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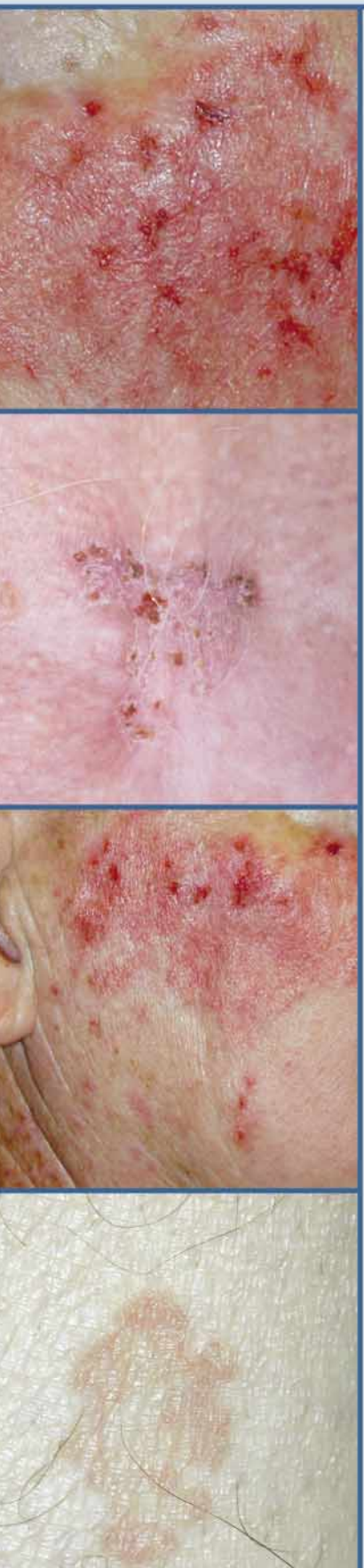

Dermatologic Dilemmas: The Role of Immune Response Modifiers In Challenging Cases

Proceedings of a Clinical Roundtable

Case Studies Featured:

- *Actinic Keratosis*
- *Basal Cell Carcinoma*
- *Bowen's Disease*
- *Extramammary Paget's Disease*
- *Molluscum Contagiosum*

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ELSEVIER SCIENCE

Dermatologic Dilemmas: The Role of Immune Response Modifiers In Challenging Cases

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ACCREDITATION

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TARGET AUDIENCE

Dermatologists and other clinicians who treat patients with nonmelanoma skin cancers, actinic keratoses, and lesions caused by cutaneous viruses.

EDUCATIONAL NEEDS

Since the introduction of immune response modifier therapy and the approval by the U.S. Food and Drug Administration of the first topical drug in that class, imiquimod, for use in the treatment of genital warts, dermatologists have watched the literature with great interest for further research in this new area of therapy. Many clinicians throughout the United States and abroad are aware of the clinical trials that have been conducted and are currently under way using topical imiquimod to treat a variety of diseases, including nongenital warts, nonmelanoma skin cancers (basal cell and squamous cell carcinoma), and actinic keratosis. Difficult cases—such as those presented in this supplement—are those in which standard treatment has not worked or for some other reason is deemed inappropriate for specific patients. It is important for physicians to know what the currently available data demonstrate concerning these investigational uses for imiquimod.

LEARNING OBJECTIVES

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

- List and explain the factors that make each of the cases presented in this supplement clinically challenging.
- Discuss the utility of immune modification—including both immune response modifiers (IRMs) and topical immune response modifiers (TIMs)—in difficult dermatologic cases.
- List and describe alternatives to standard therapies for the treatment of patients with difficult dermatologic conditions.

FACULTY DISCLOSURES

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

Dr. Anhalt is a consultant to 3M Pharmaceuticals and discusses the unlabeled use of imiquimod for treating basal cell carcinoma (BCC). **Dr. Babinski** has nothing to disclose. **Dr. Berman** has received clinical grants from and is a consultant to 3M and discusses the unlabeled use of imiquimod for treating various dermatological conditions (keloids, BCC, actinic keratoses [AK], warts). **Dr. Bhatia** is on the speakers' bureau of 3M and discusses the unlabeled use of imiquimod for treating skin cancer. **Dr. Chow** discusses the unlabeled and investigational use of imiquimod for treating BCC. **Dr. Huie** discusses the unlabeled use of imiquimod for treating superficial BCC. **Dr. Johnson** has received clinical grants from 3M. He discusses the unlabeled use of imiquimod for treating AK, squamous cell carcinoma (SCC) in situ, and BCC. **Dr. Maibach** has nothing to disclose. **Dr. McGovern** is on the speakers' bureau of 3M and discusses the unlabeled use of imiquimod for treating SCC in situ, BCC, AK, and keloid prevention. **Dr. Pandya** has received clinical grants from and is on the speakers' bureau of 3M and discusses the unlabeled use of imiquimod for treating superficial basal cell carcinoma. **Dr. Rosen** has received clinical grants from and is a consultant to 3M. He discusses the unlabeled use of imiquimod for treating intraepidermal SCC and molluscum contagiosum. **Dr. Roth** has received clinical grants from and is on the speakers' bureau of 3M and discusses the unlabeled use of imiquimod for treating intraepithelial SCC. **Dr. Smith** discusses the unlabeled use of imiquimod for treating BCC. **Dr. Weinberg** has received clinical grants from and is on the speakers' bureau of 3M and discusses the unlabeled use of imiquimod for treating vulvar intraepithelial neoplasia.

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Foreword

Topical immune response modifier therapy offers a novel approach to the treatment of dermatologic conditions. The immune response modifier agent available currently, imiquimod, is package labelled by the U.S. Food and Drug Administration (FDA) for the treatment of genital and anal warts. However, because of its unique mechanism of action, the induction of local cytokine responses, this agent has been and is being studied for its potential utility in a number of other dermatologic conditions, including actinic keratosis (AK), basal cell and squamous cell carcinomas, nongenital human papillomavirus lesions (for example, common, plantar, and periungual warts), as well as molluscum contagiosum and extramammary Paget's disease.

The ideal treatment circumstance is, of course, one in which an individual patient has a condition that:

- Responds as expected;
- Responds to treatment that has a long history of safety and efficacy;
- Responds to treatment with a history that is well documented in the literature.

Every day, however, clinicians are faced with individual patients who do not meet these ideal criteria, and new treatments, such as imiquimod—still under investigation for various indications—are applied. Many studies involving investigation of imiquimod for potential new indications have been published; other clinical trials are under way.

