Hypertrophic Lichen Planus–Like Reactions Combined With Infundibulocystic Hyperplasia

Pathway to Neoplasia

Steven Kossard, FACD; Carol Thompson, PhD; Gary M. Duncan, FRACS

Background: Retinoids have the capacity to accelerate the involution of multiple keratoacanthomas, including unusual variants such as keratoacanthoma marginatum centrifugum and keratoacanthoma en plaque that may persist and be associated with progressive growth and provide difficulties in diagnosis and management.

Observations: We describe 3 patients who had unusual infiltrated and keratotic plaques affecting the lower legs or nasolabial area that persisted or recurred that may be related to this group of unusual keratoacanthomas. The 3 patients had differing clinical lesions that did not resemble classic keratoacanthomas, but were linked by their biopsy findings of hypertrophic lichen planus–like reaction and pseudoepitheliomatous hyperplasia with a prominent infundibulocystic component that progressed to multiple keratoacanthomas or infundibulocystic squamous cell carcinoma. Polymerase chain reaction analysis of biopsy material from 2 patients failed to detect human papillomavirus. All 3 presentations provided a therapeutic dilemma, but responded rapidly to acitretin treatment at a dosage of 10 to 25 mg daily, which was continued for 15 to 24 months.

Conclusions: These cases illustrate an unusual reaction pattern that is hypertrophic lichen planus–like but, instead of evolving to classic lichen planus, progresses to infundibulocystic hyperplasia and the development of multiple keratoacanthomas or infundibulocystic squamous cell carcinomas. Retinoids represent a therapeutic option for this difficult clinical problem and may obviate repeated and extensive surgery.

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Keratoacanthomas usually arise as solitary lesions but may occasionally present as multiple lesions or as unusual variants such as keratoacanthoma marginatum centrifugum or keratoacanthoma en plaque. These unusual variants may persist and can be associated with progressive growth and provide difficulties in classification, particularly in reference to squamous cell carcinomas and their treatment. Retinoids have been used successfully to treat all variants of keratoacanthoma and appear to accelerate their involution, possibly by promoting differentiation. The relationship of keratoacanthoma and squamous cell carcinoma has been a subject of debate, and even the use of newer probes capable of quantitating proliferation markers and detecting abnormalities in tumor suppressor genes and upgraded cellular oncogenes has not provided an answer.

We describe 3 patients who had unusual infiltrated keratotic plaques that were progressive and may be related to this group of unusual persistent keratoacanthomas. The 3 patients had differing clinical presentations that did not resemble classic keratoacanthoma but were linked by their biopsy findings, which showed pseudoepitheliomatous hyperplasia combined with hypertrophic lichen planus–like areas and infundibulocystic follicular hyperplasia merging with keratoacanthoma or infundibulocystic squamous cell carcinoma. Infundibulocystic squamous cell carcinoma may be a more appropriate term for tumors that fail to fulfill the clinical and histologic features of keratoacanthoma but share a common path of initial follicular infundibulocystic hyperplasia. The atypical clinical appearance, lack of spontaneous involution, and deeply infiltrative growth of cords of atypical keratinocytes on biopsy are key clues to the diagnosis of infundibulocystic squamous cell carcinoma. These infundibulocystic follicular tumors share the capacity, in some cases, to respond to acitretin treatment, but their identification may be delayed because of the unusual reaction pattern dominated by hypertrophic lichen planus–like lesions with infundibulocystic hyperplasia.


REPORT OF CASES

PATIENT 1

An 86-year-old woman developed a keratotic papule on the lower left pretibial area. The papule grew gradually during 6 months into a large plaque measuring 5.5 cm x 4.0 cm in diameter (Figure 1A). The plaque had a violaceous color and an elevated keratotic rim. The patient had been referred to a plastic surgeon, who was reluctant to excise the plaque because of her poor general health. Her medications included enalapril maleate, atenolol, diltiazem hydrochloride, and frusemide for hypertension and cardiac failure. The patient had previous skin cancers that had been removed from her nose and lip. General skin examination revealed evidence of long-term solar damage but no other lesions resembling lichen planus. A skin biopsy specimen from the keratotic nodule showed pseudoepitheliomatous hyperplasia and lichenoid inflammation.

