

## CME RECOGNITION

This SKIN & ALLERGY NEWS supplement is recognized by the American Academy of Dermatology (AAD) for 1 hour of AAD Category 1 CME credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.

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## TARGET AUDIENCE

This activity has been developed for dermatologists and other health care professionals involved in the diagnosis and treatment of skin conditions for which immune response modifier therapy may be considered.

## EDUCATIONAL NEEDS

The treatment of many commonly encountered skin disorders necessitates elimination of lesions. Such cutaneous disorders include actinic keratoses, external anogenital warts, superficial basal cell carcinomas, squamous cell carcinomas, and common warts. Historically, these lesions have been treated with a variety of surgical and/or chemical lesion-destructive modalities. These therapies have varied in their success rates; in addition, they often produce adverse effects such as pain, swelling, and scarring.

Within the past decade, the concept of local immune response modifier (IRM) treatment for many of these diseases has emerged. With IRM therapy, topical application of the medication produces a local upregulation of activity in both the innate and the acquired immune system, yielding proven, safe, antiviral and antitumor activity with limited side effects and ease of application.

The results of well-controlled clinical trials form the foundation of an evidence-based approach to medical treatment. In treating individual patients, however, clinicians also receive valuable knowledge from their own experience and that of their colleagues. Using case studies as a basis, this supplement offers the clinical experiences of experts who have used imiquimod in a variety of skin diseases.

## LEARNING OBJECTIVES

By reading and studying this supplement, participants should be able to:

- Discuss the indications and dosing schedule for the use of imiquimod that are currently approved by the US Food and Drug Administration.
- Describe the experience of clinicians who treated an elderly patient with sebaceous carcinoma in a case presented in this supplement.
- Discuss the treatment regimen used for treating a patient with extensive actinic keratoses on the face and upper extremities.

## FACULTY AND UNAPPROVED USE DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. The faculty must also disclose any discussion of investigational or unlabeled uses of products.

**Dr Baldwin** has nothing to disclose nor does she discuss the unlabeled use of any drugs. **Dr Chow** has received honoraria from 3M Pharmaceuticals. She discusses the alternatives to approved dosage regimens of imiquimod; the unlabeled use of tazarotene as an adjunct to imiquimod therapy in actinic keratosis; prophylactic maintenance treatment with imiquimod; and the use of imiquimod to treat sebaceous carcinoma or nodular basal cell carcinoma.



A SUPPLEMENT TO

Skin & Allergy News®



SKIN DISEASE  
EDUCATION  
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# DERMATOLOGISTS' CASE FILES

## Use of Immune Response Modifier Therapy in Challenging Patients

### Introduction

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*When the topical immune response modifier imiquimod was approved by the US Food and Drug Administration (FDA) in 1997 for the initial indication of external anogenital warts, its mechanism of action was not completely understood. Since that time, research has further defined the drug's antiviral and antitumor properties and has demonstrated that imiquimod is an effective treatment for other dermatologic diseases as well.*

It is now known that imiquimod stimulates cell-surface receptors on antigen-presenting cells, which, in turn, enhances the activity of both the innate and the acquired immune response. Readers are invited to access a number of supplements to SKIN & ALLERGY NEWS that have been published in the last several years. In these supplements, panels of distinguished experts with academic, research, and clinical credentials discuss various aspects of how imiquimod works, the indications for which it currently is FDA approved, and the disease states for which it may prove beneficial. These publications also address the full range of surgical and pharmacologic approaches to treating these diseases. These supplements may be accessed online at [www.skinandallergynews.com](http://www.skinandallergynews.com) in the Medical Education Library section.

Currently, imiquimod is approved by the FDA for the treatment of external anogenital warts, actinic keratoses of the face and bald scalp, and superficial basal cell carcinoma. The strategy of immune response modification also is being tested—albeit, not in formal clinical trials at this time—in a variety of other disease states. These include actinic cheilitis, Bowen's disease, bowenoid papulosis, molluscum contagiosum, and keloid scars.