Meanwhile, clinicians are using immune response modifier therapy when the standard therapies for some conditions fail or for some reason are less than optimal choices in individual cases, such as those presented in this supplement. A panel of physicians described their personal perspectives in a give-and-take manner concerning the cases presented. The actual discussions were longer; the comments have been edited to create a document of sufficient brevity to interest the reader. It is hoped that the difficult cases presented in this supplement and the commentary from our faculty—Brian Berman, MD, PhD, Richard Allen Johnson, MD, and Theodore Rosen, MD, with Howard I. Maibach, MD, moderating—will provide some interim guidance for the rational use of immune response modifier therapy. The panel hopes that readers will use the "comments" section of the CME evaluation form to express their own views and experiences.

Introduction

Decisions regarding prescription writing in the physician's office depend on multiple levels of information. Most physicians are aware of phase I, II, and III studies leading to FDA regulatory approval. The regulatory process mandates an efficient and formalized system in which hundreds to thousands of patients may be treated in phase III studies under rigorously controlled conditions, providing data permitting approval.

After drug approval, the next several years are marked by a more complex decision-making process based on individual clinical trials that are more difficult to evaluate and are not rigorously controlled. An agent is tested patient by patient, and its use is supervised by the physician and executed by the patient. This complex interaction results in many evidential experiences that lead the health care worker to prescribe off-label and to alter dosing regimens.

Imiquimod is described as a biological modifier on the basis of preclinical studies utilized in identifying its activity. We have not had the opportunity to explore the panoply of other drugs used in the treatment of viral warts, AKs, and melanoma and nonmelanoma malignancies, to ascertain how many similar properties these drugs might share (in similar assays) with imiquimod.

The era of formal identification of biological modifiers is in its infancy. With subsequent generations of drugs—now under study—the subtleties of their mechanisms of action should unfold.

—Howard I. Maibach, MD

Actinic Keratosis

Case: 82-Year-Old Female

- Patient presented with a painful lesion on the nose (**Photo 1**).
- Previous lesion at the site was diagnosed as squamous cell carcinoma (SCC) in situ on biopsy; treatment with 5-fluorouracil (5-FU) for 1 month resulted in clearance of the lesion.
- History of extensive sun exposure from working outdoors in a prisoner of war camp for 4 years.
- Six months after initial clearance, the lesion recurred; repeat biopsy demonstrated AK; repeat therapy with 5-FU failed to eliminate lesion.
- Treatment strategy and results: Imiquimod was prescribed for twice weekly application. A follow-up visit at 1 month after the start of treatment showed an intense reaction (**Photo 2**). Patient discontinued use of imiquimod cream at that point. Four months later, the treated site was clear of lesion and asymptomatic.
- Final report: At 1 year posttreatment, the patient remains free of recurrence (**Photo 3**).

Discussion

Numerous treatments are available for effectively eliminating AKs. The most commonly used is cryotherapy. However, when a patient has many lesions or when lesions are ill-defined, freezing is a painful and prolonged prospect. In addition, when multiple AKs are on areas where appearance is a concern—such as the face or bald scalp—the hypopigmentation that is a common consequence of cryotherapy may be problematic.

This case was challenging both because 5-FU treatment failed and because of the location and size of the lesion. Destructive modalities such as cryosurgery would not have been appropriate in this case.

The newest treatment for AKs is photodynamic therapy (PDT), which involves application of aminolevulinic acid (ALA) followed by photoactivation by a light source. The ALA must be applied to each lesion, so although PDT is impractical for patients with many diffuse lesions, it would be an appropriate option for solitary or multiple discrete AKs. However, PDT was not a good choice for treatment in this particular patient for two reasons: First, it would have required application of ALA to the entire nose; second, the convex surface to be treated presented a potential problem in that the areas of skin closer to the light source would have received a greater dosage of light than other areas.

Topical diclofenac has been approved for the treatment of AKs. However, the cure rate with diclofenac, according to the drug's package insert, is 30% with 3 months of treatment to 40% with 4 months of therapy, far lower than that seen with almost all other AK treatments, with a prolonged treatment period, compared with other modalities.

Topical 5-FU has been a standard patient-applied therapy for AK for 4 decades and is a good modality for clearing a large field. Studies with imiquimod in patients with AKs have demonstrated that immune response modifier therapy is also an important option for eliminating these lesions.[1-3] However, with both 5-FU and imiquimod, patients should be made aware that an inflammatory response is to be expected and may be severe.

Another type of AK that should be mentioned is AK on the lips—that is, actinic cheilitis. Actinic cheilitis presents two main challenges: cosmetic outcome and

Continued on page 17

AK Refractory to Standard Therapy

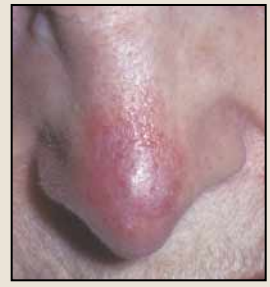

Photo 1. This painful lesion, an AK demonstrated on biopsy, occurred at the site of a previous biopsy-proven SCC in situ. Treatment with 5-FU failed to eliminate the AK.

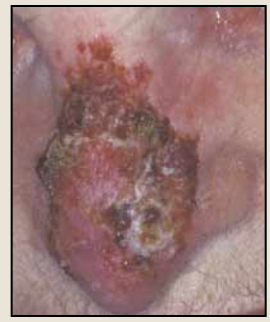

Photo 2. After 4 weeks of imiquimod applications two times weekly, the patient had an intense reaction to treatment.

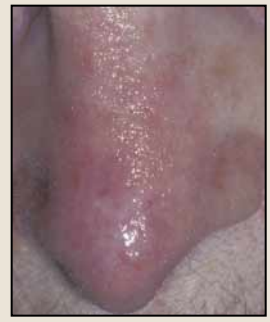

Photo 3. At 1 year posttreatment, the area remains clear.

Photos courtesy of Richard Allen Johnson, MD

Basal Cell Carcinoma of the Nose

Case: 58-Year-Old Male

- Patient presented with a 1½-year history of an enlarging pink patch on the nose (**Photo 1**), which bled occasionally when subjected to minor trauma. Lesion covered 80% of the nose.
- Biopsy demonstrated basal cell carcinoma (BCC) with both superficial and nodular components.
- Treatment strategy and results: Because of the extensive nature of the surgery that would be required for operative intervention, the patient chose a trial of therapy with imiquimod, five times weekly.

