Eruptive Keratoacanthoma in a 59-year-old Female with Chronic Kidney Disease: A Case Report and Review of Treatment Approaches

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ABSTRACT

We present the case of a 59-year-old female with multiple squamous neoplasms, including keratoacanthomas, well-differentiated squamous cell carcinomas, and prurigo nodules. The patient developed dozens of lesions progressively over the course of a few years. Keratoacanthomas can be challenging to distinguish from well-differentiated squamous cell carcinomas; this and the presence of numerous lesions poses a major challenge with diagnosing and managing this condition. The pathogenesis, challenges with diagnosis and management, and treatment regimens for eruptive keratoacanthomas are further discussed.

INTRODUCTION

Keratoacanthoma (KA) is a low-grade tumor of the skin that appears as a rapidly growing, dome-shaped papule in sun-exposed areas of the body.1 Clinically, KAs may present as solitary or multiple lesions due to sporadic development, an underlying inherited syndrome, or in association with chronic inflammation.2 These lesions tend to develop with a rapid onset followed by relative tumor stability and eventual regression. The most common subtype presents as a single lesion with a central keratin-filled crater that may regress without intervention, though many are biopsied to rule out other diagnoses such as squamous cell carcinoma (SCC), amelanotic melanoma, Merkel cell carcinoma, and cutaneous infections.3 4 Despite many shared histological features between KA and SCC, most authors regard KA as benign.5 However, due to the ambiguity and difficulty with histological differentiation between KA and invasive well-differentiated SCC, and sometimes only partial sampling techniques, current guidelines recommend surgical excision for KAs to ensure treatment of potential malignancy.1

While the most common variants of KAs manifest as sporadic and solitary lesions, a number of syndromes have been described in which individuals develop hundreds to thousands of KAs.6 Unlike solitary KAs, multiple KA syndromes affect the skin regardless of sun exposure.7 Although the mechanism of progression for multiple KA syndromes is poorly understood, risk factors are known to include a state of chronic injury, inflammation, or immunosuppression.6
Multiple KA syndromes may be familial or sporadic and are classified into different subtypes based on specific disease criteria and characteristics. A correct diagnosis of multiple KA syndrome provides medical treatment options other than surgical methods used for conventional solitary KAs and well-differentiated SCCs and provides an opportunity to avoid surgical overtreatment of lesions.

**CASE REPORT**

We report the case of a 59-year-old Caucasian female who presented with a 5-year history of disseminated skin lesion development on her upper and lower extremities, sparing the trunk, head, and neck associated with extreme pruritus (Figure 1). Her medical history was significant for a 4-year history of stage 4 chronic kidney disease as well as a 36-year history of type 2 diabetes mellitus. Analysis of peripheral blood and serum biochemistry revealed a hemoglobin A1c of 5.8%, estimated Glomerular Filtration Rate (eGFR) of 22, creatinine of 2.37, and BUN of 37. Her social history consisted of 10+ pack years of tobacco use and 10+ years of daily alcohol consumption. The patient’s family history was noncontributory.

Biopsies and excisions were taken for diagnostic and curative reasons. Histopathology of the submitted specimens revealed two prurigo nodules on deep shave saucerizations (Figure 2), three well-differentiated SCCs on deep shave saucerizations, KA-type SCCs on two excisions (Figure 3), and well-differentiated invasive SCC on three excisions (Figure 4). All specimens were examined by dermatopathologists. Features of perforating diseases, such as collagen or elastic fiber degeneration and expulsion through the epidermis, were not seen in the submitted specimens. In light of the abundance of her lesions, further diagnostic workup was initiated to determine her risk of metastasis. One of the well-differentiated SCCs was sent for molecular testing via DecisionDx-SCC. Results of the test determined the patient to be in a Class 1 category, which is associated with a low risk of metastasis within a 3-year period.

![Figure 1. Lesions on the upper and lower extremities.](image1)

![Figure 2. Histopathology of prurigo nodule on deep shave saucerization.](image2)
Figure 3. Histopathology of excised KA-type SCC at (A) 4x power and (B) 10x power.