The body of literature continues to grow, addressing all of these areas of interest in our specialty. Of course, large, well-controlled clinical trials provide solid data that lay the crucial foundations for evidence-based patient management. However, as we all readily know, even the best of these studies cannot address all of the circumstances we face in everyday clinical practice as we deal with individual patients and their specific presentations. Reports of cases from real-world clinical experience often are useful additions to our knowledge base.

This supplement is the first in a new series titled *Dermatologists' Case Files*. In this and the next three issues, recognized experts share their experiences with the use of imiquimod in some of their own patients. In some of these cases, imiquimod has been used off-label; these are clearly identified in the text. The complete roster of therapeutic options available for the diseases discussed in the presented cases is beyond the scope of this supplement and is not addressed here. In the current issue, May J. Chow, MD, and her colleagues present three of their patients. We hope these profiles will be interesting and instructive.

Please go to [www.managingactinickeratoses.com](http://www.managingactinickeratoses.com)  
for more information on the treatment of actinic keratoses.

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INTERNATIONAL  
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## Sebaceous Carcinoma in an Elderly Patient

May J. Chow, MD, Andrea Hui, Jon Ferguson, DO, and John Abram, MD

The patient is a 91-year-old woman with Alzheimer's disease who presented with an ulcerated lesion on the left side of her neck. Her family reported having seen multiple "sores" at the site for the previous several years. The patient had been unsuccessfully treated with topical corticosteroids and antibiotics.

Physical examination revealed a large nodular lesion on the neck of approximately 3 to 4 cm in diameter (Figure 1). No lymphadenopathy was found within the cervical or supraclavicular region during the initial visit; the rest of the head and neck examination was unremarkable. A tentative diagnosis was made of nodular basal cell carcinoma (BCC) and an incisional biopsy was performed under local anesthesia.

Histologic examination of a specimen revealed an ulcerated sebaceous carcinoma extending to the deep margin of resection. Review of the pathologic sections demonstrated portions of skin with marked solar elastosis and moderate cytologic atypia of the epidermis. The specimen also revealed a proliferation of basaloid cells with peripheral palisading retraction artifact,

and cytologic atypia. Sebaceous-appearing clusters of cells with prominent lipids, marked cytologic atypia, and markedly increased mitotic activity were also seen. Atypical mitoses, including tripolar and tetrapolar mitoses, were present. Nuclear pleomorphism and foamy cytoplasm also supported the diagnosis of sebaceous carcinoma (Figure 2). BCC was also found immediately adjacent to the sebaceous cancer in a pattern that can be described as a collision tumor. Light microscopy with hematoxylin and eosin stain revealed a clear distinction between the two cancerous cells. An epithelial membrane antigen assay was performed for

greater specificity; it was strongly positive in the sebaceous carcinoma region of the tumor and negative in the BCC region (Figure 3). A diagnosis of sebaceous carcinoma was made on the basis of clinical and histologic findings. The patient's family refused further surgery,

chemotherapy, or radiation treatment as management options.

### Treatment Rationale

Sebaceous carcinoma is a rare malignancy that most commonly originates within the meibomian glands of the eyelid. The definitive treatment for this tumor is Mohs surgical excision and removal of locally involved lymph nodes.<sup>1-3</sup> Although there are no reported cases of the use of imiquimod as a treatment for sebaceous carcinoma, BCC has been demonstrated to respond favorably to this treatment.<sup>4,6</sup> Imiquimod, an immune response modifier, activates the cellular pathway of innate immunity through the indirect release

of tumor necrosis factor- $\alpha$  and other cytokines.<sup>5,7</sup> It has been theorized that a poor immunologic response to sebaceous carcinoma contributes to the aggressiveness of this cancer.<sup>1</sup> The use of imiquimod to increase the local

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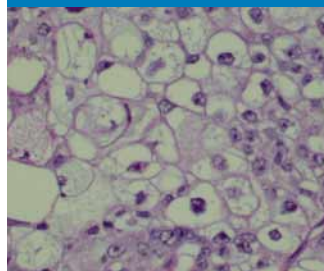
Figure 1.  
Sebaceous Carcinoma  
of the Neck



This ulcerated lesion on the left side of the patient's neck measured 3 to 4 cm. The lesion appeared to be nodular basal cell carcinoma, but an incisional biopsy revealed ulcerated sebaceous carcinoma.