Large BCC of Nose

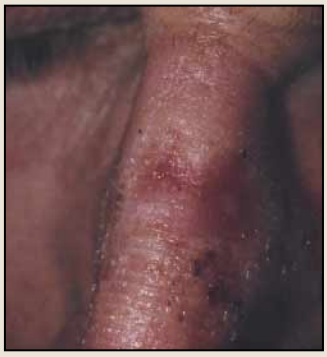

Photo 1. This patient's lesion covered approximately 80% of his nose. A biopsy demonstrated that the lesion was BCC, with both superficial and nodular components.

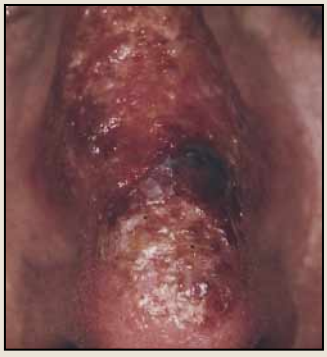

Photo 2. The severe reaction to imiquimod therapy by week 3 required that the patient take a 1-week drug holiday. He required one more 1-week rest period before therapy was completed.

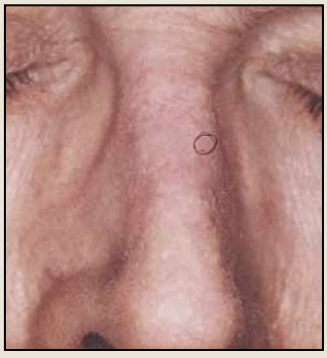

Photo 3. At 6 months posttreatment (shown here), the patient was tumor-free; at 13 months posttherapy there had been no recurrence.

Photos courtesy of Todd S. Anhalt, MD

After 3 weeks of three-times-weekly applications, the patient returned complaining of significant irritation; he had extensive black and yellow crusting on the treated area (**Photo 2**). A culture was obtained, and the patient was started on cephalexin 500 mg b.i.d. for 10 days and was instructed to apply mupiricin ointment t.i.d. (The culture was negative for pathogens.) He was instructed to take a 1-week rest period from imiquimod therapy. He resumed three-times-weekly applications of imiquimod for the next 11 weeks.

During week 7 he required another 1-week drug holiday. After a total of 14 weeks from the start of imiquimod therapy, physical examination suggested that the tumor had resolved. Mild residual erythema continued, without scaling, papules, or crusting. The skin did not appear to be scarred. Biopsies of several scout sites on the treated area revealed no evidence of BCC. At 6 months posttherapy, the patient was tumor-free (**Photo 3**).

- Final report: The patient was last examined 13 months after cessation of therapy; there had been no recurrence.

Discussion

This case was difficult because of the lesion's size and location. Standard therapies, including surgery and radiotherapy, would have resulted in severe cosmetic consequences. In addition, radiation therapy in this region poses a risk for some loss of olfactory function. Because of the extent of the lesion, Mohs' surgery would have been a technical challenge and would have required movement of tissue from the forehead; surgery would have been extensive and healing would have been prolonged.

Although 5-FU is an option for superficial BCC, it should not be considered for nodular BCC for reasons explained elsewhere (see "Superficial Basal Cell Carcinoma," page 14). Carbon dioxide (CO_2) laser surgery is not an option because there were no clear parameters to this patient's lesion. The trial of therapy with imiquimod was a reasonable attempt and, fortunately, the patient responded.

This case also illustrates what was demonstrated in several other cases reviewed in this supplement—the fact that the response to imiquimod can be brisk, even severe, and yet represents eczematous oozing but no infection. This case further shows the importance of individualizing therapy. If the patient requires a drug holiday, therapy should be temporarily interrupted, a strategy that has not been shown to impair drug efficacy. ■

Bowen's Disease
Squamous Cell Carcinoma in Situ

Case: 90-Year-Old Male

- Patient presented with a 5 x 6.5-cm scaling, papular/patchy lesion of the right leg, which patient reported had first appeared 1 year previously (**Photo 1**).
- History of multiple BCCs and invasive SCCs, which had been treated by surgical excision with excellent results.
- Avid golfer currently, and has always participated extensively in outdoor activities.
- Biopsy confirmed a diagnosis of intraepithelial SCC (Bowen's disease).
- Treatment strategy and results: The main issues considered in choosing treatment for this patient included his age and the large size of the area to be treated. It was important that therapy carry a low risk for morbidity and that it allow this patient to maintain his active, high-quality lifestyle. Imiquimod therapy was prescribed, with daily applications for 8 weeks. The lesion cleared within 6 weeks after initiation of therapy. During treatment the patient developed a severe reaction (**Photo 2**) characterized by erosion and crusting; a course of oral antibiotics was given for a presumptive diagnosis of impetigo, and the area cleared without further incident.
- Final report: At 10 months posttreatment, the lesion site remained clinically clear (**Photo 3**).

Bowen's Disease in Pretibial Area

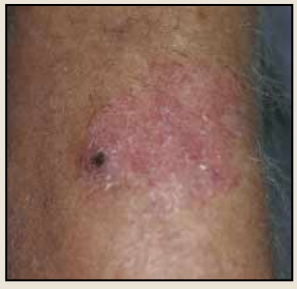

Photo 1. On presentation, the patient reported that the 5 x 6.5-cm scaly lesion had first appeared on his right leg 1 year earlier.

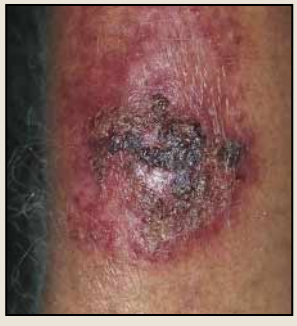

Photo 2. During treatment with imiquimod, the treated area developed erosions and crusting.

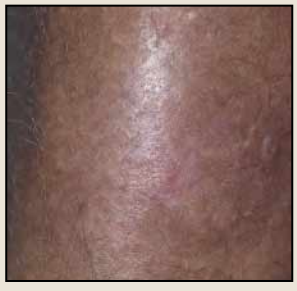

Photo 3. At 10 months posttreatment, the site remains clinically clear.

Photos courtesy of Peter I. Babinski, MD, PhD

Case: 68-Year-Old-Male

- Patient presented with a 8 x 6-cm scaling plaque involving the lower abdomen, which the patient reported had first appeared 8 months previously (**Photo 1** on page 8).
- History of multiple malignant skin neoplasms and adenocarcinoma of the colon.
- Patient, who grew up and continued to live on a farm, reported a lifetime exposure to arsenical insecticide.
- Biopsy confirmed a diagnosis of intraepidermal SCC (Bowen's disease).
- Treatment strategy and results: The main issues considered in this case included the large size of the lesion and the patient's adamant desire to avoid surgery for fear of "down time" during harvest season. Imiquimod therapy was instituted, with daily applications for 8 weeks. During treatment, the patient developed an impressive erosive response (**Photo 2** on page 8). No measures were undertaken to treat the erosion other than compresses of cool tap water; the area gradually cleared without treatment.
- Final report: At 1 year posttreatment, the site was clinically clear. Several random biopsy specimens were free of histologic evidence of SCC. At 2 years posttreatment, the site remained clinically clear.