Acitretin was prescribed at a dosage of 10 mg daily and was increased to 20 mg after 2 weeks. The patient was unable to tolerate this dosage, and the acitretin was reduced to 10 mg again. After 3 months at this dosage, the plaque had flattened and was no longer infiltrated. At 6 months’ follow-up, the patient had a series of lichenoid plaques resembling lichen planus on the right leg (Figure 1C) corresponding to keratoses that had been treated with cryotherapy by her local referring physician. The plaque on the left leg had completely resolved. Therapy with acitretin, 10 mg daily, was continued, and at the 1-year follow-up, all the lichenoid lesions had cleared, with no recurrence of the plaque on the left leg (Figure 1D).

PATIENT 2

A 73-year-old man, after trekking in Kathmandu (Nepal), developed rhinorrhea and a vegetative nodule over the left side of the columella of his nose. During the following month, the lesion became ulcerated and an indurated erythematous plaque developed below the nose extending to his upper lip (Figure 2A). An initial biopsy specimen from the nasal nodule showed pseudoepitheliomatous hyperplasia. Cultures grew Proteus organum. Hyperplastic lobules of keratinocytes demonstrated premature keratinization and focal atypia projected into the mid dermis (Figure 1B). These findings were reported as squamous cell carcinoma arising in a background of infundibulocystic pseudoepitheliomatous hyperplasia with lichenoid inflammation.

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Figure 1. A, Violaceous plaque with keratotic rim on the left leg, B, Skin biopsy specimen demonstrating infundibulocystic hyperplasia with lichenoid inflammation and irregular lobules of keratinocytes penetrating into the mid dermis (hematoxylin-eosin, original magnification ×40). C, Violaceous lichen planus-like reaction on the right leg at sites of cryotherapy. D, Appearance of the left leg 1 year after commencing treatment.
acitretin was continued for 20 months, and the area remained clear of recurrent tumor a year after stopping the drug.

PATIENT 3

A 76-year-old man recalled that 30 years before consultation he had sustained a hot water burn to both lower legs, which had resulted in extensive blisters that had taken 5 weeks to heal. Two years before consultation, 2 small keratotic papules had developed on his right lower leg that were excised by his local physician. The pathologic findings had been reported as well-differentiated squamous cell carcinoma with lichenoid inflammation. Seven months later, the papules recurred, were reexcised, and were reported as showing only pseudoepitheliomatous hyperplasia with lichenoid inflammation. One year before consultation, 2 infiltrated nodules developed on his other leg. A punch biopsy specimen was reported as squamous cell carcinoma with lichenoid inflammation. He was referred to a plastic surgeon, who excised both lesions on the left calf and performed skin grafts. The surgical specimen showed pseudoepitheliomatous hyperplasia with lichenoid inflammation. Two months later, 2 keratotic and infiltrated papules on the right calf were removed, with skin grafting. The pathologic findings were reported as representing keratoacanthomas. During the subsequent 6 months, both grafts developed recurrent nodules. At the time of his initial consultation at our center, there were 2 violaceous hyperkeratotic nodules measuring 2 cm in diameter within the graft on the right calf and a violaceous papule within a scar below the graft. The left skin graft was totally replaced by confluent keratotic and verrucous nodules that were separated by fissures (Figure 3A). The skin graft donor site was unaffected. There was no associated lymphadenopathy, and the rest of the clinical examination showed no evidence of lichen planus or other skin cancers. The patient was taking prazosin hydrochloride, dipyridamole, and temazepam, as well as perindopril erbumine, which had been substituted for amlodipine besylate 1 month before consultation. A biopsy specimen taken from the verrucous keratotic plaque from the left graft showed multiple infundibulocystic cavities par-
tially outlined by lichenoid inflammation. These extended into the deep dermis. Under the base of the cystic cavities, there were irregular cords of keratinocytes that showed premature keratinization and focal nuclear atypia (Figure 3B). A biopsy specimen from the nodule on the right calf showed a central cavity, under which there were lobular clusters of keratinocytes extending into the mid dermis (Figure 3C). In areas, there was an infundibulocystic component, and the lobules were associated with focal lichenoid inflammation. There was focal nuclear atypia and a disorganized pattern of maturation. The biopsy specimen of the papule below the graft and within a scar showed changes that were identical to those seen with hypertrophic lichen planus. These findings were equated with squamous cell carcinoma arising in the background of lichenoid pseudoepitheliomato- nous infundibulocystic hyperplasia and hypertrophic lichen planus–like reaction. Acitretin was prescribed at a dosage of 25 mg daily, and within a month, the nodules over both grafts were disintegrating and the infiltrative areas were resolving. The violaceous plaque below the graft on the right leg had resolved. The dosage of acitretin was reduced to 10 mg daily, but 4 months later, 2 further nodules emerged over the left graft and the treatment regimen acitretin was again increased to 20 mg daily, with clearance. At the 10-month follow-up, all areas were free of tumor, including the left graft (Figure 3D). The acitretin regimen was continued for 2 years and then discontinued, without recurrence after 6 months of stopping the drug.

