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.2 Several drugs have been associated with eruptive KAs, including sorafenib, imiquimod, cyclosporine, and vemurafenib.2

Treatment for eruptive KAs is challenging. Oral retinoids have become the preferred treatment option for eruptive KAs. Systemic methotrexate3 and cyclophosphamide4 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.

W. James Tidwell, MD
Janine Malone, MD
Jeffrey P. Callen, MD

Author Affiliations: Division of Dermatology, Department of Medicine, University of Louisville School of Medicine, Louisville, Kentucky.

Corresponding Author: W. James Tidwell, MD, Division of Dermatology, Department of Medicine, University of Louisville School of Medicine, 3810 Springhurst Blvd, Louisville, KY 40241 (wjamestidwell@gmail.com).


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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.1 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.2 Squamous cell carcinomas may be particularly amenable to immunotherapy because they are enriched in patients with immunosuppression.3 Preclinical studies have shown that transgenic mice overexpressing PD-L1 in keratinocytes show accelerated SCC formation.4 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 poststyloid 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 V, and dura of the right middle fossa (Figure 1). Immunohistochemical staining of a
Figure 1. Magnetic Resonance Imaging (MRI) of Unresectable Cutaneous Squamous Cell Carcinoma

A. Coronal MRI with contrast shows an abnormal enhancing soft tissue mass to the right of the Meckel cave measuring 1.4 × 1.8 cm (arrowhead).
B. Axial MRI with contrast shows the same mass (arrowhead). There was enhancement within the cisternal segment of cranial nerve V, Meckel cave, and right middle fossa dura consistent with tumor involvement.
C and D. After treatment with 3 cycles of a programmed cell death protein 1 (PD-1) inhibitor, the coronal (C) and axial (D) MRIs with contrast show reduction of soft tissue bulk consistent with treatment response (arrowheads). In addition, there was reduced enhancement within the right facial nerve at the genu and descending segment consistent with response to treatment. There was also reduced enhancement within the cisternal segment of cranial nerve V, Meckel cave, and right middle fossa dural-based thickening, which indicates markedly regressed tumor involvement.

Figure 2. Unresectable Cutaneous Squamous Cell Carcinoma Specimens With Strong Immunostaining of Programmed Cell Death Protein 1 Ligand 1 (PD-L1)

A. Biopsy specimen of the patient’s unresectable cutaneous squamous cell carcinoma (SCC) prior to treatment with pembrolizumab.
B. Immunostaining of another SCC biopsy specimen shows a strong signal on the tumor cells (original magnification ×200 for both images).
specimen from the patient’s cutaneous SCC lesions was strongly positive for PD-L1 (Figure 2), suggesting that blockade of the PD-1/PD-L1 pathway might be a therapeutic option.

After considering several factors—adaptive immunotherapy in the form of PD-1 inhibitors had recently been approved by the FDA for metastatic melanoma and was now commercially available; early data in head and neck squamous cells showed potential efficacy; and no good treatment options were available that would preserve quality of life—the patient decided to pursue an off-label trial of pembrolizumab (intravenous infusions, 2 mg/kg every 3 weeks). He tolerated the treatment with adverse effects of mild fatigue, chills, malaise, arthralgias, and weight loss. After 2 cycles, dramatic tumor response was observed (Figure 2). After 6 cycles, the patient was still progression free.

Discussion | A recent retrospective study of patients with unresectable cutaneous SCC showed that only 30% responded to therapy of any kind, and overall survival of such patients was only 10.9 months. Hence, unresectable cutaneous SCCs represent an unmet medical need. This case highlights the potential for immunotherapy in the form of PD-1/PD-L1 inhibition to address this need, a finding that requires further investigation through clinical trials.

Anne Lynn S. Chang, MD
Jinah Kim, MD, PhD
Richard Luciano, NP
Loretta Sullivan-Chang, MD
Alexander D. Colevas, MD

Author Affiliations: Department of Dermatology, Stanford University School of Medicine, Redwood City, California (Chang, Kim); Department of Pathology, Stanford University School of Medicine, Palo Alto, California (Kim); Department of Medicine-Head and Neck Oncology, Stanford University School of Medicine, Stanford, California (Luciano, Sullivan-Chang, Colevas).

Corresponding Author: Anne Lynn S. Chang, MD, Department of Dermatology, Stanford University School of Medicine, 450 Broadway St, Pavilion C, Second Floor, MC 5334, Redwood City, CA 94063 (alschang@stanford.edu).


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Facial Papules in a Patient With Long-Term Cystinosis
Cystinosis is a rare autosomal recessive inherited metabolic disorder. It is caused by an excessive intracellular accumulation of the amino acid cystine owing to a defect in the transport of cystine across the lysosomal membrane.1

Report of a Case | To our knowledge, this is the first published photographic evidence of cutaneous cystinosis and only the fourth case report in the literature of cutaneous accumulation of cystine crystals in a patient with cystinosis.2-4 A 28-year-old white man was referred for further investigation of skin-colored, dome-shaped firm papules over the chin, nose, and perinasal region (Figure 1). The facial papules had increased in size and number since he first noticed them at about age 18 years. The referring physician had questioned a diagnosis of multiple angiofibromas in the context of tuberous sclerosis. Multiple trichoepitheliomas could have also been considered. The patient had a medical history of cystinosis requiring a right renal transplant at age 14 years.

The physical examination findings were significant for dozens of skin-colored dome-shaped papules over the chin, nasal, and perinasal regions of the face. Aside from the firm facial papules, there were no other features suggestive of tuberous sclerosis, such as hypopigmented macules, perungual fibromas, or Shagreen plaques. Dental examination was remarkable for several teeth with a conical shape.

Histologic analysis of a biopsy specimen from a facial papule showed a dome-shaped lesion with several plump fibroblasts and increased blood vessels, compatible with an angiofibroma. No crystals were observed, even after examination with polarized light microscopy by an experienced dermatopathologist.

A second biopsy specimen was sent for electron microscopy, required to make the diagnosis of cutaneous cystinosis. Under electron microscopy, the dermatopathologist was able to identify the intracrystalline inclusions (Figure 2) consistent with cystinosis. We did not confirm the absence of cystine crystals in unaffected skin.

Figure 1. Cutaneous Cystinosis on the Face of a Young Man
This photograph shows firm, dome-shaped, shiny facial papules.