Discussion

Several options exist for the treatment of intraepithelial SCC, or Bowen's disease, including surgery, desiccation and curettage, cryotherapy, and medical treatment with 5-FU or imiquimod. What made the case of the 90-year-old man challenging was the lesion's location and size as well as the patient's age. The size of the lesion was

the greatest problem in the case of the 68-year-old man, and an important consideration in determining treatment for him was his concern to avoid disability during harvest season. Most of the standard options can present problems for patients with such profiles.

If cryotherapy is used for Bowen's disease, the freeze must be exceptionally hard to be effective. This virtually always results in a depressed and hypopigmented or depigmented area, especially when treatment is on the legs. Even when cosmesis is not an issue, cryotherapy and other destructive modalities present the problem of wound healing at a site—in this case, the pretibial area—that is typically problematic.

A commonly used and effective option for the treatment of Bowen's disease is 5-FU (currently not package labelled by the FDA for this indication). When using this agent, remember that Bowen's disease is not just a superficial tumor; it extends down the hair follicles. For this reason, the efficacy of 5-FU requires an extensive period of therapy—4 weeks. Some clinicians use 5-FU under occlusion, in fact, in an attempt to enhance the concentration down the hair follicle. (No studies have been done to demonstrate enhanced follicular concentration of 5-FU with occlusion.)

The rationale for immune response modifier therapy in patients with Bowen's disease is the previous experience with interferon.[1] Intralesional injections of interferon were used in both invasive SCC and SCC in situ, yielding a 97% cure rate for both. When the 27 cases of invasive SCC in this study were considered alone, the cure rate was greater than 96%. Imiquimod's main mechanism of action is thought to be local induction of interferon,[2] so there is support for exploring the utility of immune response modifiers in SCC.

The use of imiquimod for the treatment of SCC in situ, including Bowen's disease, has been studied.[3-6] An uncontrolled, open-label Australian study[6] using imiquimod for Bowen's disease demonstrated that aggressive use of this agent—in this study, daily applications for 4 months—can be effective in clearing Bowen's lesions on the lower extremities. Sixteen patients were enrolled; one died soon after the start of the study from causes unrelated to the treatment. The remaining patients had clinical clearance of their disease, confirmed by biopsies.

The severe reaction that caused the clinician to provide antibiotic coverage for the patient in the case study above bears some discussion. Although the appearance of the site would lead one to suspect impetiginization, crusting—even if it is honey-colored—is not diagnostic. Even a positive culture may indicate only that a wound has been colonized, not infected. In most cases, the eczematous oozing that may occur during imiquimod therapy is characteristic of inflammation rather than bacterial infection, particularly in the absence of other symptoms of infection (such as rubor and loss of function). Nevertheless, applications of a topical antibiotic medication such as mupiricin may increase the comfort level of both patient and clinician. ■

Bowen's Disease on Abdomen

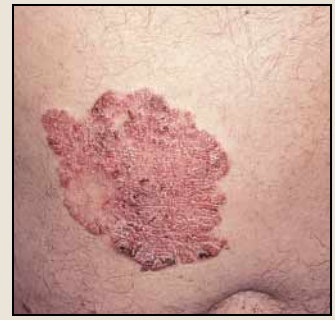

Photo 1. This scaling plaque on the lower abdomen, measuring 8 x 6 cm, first appeared 8 months prior to presentation.

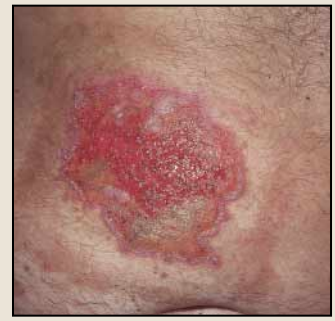

Photo 2. The erosive response that occurred during imiquimod therapy resolved without treatment.

Photos courtesy of Theodore Rosen, MD

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Extramammary Paget's Disease

Case: 68-Year-Old Male

- Patient presented with an eczematous eruption on the right scrotum. On histologic examination, atypical cells were identified which stained strongly positive with mucicarmine, endomysial antibody, carcinoembryonic antigen, cell adhesion molecule 5.2 (CAM5.2), and cytokeratin (CK) 7 and were negative with S100, HMB45, and CK20. Dermal microinvasion with rare atypical CAM5.2-positive cells was noted.
- Extensive workup was negative for underlying malignancy or nodal involvement.
- Four years previously, patient had presented with an indolent eczematous eruption on the right groin and scrotum; he had been treated for extramammary Paget's disease with Mohs' surgery.
- Treatment strategy and results: The patient refused surgery and was treated with imiquimod daily for 6 weeks. Within 2 weeks, moderate erythema developed in the treated area, although myalgia, nausea, vomiting, and fever did not occur. Erythema resolved by the fourth week of treatment, as did the original eczematous eruption.
- Final report: The patient has remained clinically and histologically free of symptoms for 6 months.

Discussion

Extramammary Paget's disease is itself a clinical challenge, regardless of individual patient characteristics that may make one case more or less problematic than another. The standard of care for extramammary Paget's disease is Mohs' surgery, a modality that yields a low long-term cure rate. For example, the recurrence rate for extramammary Paget's disease of the scrotum treated with Mohs' surgery is 27%.[1]

This patient had undergone surgery previously and was extremely reluctant to submit to further surgical intervention. He was treated with imiquimod daily for 6 weeks. During this time, he developed mild erythema and erosions that did not require cessation of therapy or a rest period from treatment. Biopsies at 3 and 6 months after cessation of treatment revealed no residual disease; close surveillance will continue.[2]

The high recurrence rate seen in this disease actually may represent new manifestations of preexisting disease. Extramammary Paget's disease is multifocal and the lesions are often not contiguous; so-called skip areas are the rule rather than the exception. With Mohs' surgery, the surgeon treats what can be seen, but it is virtually impossible to ensure that no areas of disease are missed.

