen is associate editor of the *JAMA Dermatology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

**Additional Contributions:** We are indebted to Taylor Mulkey, MD, for consultation and help in the care of this patient. She received no compensation for her contributions.


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**A Case Report of Unresectable Cutaneous Squamous Cell Carcinoma Responsive to Pembrolizumab, a Programmed Cell Death Protein 1 Inhibitor**

Unresectable cutaneous squamous cell carcinomas (SCCs) can be difficult to treat: only about 30% of patients respond to any type of current treatment. Substantial progress has recently been made in the development of immunotherapy for the treatment of cancer. In particular, checkpoint blockade using antibodies that impede immune inhibitory pathways, such as programmed cell death protein 1 (PD-1)/PD-1 ligand 1 (PD-L1), represents a novel strategy.

We report herein a case of dramatic response of a biopsy-proven cutaneous SCC to an immunotherapeutic agent, pembrolizumab, a PD-1 inhibitor. Pembrolizumab is a first-in-class drug recently approved by the US Food and Drug Administration (FDA) for unresectable melanoma. Squamous cell carcinomas may be particularly amenable to immunotherapy because they are enriched in patients with immunosuppression. Preclinical studies have shown that transgenic mice overexpressing PD-L1 in keratinocytes show accelerated SCC formation. Hence, blockade of the PD-1/PD-L1 pathway may control SCCs.

**Report of a Case** | A man in his 70s presented with 4-month history of a growing mass on the right temple accompanied by right temporal fossa pain and right ear discomfort. Biopsy of the lesion revealed a moderately to poorly differentiated epithelial proliferation with focal keratinization consistent with cutaneous SCC. Immunohistochemical stains confirmed the diagnosis, showing positive expression of CK5/6 and p63. A computed tomographic scan of the facial bones showed a 1.6 × 1.6-cm mass in the right temporal fossa.

The patient underwent a wide local resection and total parotidectomy with facial nerve sacrifice and right modified radical neck dissection. There was tumor involvement of the main trunk of facial nerve on pathologic analysis, but the surgical margins were negative. None of the 28 lymph nodes were positive for tumor. Due to the high-risk features of his cutaneous SCC, he received 6 months of treatment with cetuximab (250 mg/m²) and concurrent irradiation (60 Gy total). He experienced extensive cutaneous adverse effects during cetuximab treatment but remained without disease for 1 year.

At 1 year, magnetic resonance imaging (MRI) showed a new enhancing mass on the right supraorbital and infraorbital regions consistent with recurrence, which was thought to be either spread of disease along cranial nerve V1 or hematologic metastasis. He underwent right orbital exenteration, and pathological analysis confirmed recurrence of the cutaneous SCC. During the surgery, the tumor appeared to extend up the postsyloid area into the skull base, very close to basilar vascular structures, and was therefore deemed unresectable.

The patient was monitored with interval scans without evidence of disease progression until approximately 14 months after his prior surgery when an MRI showed extensive tumor involvement of the soft tissue to the right of the Meckel cave, cisternal segment of cranial nerve V1, and dura of the right middle fossa (Figure 1). Immunohistochemical staining of a...