Photo courtesy of May J. Chow, MD.

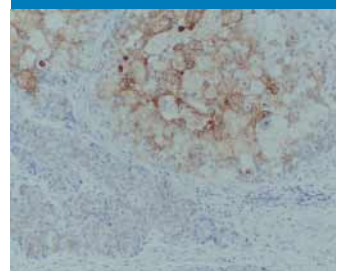
Figure 2.  
Hematoxylin and Eosin  
Stain of Biopsy Specimen



On this specimen, nuclear pleomorphism and foamy cytoplasm support a diagnosis of sebaceous carcinoma (magnification 600X).

Photo courtesy of May J. Chow, MD.

Figure 3.  
Epithelial Membrane  
Antigen Immunostaining



This photomicrograph reveals the margin of sebaceous carcinoma and basal cell carcinoma (magnification 200X).

Photo courtesy of May J. Chow, MD.

## Extensive Actinic Keratoses

May J. Chow, MD, and Andrea Hui

The patient is an 81-year-old retired high school football coach with a long history of actinic keratoses (AKs) and basal cell carcinomas (BCCs) on his face and upper extremities. For the past 30 years, he had been treated with liquid nitrogen cryotherapy and 5-fluorouracil for his AKs and with excision for his BCCs.

In April 2004, the patient first received imiquimod 5% cream treatment and was instructed to apply one sachet to the sun-exposed area of each arm\* every Monday, Wednesday, and Friday for 6 weeks. Three weeks after the initial treatment, the patient developed erythema, oozing, and crusting on both arms (Figure 1).

To manage his brisk cytokine dermatitis, the patient was instructed to take a 2-week rest period from treatment.

Washing the affected area with sodium sulfacetamide 10% and sulfur 5% cleansing cloths twice daily, followed by application of mupirocin 2% ointment, was prescribed during this rest period.

Following the rest period, the patient resumed the Monday, Wednesday, and Friday imiquimod regimen. He again experienced a local reaction during the second 6-week course of treatment but of

much less intensity than before. Four weeks after the conclusion of imiquimod therapy, there were no visible AKs and satisfactory results were documented (Figure 2).

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Figure 1. Local Reaction to Therapy



By 3 weeks of imiquimod applications, erythema, oozing, and crusting had developed on both arms. The patient's right arm is shown here.

Photo courtesy of May J. Chow, MD.

Figure 2. 4 Weeks Posttreatment



At 4 weeks after cessation of therapy, the local skin reaction was resolved and the AKs were cleared. The patient's right arm is shown here.

Photo courtesy of May J. Chow, MD.

## Sebaceous Carcinoma in an Elderly Patient

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cell-mediated immunity was deemed to be potentially helpful in this patient.

### Treatment Regimen and Outcome

Topical imiquimod 5% cream was administered for 6 months, with a regimen of 1 month on and 1 month off. During the month-long treatment periods, the medication was applied in the evening, Monday through Friday, with no applications on Saturday or Sunday.\*

After 12 weeks of active treatment with imiquimod, a repeat biopsy was performed at two sites; no residual sebaceous carcinoma or BCC was detected. The patient was followed monthly for 1 year, then every 3 months. Currently, at 3 years, there are no clinical signs of recurrence of the lesion (Figure 4). Long-term follow-up is in

Figure 4. Lesion Site at 3 Years Posttreatment



This patient has been followed for 3 years. Currently, there are no clinical signs of recurrence of sebaceous carcinoma. In this photo, note that poikilodermatous changes and pigmentation have resolved (compare with Figure 1). In addition, substantial improvement in skin texture was seen.

Photo courtesy of May J. Chow, MD.

progress, as the patient is now receiving imiquimod prophylaxis once weekly.\*

### Conclusion

This clinical case suggests a prime benefit in using imiquimod 5% cream as a noninvasive modality in the management of this elderly patient. Cycle therapy may retain the efficacy and enhance the safety profile of imiquimod. There is an additional benefit of superior cosmetic outcome in the treatment site as documented.

\*Sebaceous carcinoma and nodular BCC are not US Food and Drug Administration (FDA)-approved indications for imiquimod at this time. The dosage regimen described is not within product labeling for imiquimod. Prophylactic use of imiquimod is not FDA approved.