For this reason, one member of this panel has used imiquimod in this disease not as primary therapy but as a method of identifying (or "lighting up") lesions that would otherwise not be apparent: Imiquimod was applied for several weeks well outside the margins of the visible lesion. Several areas on previously normal-appearing skin became erythematous. Surgery was performed to excise all the areas that had reacted to imiquimod, and all were found to be foci of extramammary Paget's disease.

Finally, remember that extramammary Paget's disease is clearly associated with underlying malignancy, so the workup should be extensive. Usually malignancies are identified in the genitourinary system, but they have been found—albeit rarely—beyond the genital area. In addition, application of imiquimod to large areas of occluded, moist skin may make the patient susceptible to systemic, flulike symptoms. These symptoms, if they require treatment at all, usually respond to acetaminophen. ■

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Molluscum Contagiosum

CASE: 9-Year-Old Male

- Patient presented with multiple umbilicated papules of 2 to 3 months' duration; more than 100 papules were counted on the abdomen, lower back, and both axillae.
- No history of antecedent inflammatory or sexually transmitted disease was elicited.
- Treatment strategy and results: The patient's parents refused the options of cryosurgery and/or curettage. Topical therapy with imiquimod was therefore chosen. The drug was applied daily. After 1 week, the lesions became erythematous and crusty (**Photo**). However, since the child had few complaints referable to the clinical inflammatory response, treatment was not discontinued. After 35 days, the lesions were totally resolved and therapy was discontinued.
- Final report: At follow-up 1 week after cessation of treatment, the patient had no signs of postinflammatory dyschromia. At 6 months posttherapy, the lesions had not recurred.

Molluscum Contagiosum

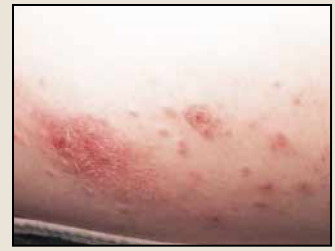

Photo courtesy of Theodore Rosen, MD

Photo. Molluscum contagiosum was the diagnosis in this patient, who presented with more than 100 umbilicated papules on the trunk.

Discussion

The standard treatment for molluscum contagiosum involves destruction of each lesion by cryotherapy, extraction of the central core of the papule, or chemical destruction with cantharidin. In some cases, such as the one presented here, the sheer number of lesions makes treatment difficult.

The use of an immune response modifier in such cases is a welcome alternative. The safety and efficacy of imiquimod in molluscum contagiosum has been studied.[1-8] Barba and colleagues[1] documented the safety of imiquimod in patients with molluscum contagiosum as young as 4 years of age. In their study, no systemic symptoms of interferon toxicity (important since imiquimod induces interferon) were found. In patients with atopic dermatitis, a small number of patients developed superficial erosions at the site of the molluscum lesions located in the antecubital or popliteal fossae and groin areas. The investigators postulate that more imiquimod penetrated in those areas than in nonoccluded areas, and that patients with atopic dermatitis have a suboptimal stratum corneum that permits greater-than-normal absorption of the medication. No data are available to date on the safety of imiquimod in patients less than 4 years of age.

The optimum treatment schedule for imiquimod in this disease appears to be daily, or at least three times weekly, until the lesions resolve. When used less frequently, the therapeutic course is prolonged. Some clinicians advocate twice-daily treatment to significantly shorten the treatment course, but the attendant risk is increased inflammation and patient discomfort.

In the clinical experience of the panel, patients with active eczema can experience substantial inflammation on exposure to imiquimod, not just in occluded areas such as the antecubital fossa but at any site where active eczema is present. Therefore, to prevent excessive discomfort, ensure that eczema is well controlled before initiating imiquimod treatment.

In addition to imiquimod monotherapy, a new approach being studied for treating patients with molluscum contagiosum—particularly those with concomitant atopic dermatitis—is to combine the immune response modifier with one of the new topical formulations of the immune modulators tacrolimus or pimecrolimus. ■

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Nodular Basal Cell Carcinoma

Case: 63-Year-Old Male

- Patient presented with a pearly nodule on the right side of the nose (**Photo 1**) and on the bridge of the nose, a classic presentation of BCC; a 3-mm punch biopsy confirmed the diagnosis of BCC.
- History of multiple episodes of sunburn during childhood.
- History of BCC and AKs of the face; previous BCCs treated with surgical excision.
- Family history of melanoma and nonmelanoma skin cancer.
- Treatment strategy and results: Because of his history of multiple surgical procedures for BCC, this patient requested medical treatment. He was given a prescription for imiquimod and instructed to apply the medication to the lesion three times weekly at bedtime. After 3 weeks, the applications were stopped for 2 weeks because of crusting (**Photo 2**). After this rest period, imiquimod therapy was restarted, five times a week at bedtime, and continued for 4 weeks.
- Final report: Clinical clearance was complete, with a good cosmetic outcome (**Photo 3**). A 3-mm punch biopsy performed after cessation of imiquimod therapy demonstrated histologic resolution of BCC.

Discussion

Excision is among the standard treatments for nodular BCC. In a problem area like the nose—particularly in this case, in which the lesions were close to the inner aspect of the eye—Mohs' micrographic surgery is often the technique of choice.

In this case, the patient strongly desired to avoid surgery, so the clinician chose to use imiquimod. Most current evidence suggests that imiquimod's efficacy is not high enough to warrant its placement on the list of standard therapeutic options for most cases of nodular BCC. However, a recent article summarizing the results of two major studies (one using a 6-week protocol, the other a 12-week regimen) noted that the efficacy of imiquimod in nodular BCC is in the range of 50%-70%, depending on application frequency.[1]

Topical 5-FU is sometimes considered as an alternative therapy for BCC, but this drug must reach 1-millimolar concentration to be effective—which is virtually impossible to achieve under normal conditions in a BCC. The result is that the BCC may resolve superficially but persist deeper in the dermis, and the presence of residual tumor may not be recognized until the BCC recurs. The efficacy of imiquimod in resolving BCC apparently does not depend on a direct interaction of the drug with the involved basal cells, and imiquimod therapy seems to result in resolution of both the superficial and intradermal portions of the tumor. In addition, a secondary phenomenon, the evocation of an immune response directly against the involved basal cells, may be involved.

In individual cases in which the nodular BCC is a small, solitary lesion, several factors may argue in favor of a topical immune response modifier. For example, the patient—as in this case—may be reluctant to undergo treatment with a destructive or surgical method, or age or other medical conditions (such as concomitant treatment with an anticoagulant) may make more invasive modalities problematic.