POLYMERASE CHAIN REACTION ANALYSIS FOR HUMAN PAPILLOMAVIRUS

Paraffin-embedded tissue was used for polymerase chain reaction analysis for human papillomavirus (HPV) in biopsy specimens taken from patients 2 and 3. Sets of consensus primers designed to amplify a wide range of mucosal and cutaneous HPV types were applied. Amplification of a sequence of the human β-globulin gene served as a control for amplifiable DNA. The primers and amplification protocols for the detection of HPVs in this study have been previously described. All specimens were positive for β-globulin, but, despite repeated testing, none produced positive signals with any of the HPV consensus primer sets used.

COMMENT

Despite the differing clinical presentations, these cases are linked by their histologic findings and response to acitretin treatment. The histopathologic findings were characterized by epidermal and follicular hyperplasia producing pseudoepitheliomatous features with a prominent infundibulocystic component. A prominent lichenoid reaction was also a common feature and resembled hypertrophic lichen planus or lichen planopilaris. The large violaceous plaques and lichenoid patches that followed cryotherapy in patient 1 and the violaceous papule in the scar in patient 3 resembled lichen planus, but there was no evidence of lichen planus at other sites. Lichenoid reactions are commonly seen as a host response to skin malignancies, including nonmelanocytic tumors, actinic keratoses, keratoacanthomas, and squamous cell carcinomas. These reactions present as lichenoid keratoses and may resemble solitary lichen planus. In our patients, pseudoepitheliomatous hyperplasia with lichenoid reactions in association with follicular infundibulocystic hyperplasia presented as hyperplastic lichen planus–like nodules or plaques. Such lesions may provide a pitfall in diagnosis and require multiple biopsy samples that extend into the deep tissue. In 2 of our patients, infiltrating cords of atypical keratinocytes were present in the deep dermis and were masked by overlying lichenoid infundibulocystic follicular hyperplasia. Although squamous cell carcinoma may develop in the setting of classic hypertrophic lichen planus, this usually emerges in the background of long-standing lichen planus, in contrast to the short history and early lichenoid reactions seen in our patients.

The distinction between pseudoepitheliomatous hyperplasia and squamous cell carcinoma can be problematic. Pseudoepitheliomatous hyperplasia may merge with squamous cell carcinoma. The histopathologic findings of pseudoepitheliomatous hyperplasia usually reveal bulbous acanthotic down-growth of the epidermis and usually involve the follicular infundibular canals and sweat ducts. The phenomenon of pseudoepitheliomatous hyperplasia may occur, particularly in the wake of injury or surgery and as a response to different infections. These factors were present in our patients, one of whom developed the reaction in his skin grafts and the other as a vegetative nasal nodule after trekking in Kathmandu. The shin is particularly prone to injury and appears to be a common site associated with infundibulocystic follicular reactions that can be difficult to classify. Multiple biopsy specimens of the vegetative nodule failed to reveal suppurative granulomas or abscesses typical of an infective process, and the biopsy findings were a key to diagnosis and management. The presence of lichenoid inflammation in addition to pseudoepitheliomatous hyperplasia was an important clue in recognizing our cases.