Figure 4. Histopathology of well-differentiated invasive SCC on excision.
Given the diffuse nature of her lesions, oral Acitretin 25mg once daily was initiated. After three months of therapy, new lesions ceased to develop, and existing lesions decreased in size. However, the patient reported significant levels of pruritus and xerosis associated with Acitretin, which led to the patient discontinuing Acitretin. Going forward, our plan is to begin intralesional triamcinolone acetonide injections once every four weeks in an attempt to alleviate pruritus associated with her lesions and potentially reduce the possibility of overlapping reactive epithelial changes leading to prurigo nodularis-like lesions. The patient may also benefit from Unna boot applications to help protect the lesions from manual trauma due to pruritus, also leading to reactive prurigo nodularis-like changes. Unna boots may be combined with topical 5-fluorouracil each week for a 4–6-week period to target the patient’s hyperplastic epithelial neoplasms (prurigo nodules, KAs, well-differentiated SCC). The patient will continue to be carefully observed on a regular basis to monitor for development of high-grade squamous cell carcinomas with higher morbidity potential, requiring more aggressive surgical treatment.

**DISCUSSION**

KAs may present as solitary or multiple lesions; multiple KAs can be further divided into the Ferguson-Smith and Grzybowski’s eruptive KA syndromes. Ferguson-Smith syndrome is an autosomal dominant variant of multiple KA syndrome seen predominantly in individuals of Scottish descent. These patients present during adolescence with multiple KAs that tend to spontaneously regress, resulting in the formation of an atrophic scar. The other form of multiple KA syndrome, Grzybowski’s eruptive KA (GEKA), was first described by Grzybowski in 1950 and published under the title “A Case of Peculiar Generalized Epithelial Tumors of the Skin”. This particular variant of multiple KA syndrome is sporadic and characterized by some (see below) as an abrupt or progressive development of hundreds to thousands of small 0.5cm to 1cm KAs during the fifth to seventh decade of life on the torso and extremities, sometimes involving the palms, soles, genitals, and mucous membranes of the lips and eyelids.

Despite continued reports of new GEKA cases since its discovery in 1950, the medical community has failed to establish a definitive set of diagnostic criteria for the condition. Nofal et al. have proposed the following as potential criteria for GEKA diagnosis: generalized eruption of multiple well-demarcated papules with some having a keratotic center, lack of family history, onset in adulthood (most often fifth to seventh decade), and severe and persistent pruritus. Variable features include the presence of mucosal lesions, masked facies, and ectropion. Some of our patient’s presentation, such as histological findings of KAs, late onset of presentation during the fifth decade of life, lack of family history, and severe pruritus all point to a diagnosis of GEKA. Other characteristics of our patient favor the diagnosis of Eruptive Squamous Atypia (ESA), given her lesions were confined to her extremities, accessible to picking and koebnerization, and some lesions not meeting diagnostic criteria for KAs and showing features of prurigo nodules and well-differentiated SCCs. In real-life clinical settings, many patients present with overlap features of entities with multiple generalized KAs, and this contributes to the difficulty in the literature to consistently define GEKA. Therefore, we propose our patient may have overlapping features of GEKA and ESA. The distinction may only be of
A unique challenge of managing GEKA/ESA is differentiating clinical and histological features of well-differentiated SCC (that require surgical intervention) from multiple eruptive KAs and reactive hyperplasia and atypia as a result of chronic scratching and picking (that require more conservative treatment approaches). In practice, to distinguish a true neoplastic carcinoma from a low-grade generalized KA or reactive squamous proliferation, clinicians often rely on clinical features such as duration, morphology, and growth rate. While this information can be helpful, studies suggest that these features are extremely variable and unreliable as diagnostic criteria. Histopathology and distinctive microscopic criteria, mainly architectural silhouette of completely excised lesions and degree of epithelial atypia, have been proposed in distinguishing between KAs/reactive squamous proliferations and well-differentiated SCCs on the other side. In spite of these suggested criteria, differentiating the two histologically continues to be a challenge due to shared silhouette, cytology, and architectural growth patterns. A study conducted by Criber et al. examining pathology features of 296 KA and SCC found that the criteria historically used to differentiate these lesions is unreliable. They observed that the 5 most useful criteria in distinguishing between KAs (epithelial lip, sharp outline between tumor and stroma) and SCCs (ulceration within the tumor, numerous mitoses, marked pleomorphism) did not significantly increase the sensitivity and specificity of a histological diagnosis. While recent studies have shown potential in differentiating SCCs from KAs using apoptotic and cell adhesion markers, further research is necessary before such techniques can be implemented into clinical practice.