An additional message from this case concerns the appearance of the lesion during treatment. The patient had three relatively discrete lesions, yet after 3 weeks of treatment, there was a field of erythema, erosion, and crust-

Classic BCC in 63-Year-Old Man

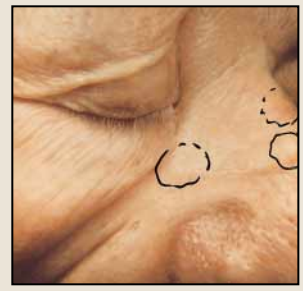

Photo 1. Patient presented with a pearly nodule on the right side of the nose and on the bridge of the nose; a 3-mm punch biopsy confirmed the diagnosis of BCC.

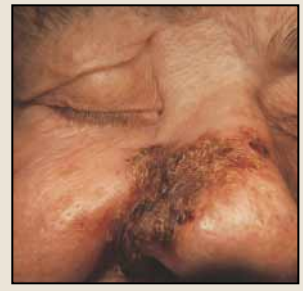

Photo 2. BCC after 3 weeks of imiquimod applications three times weekly at bedtime.

Photo 3. One week posttherapy (after 7 weeks of treatment), the lesion was clinically resolved; repeat biopsy was negative.

Photos courtesy of May J. Chow, MD

ing. This is a common response to the therapeutic activity of imiquimod in skin with actinic damage—the milieu in which BCCs occur. Thus, we see in this case the activity of imiquimod on BCC and also on sun-damaged skin in the areas beyond the margins of the lesions.

Case: 95-Year-Old Woman

- Patient presented with a 6-mm translucent papule on the left nasal ala of 6 months' duration (**Photo 1**). A clinical diagnosis of BCC was made; no biopsy was performed.
- Long history of sun exposure and many previous nonmelanoma skin cancers.
- Treatment strategy and results: The patient expressed a preference for nonsurgical therapy. Imiquimod was prescribed, daily applications for 2 months.
- Final report: The lesion resolved completely, with no sign of recurrence at 4 months following cessation of treatment (**Photo 2**).

Discussion

The standard treatments for a small, nodular BCC are excision, electrosurgery, and electrodesiccation. However, surgery in this area of the nose may require tissue movement, such as an advancement or a transposition flap, complex procedures that would be taxing for a patient 95 years of age. ■

Nodular BCC in 95-Year-Old Woman

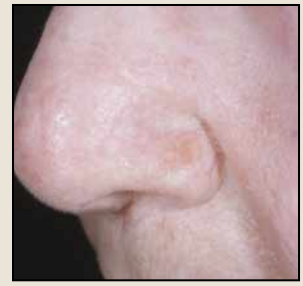

Photo 1. This 95-year-old woman presented with a 6-mm translucent papule on the left nasal ala.

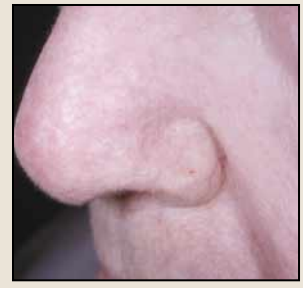

Photo 2. After imiquimod treatment, the lesion has resolved completely.

Photos courtesy of Jason L. Smith, MD

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Nonmelanoma Lesion
in a Renal Transplant Patient

Case: 66-Year-Old Male

- Patient who had undergone kidney transplantation presented for full-body examination for skin cancer. Identified were six AKs on the face and a slightly raised, erythematous and tan plaque on the right shin measuring 2 x 1.3 cm (**Photo 1**).
- Differential diagnosis of shin lesion included SCC in situ, seborrheic keratosis, and AK.
- Treatment strategy and results: Because the patient wished to avoid a surgical procedure, no biopsy was performed at this time. Imiquimod was prescribed for application three times a week in the evening for 6 weeks. There was no response to imiquimod—that is, no erythema, edema, or change in the lesion (**Photo 2**). A tangential biopsy performed after 6 weeks of therapy indicated a diagnosis of "benign keratosis."

Discussion

The clinician in this case was faced with a not uncommon dilemma: The patient wished to avoid a particular course, yet that course was the best clinical path. Because of the high rate of nonmelanoma skin cancer in patients who have received organ transplants,[1-3] it is essential that malignant lesions be identified and treated early.

In this case, the use of imiquimod led to the conclusion (confirmed, appropriately, by biopsy) that the lesion in question was not malignant. Nonresponse to imiquimod was a strong clue that the diagnosis was seborrheic keratosis because such lesions do not respond to immune response modifier treatment.

Regarding the use of imiquimod in patients who have received organ transplants, there is some theoretic concern about the induction of interferon. More investigation must be done in this area to establish the risk:benefit ratio associated with the use of immune response modifier therapy in organ transplant recipients. Meanwhile, this panel advises the cautious use of immune response modifier therapy in selected patients—such as those with SCC in situ, symptomatic warts that severely affect function and quality of life, and widespread AKs—whose symptoms seem to justify its use. ■

Lesion in Renal Transplant Patient

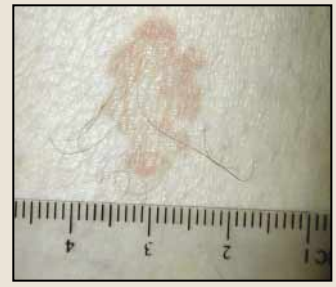

Photo 1. This patient presented with a 2 x 1.3-cm, slightly raised, erythematous and tan plaque on the right shin.

Photo 2. After 6 weeks of treatment with imiquimod, no change was seen in the lesion.

Photos courtesy of Thomas W. McGovern, MD

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Superficial Basal Cell Carcinoma

Case: 48-Year-Old Male

- Patient presented with an erythematous plaque on the left chest, approximately 4 x 6 cm (**Photo 1**), which had increased in size over an 8-year period.
- Previous treatment by his primary care physician was with topical corticosteroids and calcipotriene.
- Punch biopsy revealed a superficial BCC.
- Treatment strategy and results: The patient was concerned about scarring on his chest and expressed anxiety about the cosmetic outcome of surgery. He was treated with imiquimod three times weekly for 3 weeks, then twice weekly for another 13 weeks. The patient complained of occasional flulike symptoms but elected to continue treatment. The lesion cleared between 6 and 8 weeks. Acute erythema developed during imiquimod therapy and faded after treatment ended (**Photo 2**).
- Final report: The treated area remains clear 1½ years later (**Photo 3**).

Discussion

This patient's superficial BCC was not a life-threatening lesion, but it was large and located in an area in which a good cosmetic outcome would not have been easy to obtain with standard therapy. Because the lesion was superficial, surgical excision, including Mohs' surgery, was not called for. Desiccation and curettage generally is a good treatment for superficial BCC, but this procedure performed on the anterior chest on a lesion of this size would be likely to cause dyschromia and some induration or, possibly, a painful exophytic scar.