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## Actinic Keratoses and Warts in a Kidney Transplant Recipient

May J. Chow, MD, and Andrea Hui

The patient is a 51-year-old white woman who had received a kidney transplant 17 years earlier. At the time the patient was first seen in our office in 1990, she was taking prednisone, 5 mg daily; cyclosporine, 100 mg twice daily; azathioprine, 50 mg/day; magnesium chloride, 128 mg/day; and daily phosphate supplementation.

The patient had been treated for 16 years for recurrent actinic keratoses (AKs) and human papillomavirus (HPV) warts on her arms and legs. Until 5 years ago, the only treatment available to her was liquid nitrogen cryotherapy and topical salicylic acid. Both treatments were unsatisfactory. Liquid nitrogen cryotherapy resulted in blister formations and occasional secondary bacterial infections; subsequently, the area healed with hypopigmented scarring. Salicylic acid was ineffective in clearing the warts.

The patient first received imiquimod 5% cream treatment 5 years ago when she had recurrent warts on the extremities.\* Imiquimod treatment resulted in clearance of her warts and AKs.

We saw the patient again for a recurrence of diffuse warts and AKs on her legs in December 2005 (Figure 1). Field therapy with imiquimod cream was initiated every other day, alternating with tazarotene 0.1% cream.\* Oral retinoids have been used as prophylaxis for nonmelanoma skin cancer in organ transplant recipients, and this option was discussed with the patient. After considering the potential side effects of oral retinoid use, the patient refused this treatment. The decision to use the topical retinoid

tazarotene as an adjunct to topical imiquimod was based on the concept that retinoids, increase STAT1 protein, which works synergistically with imiquimod.<sup>1</sup> Treatment progress was documented 10 days after initiation of therapy (Figure 2).

### Conclusion

Patients who have undergone solid organ transplantation are at high risk for cutaneous cancers because of their use of immunosuppressive drugs. These patients have dramatic increases in the incidence of malignant melanoma, basal cell carcinoma, squamous cell carcinoma (SCC), and other skin cancers. For example, solid organ transplant recipients have an SCC incidence 65 to 100 times higher than that in individuals who are not immunocompromised.<sup>2</sup> Because the majority of SCCs arise from AKs,<sup>3</sup> it is critical to monitor for and treat AKs early.

**Figure 1.** Warts and Actinic Keratoses (AKs) of Right Leg



Five years after previous therapy with imiquimod 5% cream, this patient had a recurrence of both warts and AKs on her arms and legs. Shown here is the medial right aspect of her right leg.

Photo courtesy of May J. Chow, MD.

**Figure 2.** Treatment Response: Actinic Keratosis (AK)



This AK lesion on the patient's medial right leg was raised and hyperkeratotic (left). After 10 days of imiquimod and tazarotene applications, the lesion was markedly smaller, with resolution of hyperkeratosis.

Photo courtesy of May J. Chow, MD.

In addition to transplant recipients, other populations of patients who are immunosuppressed—for example, those with human immunodeficiency virus infection or patients with rheumatoid arthritis who are being treated with immunosuppressive agents—also have a higher incidence of both AKs and cutaneous HPV infection than does the general population. Imiquimod provides a new treatment milieu in which these high-risk patients may be managed. ■

\*This indication is not approved by the US Food and Drug Administration for either imiquimod or tazarotene. Imiquimod currently is approved for the treatment of AKs of the face and bald scalp.

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### Extensive Actinic Keratoses

Continued from previous page

### Conclusion

Currently, the patient continues imiquimod treatment, one sachet on each arm every Sunday for long-term prophylactic maintenance.\* Clinically, no AKs or BCCs are detectable on either arm. ■

\*The US Food and Drug Administration (FDA) has approved imiquimod for the treatment of AKs of the face and bald scalp. The treatment of superficial BCC is an FDA-approved indication for imiquimod. Prophylactic maintenance therapy with imiquimod for AKs has not been approved by the FDA.

Please go to [www.managingactinickeratoses.com](http://www.managingactinickeratoses.com) for more information on the treatment of actinic keratoses.

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