The biopsy method has also been observed to affect the diagnosis of KA versus SCC. According to Popkin et al., biopsy specimens obtained via shave, partial punch, or piecetrain provide inadequate tissue for a pathologist to examine when suspecting a diagnosis of KA. The downfall to these methods is the inability to consistently obtain the base or overall architectural silhouette of the lesion. This increases the possibilities of overlooking a more aggressive and invasive growth pattern. Therefore, a fusiform sample obtained via scalpel excision is regarded as the recommended technique when suspecting KA. As the majority of our patient’s biopsies were obtained via shave and saucerization, we question the degree to which KAs may have been misdiagnosed as SCCs. As a result, individuals like our patient presenting with GEKA/ESA overlap features may have biopsy reports indicating both KAs and well-differentiated SCCs.

A variety of systemic and topical agents have been explored in the treatment of GEKA and ESA, but none are considered to be satisfactory. For singular KAs, treatment via surgical excision or other physical modalities including cryotherapy, laser ablation, and curettage have been well described. Topical agents such as 5-fluorouracil, tretinoin, imiquimod, bleomycin, and methotrexate have also been utilized. However, some of these methods pose challenging to use in GEKA and ESA due to the diffuse nature of lesions in these patients. Therefore, systemic therapy represents the most practical approach in management of GEKA and ESA. Oral retinoids such as isotretinoin and acitretin are proposed as first-line agents, although response to these medications is variable. Our patient responded well to a three-month trial of 25
mg Acitretin, where her lesions decreased in size and no new lesions were noted. However, the response to systemic retinoids in GEKA and ESA patients is incredibly variable; some patients experience minimal or no improvement following treatment.\(^\text{18}\)

Because our patient became non-adherent to systemic retinoids due to side effects, treatment with intralesional triamcinolone acetonide and weekly application of an Unna boot combined with topical 5-fluorouracil cream until achieving treatment goal were discussed. Sanders et al. reported a case in which treatment with intralesional triamcinolone acetonide in a GEKA patient resulted in complete clearance of lesions and minimal scarring within 2-4 weeks.\(^\text{19}\)

Compared to intralesional methotrexate and 5-fluorouracil, which are both commonly used in practice, intralesional triamcinolone acetonide holds the benefit of immediately reducing inflammation and itching in the patient. Advocates of intralesional triamcinolone acetonide believe eruptive KAs are reactive in nature and due to low-grade cutaneous injury or inflammation.\(^\text{20}\)

Supplemental weekly treatment with topical 5-fluorouracil wrapped with an Unna boot has also shown to be effective for inducing KA regression.\(^\text{20, 21}\) Use of an Unna boot containing zinc oxide further reduces inflammation, promotes healing, and provides a physical barrier to prevent further trauma inflicted by the patient scratching intensely itchy lesions and thereby potentially perpetuating lesions or contributing to reactive changes such as prurigo nodules and reactive squamous hyperplasia.\(^\text{20}\)

This case describes a 59-year-old female with generalized KAs, prurigo nodules, and well-differentiated SCCs on her extremities, demonstrating characteristic features of GEKA and ESA. Because KAs and well-differentiated SCCs have similar clinical and histologic features, it is often a challenge to diagnostically distinguish the two. While three months of oral Acitretin therapy was mildly effective in our patient, adherence to treatment was inconsistent due to intolerable xerosis and worsening pruritus. Our treatment plan moving forward will include continued systemic therapy with Acitretin at a reduced dose of 12.5 mg daily, intralesional triamcinolone acetonide every four weeks, and weekly topical 5% fluorouracil covered by an Unna boot on one leg at a time for 4-6 weeks. With our patient’s comorbidities of diabetes and chronic kidney disease, we plan to monitor complete blood count (CBC), renal function, blood glucose, and fasting lipid profile throughout treatment.

**Patient Consent:** Consent for the publication of recognizable patient photographs or other identifiable material was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

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**CONCLUSION**

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