The efficacy of imiquimod in the treatment of superficial BCC was first reported by Beutner and coworkers[1] and continues to be documented.[2-7] Stockfleth and Sterry[8] recently reported an 80% clinical and histologic cure rate in patients with superficial BCC treated with imiquimod daily for 6 weeks.

This panel has had some experience with flulike symptoms in patients using imiquimod. Such symptoms appear infrequently and their occurrence does not seem to correlate with the size of the lesion, the duration of therapy, or the depth of any local response (erythema, erosion, crusting) that may accompany imiquimod use. In two cases of extramammary Paget's disease known to this panel, the lesions were large and located in the scrotal region, so it is possible that natural occlusion may have resulted in increased penetration of the medication and, possibly, may explain the occurrence of systemic symptoms. However, not all cases known to this panel involve such clinical circumstances—in another case, a patient who was treated with imiquimod for Bowen's disease (squamous cell carcinoma in situ) on the forehead developed such symptoms. Until more is known about the cause of flulike symptoms that occur occasionally in patients using imiquimod, it may be helpful to use a shorter rather than a longer course of therapy in those patients who do develop systemic symptoms.

The size of a superficial BCC should not be a deterrent to treatment with an immune response modifier. Chen and colleagues[9] describe the treatment of a superficial BCC of 30 cm^2 with imiquimod. The cosmetic outcome was highly acceptable, and random biopsy tests of cure at the conclusion of treatment were negative for residual disease. The follow-up at 2 years posttreatment (and 1 year after the submission of the case for publication) shows no recurrence.

Large Superficial BCC on Chest

Photo 1. A punch biopsy confirmed the diagnosis of superficial BCC. This lesion measured approximately 4 x 6 cm.

Photo 2. Erythema developed during treatment with imiquimod and faded after treatment ended.

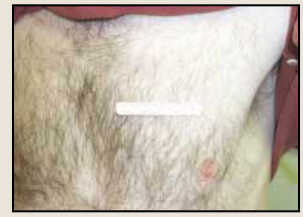

Photo 3. At 1½ years of follow-up, the treated area remains clear.

Photos courtesy of Michael A. Huie, MD, PhD

Case: 59-Year-Old Male

- Patient presented with a red, scaly, well-circumscribed plaque on his right upper back, almost 2 cm in diameter at the widest (**Photo 1** on page 15).
- History of multiple blistering sunburns as a child; still participates in outdoor activities.

- Precancerous lesions treated previously with liquid nitrogen.
- Biopsy confirmed diagnosis of superficial BCC.
- Treatment strategy and results: The patient was concerned about the scar that would result from surgical or other treatment of the BCC on his back. To maximize the possibility of a good cosmetic outcome, the BCC was treated with imiquimod daily for 6 weeks. The patient developed erythema and some edema of the lesion, along with mild discomfort, during the 6 weeks of therapy (**Photo 2**), but no interruption in treatment (rest period) was required. The site was well healed 12 weeks after the completion of therapy, with no sign of residual BCC (**Photo 3**).
- Final report: Eight months after completion of therapy, there is no sign of recurrence of this patient's BCC.

Discussion

This was a lesion on the back and, in most patients, the treatments of choice would include electrodesiccation and curettage (EDC), a procedure that takes approximately 10 minutes and is associated with a cure rate of 90%-95%. The therapy chosen was one that required 6 weeks of attention. However, the longer-term, more involved treatment may have been justified in this case because of the patient's strong concern with cosmesis, specifically with scarring. Surgery on the back is likely to result in some hypertrophic scarring. The clinical and histologic cure rate with daily imiquimod treatment is comparable to that seen following EDC treatment for superficial BCC—88% cure following treatment with imiquimod versus 63%-70% histologic cure immediately following EDC.[10]

The introduction of immune response modifier therapy also offers a potential option for combination therapy to increase efficacy in the treatment of superficial BCC. A study is currently under way using EDC to eliminate the lesion and imiquimod applications post-surgery, with the potential for eliminating residual malignant basal cells.

Superficial BCC on Back

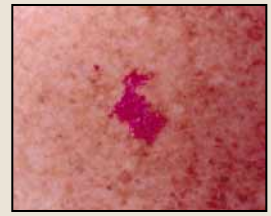

Photo 1. This fair-skinned, blue-eyed patient presented with a 2-cm red, scaly, well-circumscribed plaque on the right upper back.

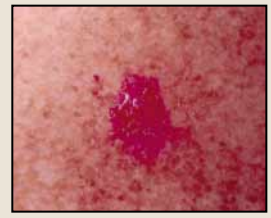

Photo 2. By the third week of treatment with imiquimod, erythema, edema, and mild discomfort had developed; however, no interruption in therapy was necessary.

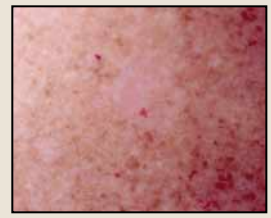

Photo 3. Twelve weeks after cessation of imiquimod therapy, the area is clinically clear.

Photos courtesy of Amit G. Pandya, MD

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Verruca Vulgaris of the Digits

Case: 52-Year-Old Male

- Patient presented with periungual warts involving all digits on both hands (**Photo 1**); lesions had first appeared 5 years previously.
- No family history of warts; no history of immunosuppressive therapy or illness.
- Previous treatment by other clinicians had included CO_2 laser and pulse-dye laser, at a total estimated out-of-pocket cost of $10,000.
- Lesions causing severe disability; this patient, an accountant, was having difficulty performing essential fine motor functions with his hands, including fastening buttons, tying shoelaces, and using a computer keyboard.
- Treatment strategy and results: A daily regimen consisting of multiple agents was tried: mornings, application of 40% urea gel and, because of anecdotal reports of the benefits of cimetidine in warts, oral esomeprazole magnesium 40 mg; afternoons, application of tea tree oil; evenings, imiquimod under occlusion with duct tape. After 4 weeks of this regimen, the warts turned purple and resolved. At 2 months following cessation of therapy, the patient's hands remained clear (**Photo 2**). There was no residual pain or tenderness at the digital tips.
- Final report: This patient has been followed every 2-3 months since cessation of therapy. After 1 year, his hands remain clear. He is able to perform all activities of daily living and the fine motor skills required in his occupation.