The clinical presentations and histologic findings in our patients also raised the issue of whether the tumors represented unusual variants of keratoacanthoma. Keratoacanthomas have been observed in the setting of lichen planus and have developed within skin grafts or their donor sites and at sites of trauma. There appears to be a close relationship of some keratoacanthomas to the infundibular portion of follicles. Keratoacanthomas often are associated with infundibulocystic hyperplasia and can result in squamous metaplasia of the sweat duct apparatus. The clinical presentation of the plaque in patient 1 shares features with keratoacanthoma marginatum centrifugum and in patient 3, the confluent verrucous keratotic plaque over the graft may be compared with keratoacanthoma en plaque. These are unusual keratoacanthomas, often associated with a progressive history, and they may not readily involute. This pattern differs from that of classic keratoacanthoma. We prefer to classify our cases as examples of pseudoepitheliomatous hyperplasia with a prominent infundibulocystic component outlined by lichenoid...
inflammation, and the emerging tumors as infundibulocystic squamous cell carcinoma rather than keratoacanthomas. In contrast to previous cases of keratoacanthoma marginatum and keratoacanthoma en plaque, our patients’ initial lesions were dominated by changes that resembled hypertrophic lichen planus rather than discrete keratoacanthomas. The term infundibulocystic squamous cell carcinoma may be more appropriate for tumors that may not resemble keratoacanthoma clinically, have a prominent infundibulocystic component, and do not follow the biological course of keratoacanthoma.

The frequency of detecting HPV in keratoacanthomas in previous studies has varied. We were unable to demonstrate the presence of HPV by polymerase chain reaction analysis using several consensus HPV primer sets on tissue extracts from 2 of our patients. There were no papilloma-related viral cytopathic changes in the biopsy material, but these findings do not exclude the possible presence of HPV as a cofactor.

All 3 of our patients provided a therapeutic dilemma, as the tumors were difficult to treat surgically. The presence of infiltrative cords or lobules of atypical keratinocytes in the deep dermis under the infundibulocystic pseudoepitheliomatous hyperplasia was a feature that made us favor the diagnosis of squamous cell carcinoma. Even in the absence of proven squamous cell carcinoma, these marked hyperplastic reactions represent a therapeutic challenge. Retinoids have been used successfully to slow the development and reduce the number of solar keratoses and squamous cell carcinomas, particularly in transplant patients receiving immunosuppressive therapy. Retinoids have also been shown to accelerate the involution of keratoacanthomas and have been useful in the management of unusual variants of keratoacanthoma, including keratoacanthoma marginatum centrifugum and keratoacanthoma en plaque. We had previously used acitretin to successfully treat a patient who had hypertrophic lichen planus–like reaction in a burn scar and biopsy specimens that showed pseudoepitheliomatous hyperplasia and early squamous cell carcinoma. Because of the age of our patients, we chose a conservative dosage of 25 mg daily of acitretin to minimize adverse effects. We did not need to increase the dosage higher than 25 mg daily, as there was response to treatment in the first month. One of our patients only tolerated 10 mg of acitretin daily, but even this dosage resulted in a halt of the progression of her tumors and gradual involution of all lesions. We monitored all patients carefully, as we were concerned that these tumors may have progressed. Previous experience has indicated that skin malignancies and keratoses may rebound if retinoids are ceased, particularly in immunosuppressed patients. Lowering the dosage of acitretin in one of our patients resulted in the reappearance of nodules in the skin graft, but these resolved again by elevating the dosage. The main adverse effects observed in all 3 patients were those related to retinoids, namely, dry skin and hair loss. The 3 patients did not have a strong history of skin cancers and were not immunosuppressed, and the acitretin was discontinued after 15 to 24 months. Although we cannot exclude the possibility that the results of therapy were due to spontaneous involution, each patient had a prolonged course with tumor progression before the introduction of retinoid therapy.

Our observations suggest that there is a subgroup of patients who develop hypertrophic lichen planus–like reactions with infundibulocystic follicular hyperplasia that may progress to follicular-based squamous cell carcinomas. These tumors may be related to keratoacanthomas, but may be more appropriately classified as infundibulocystic squamous cell carcinoma. The identification of this subset of squamous cell carcinoma in the setting of hypertrophic lichen planus–like reactions may be important, as acitretin offers a potential alternative to difficult surgery and, at least in some cases, can induce tumor regression and settle the lichenoid epidermal hyperplasia.

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Correspondence: Steven Kossard, FACD, Skin & Cancer Foundation Australia, 277 Bourke St, Darlinghurst, New South Wales, Australia 2010 (skossard@scfa.edu.au).

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