Multiple Periungual Warts of Fingers

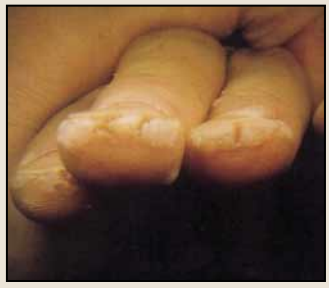

Photo 1. This patient's periungual warts caused him severe pain and difficulty in functioning.

Photo 2. After 4 weeks of treatment, the warts resolved; at 2 months posttherapy (shown here), the patient is able to function and has no pain or tenderness at the digital tips.

Photos courtesy of May J. Chow, MD

Discussion

This patient's discomfort and disability from multiple warts at the digital tips, along with the failure of a number of previous treatments and the prospect for long-term future disability arising from further treatment, made this an extremely challenging case.

Cryosurgery would have been extremely painful. Intralesional bleomycin would have been an option if the warts were located more proximally, but would have been contraindicated to treat lesions at the digital tips because of the risk for vasospasm, Reynaud's phenomenon, and digital tip necrosis. Cantharidin, with or without occlusion, is a good therapy for periungual warts, except in this case; the resulting blisters would have rendered this patient even more disabled than he was already.

Destruction of warts with acids—such as trichloroacetic acid, bichloroacetic acid, or salicylic acid—can be effective for common warts but, again, application at the digital tips would have been problematic. Electrodesiccation and laser therapy carry the risk of scarring and resulting permanent loss of tactile sensation. Sensitization therapy with agents such as dinitrochlorobenzene works by evoking allergic contact dermatitis, which, on the tips of the fingers, would have been exquisitely uncomfortable.

Other wart treatments that have been proposed and tested, but that have failed to show reasonable efficacy in controlled clinical trials, include hypnosis, cimetidine, and hyperthermia (soaking in water heated to 110 degrees Fahrenheit for 20 minutes).

More-radical proposed treatments include injections of candidin or mumps. Candidin injection is believed to work by inducing a T-cell immunity response—essentially, contact dermatitis. One study indicates that candidin injection is associated with a success rate exceeding 80%.[1] However, patients were eliminated from enrollment in this study if they did not test positive for candidin sensitivity, so the success rate in a random population is likely to be far lower than the experience in this study. The success rate reported for mumps injection was about 50%, comparable to what is seen with cryotherapy.[2] Although this strategy might be worth trying in recalcitrant cases of warts at other sites, the discomfort associated with

the resulting dermal hypersensitivity would likely be unbearable for patients with warts at the digital tips, as in this case.

This clinician's strategy involved immune response modifier treatment, which is a departure from the notion of the standard destructive therapies. Generally, experience with imiquimod monotherapy in the treatment of warts has not yielded impressive results. However, in this case, imiquimod was combined with destructive therapy and occlusion to enhance penetration of the drug and maceration of the wart tissue. ■

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Actinic Keratosis continued from page 5

patient discomfort in a highly sensitive location. Carbon dioxide (CO_2) laser treatment usually is painful, but it has the advantage of good efficacy and elimination of the lesion in just one treatment. Hypopigmentation or scarring is a risk with CO_2 lasers, but the risk is minimal in the hands of a skilled clinician.

Treatment with 5-FU or with imiquimod are also good options. Recently, Smith and colleagues[4] published the results of their experience with 15 patients with actinic cheilitis treated with imiquimod. In all cases, the lesions had resolved by the end of treatment. ■

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Conclusion

Much is already known about the relatively new class of drugs referred to as immune response modifiers. Nevertheless, the research that is needed—and will eventually be done—in the field of immune response modifiers (IRMs) really has just begun. For example, the appropriate dosage schedules of the IRM imiquimod for various dermatologic conditions is yet to be determined and, in fact, may vary with individuals and clinical entities. Several of the well-controlled clinical trials that provide evidence regarding the use of IRMs have been completed or are nearing completion; others are under way or are planned. Based on the data available to date, as well as the clinical experience accumulated thus far, it seems likely that IRMs will have an expanding role in dermatology.

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Instructions: For each question or incomplete statement, one answer or completion is correct. Circle the most appropriate response. Seven correct responses are required for credit.

1. The standard treatments for small, nodular basal cell carcinoma include:
   a. Electrosurgery **c.** Both A and B
   b. Electrodesiccation **d.** Neither A nor B

2. The standard treatments for large, superficial basal cell carcinoma include:
   a. Mohs' micrographic surgery **c.** Both A and B
   b. Surgical excision **d.** Neither A nor B

3. Which one of the following statements is *not true* concerning Bowen's disease (squamous cell carcinoma in situ)?
   a. Curettage and desiccation is an accepted, standard treatment.
   b. 5-fluorouracil is an FDA-approved, standard treatment.
   c. This cancer is considered in situ, but the lesion is not just superficial.
   d. To be an effective treatment, a cryotherapy freeze must be exceptionally hard.

4. Honey-colored crusting at a site of treatment with imiquimod:
   a. indicates that impetiginization has occurred
   b. indicates the need for empiric antibiotic treatment, regardless of whether a culture is done
   c. is a characteristic of inflammation known as cytokine dermatitis
   d. should be cultured to determine whether the wound is infected

5. With extramammary Paget's disease:
   a. lesions are seldom contiguous and skip areas are common
   b. Mohs' micrographic surgery is a standard treatment
   c. standard treatment yields a high, long-term cure rate
   d. underlying, associated malignancies are usually identified in the genitourinary area

6. Among the treatments proven effective for eliminating actinic keratoses, the most commonly used is:
   a. cryotherapy **c.** 5-fluorouracil
   b. diclofenac **d.** photodynamic therapy

7. The most important skin disease in patients who have undergone organ transplant surgery is:
   a. basal cell carcinoma
   b. human papillomavirus infection
   c. squamous cell carcinoma
   d. wound infections secondary to destructive treatments for lesions

8. The two main therapeutic challenges with actinic cheilitis are:
   a. cosmetic outcome and recurrence
   b. discomfort and cosmetic outcome
   c. discomfort and development of malignancy
   d. recurrence and development of malignancy

9. Treatments for warts that have been tested in controlled clinical trials and failed to demonstrate any benefits include all of the following *except*:
   a. candidin **c.** hyperthermia
   b. cimetidine **d.** hypnosis

10. Electrodesiccation, usually a good therapeutic option for destruction of common warts, would not be the treatment of choice for a patient with periungual warts at the digital tips because of the risk for:
    a. digital tip necrosis
    b. permanent loss of tactile sensation
    c. Reynaud's phenomenon
    d. vasospasm

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