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Case Report

A rare case of multiple keratoacanthomas of Grzybowski

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Abstract Generalized eruptive keratoacanthoma (GEKA) of Grzybowski is a rare variant of keratoacanthoma with an unclear pathophysiology. GEKA originates from the hair follicle with a keratotic center and shows histological features of keratoacanthoma. Herein, we report a case of a female 79 years of age with multiple pruritic eruptions over sun-exposed areas, including facial involvement with ectropion. GEKA represents a diagnostic and therapeutic challenge due to the lack of distinct clinical presentation and efficient treatment.

Key words
Keratoacanthomas; Ectropion: Hair follicles.

Introduction

Keratoacanthoma (KA) is a type of skin tumor that is solitary and generally locally aggressive. Although considered benign in most cases, it tends to grow rapidly over a period of weeks to months and can reach a considerable size. It originates from the glandular portion of the hair follicle with sporadic involvement. There have been reports of patients with multiple KA as in the Ferguson-Smith syndrome, Muir-Torre syndrome and multiple eruptive type Grzybowski**.**[1-2] Generalized eruptive keratoacanthoma (GEKA) of Grzybowski is a rare disease with an unknown etiology which affects the skin and mucous membrane. It was described by Grzybowski in 1950, hence the name**.**[2] There have only been about 48 cases reported in literature so far. It usually presents itself in the fifth to seventh decades of life, predominantly in sun-exposed regions with multiple pruritic papules, sometimes with keratotic centers.[1-3] Treatment is difficult due to paucity of available data, but oral retinoids seem promising.[3]

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Case Report

A 79 year-old female presented with multiple eruptions, especially over sun exposed areas. These lesions were insidious in onset and caused burning pain and intense pruritis. In addition, she developed raised nodules on both her lower eyelids which caused irritation and discomfort. She denies any history of allergies. There was no history of similar lesion in her family. She gave a history of prior exposure to sunlight in childhood.

On examination she was found to have generalized papules with keratotic centers that tend to coalesce **(Figure 1)**. Small follicular

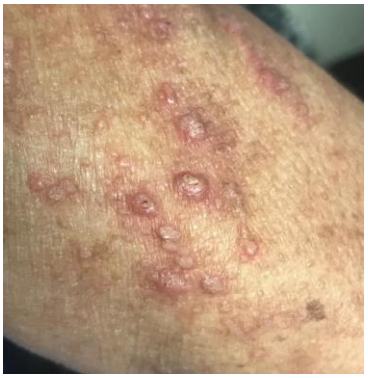

Figure 1 Eruptive domed-shaped papules with hyperkeratotic plug, some infiltrated of different sizes.

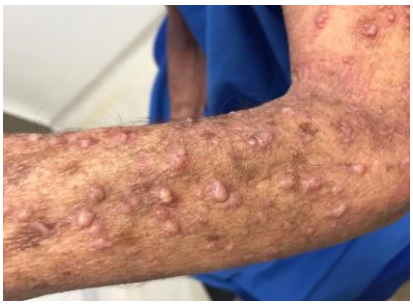

Figure 2 Multiple, flesh-coloured nodules, with sharply sloping borders, some coalescing on her left arm.

Figure 3 Small organized nodules on the ocular tarsal conjunctiva and ectropion in bilateral lower eyelids.

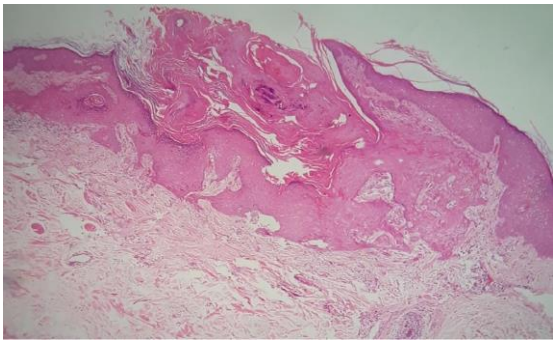

Figure 4 Left elbow (H&Ex2.5). Endophytic tumor with acanthosis, hyperkeratosis and parakeratosis, which deepens to the reticular dermis

papules were found predominantly on the scapula, upper trunk and limbs **(Figure 2).** Bilaterally pinna were studded on both the antihelix and helix with nodules There was no other involvement of the face or mucous membranes except for moderate ectropion **(Figure 3)**.

She was investigated in view of the skin lesions. A biopsy was taken from the lesions along the left elbow which showed an endophytic tumor involving the epidermis, dermis and subcutaneous tissue with irregular architecture. Squamous epithelium was enlarged due to proliferation of keratinocytes with abundant corneal layer and central parakeratosis. The lesion deepened as a single mass to the junction of the reticular dermis with subcutaneous cellular tissue and showed mild lymphocytic inflammation with occasional eosinophils **(Figure 4)**. Considering the histopathology and clinical presentation a diagnosis of GEKA was made. The patient was started on oral retinoids along with topical emollient, she was also referred for further management of the ectropion.

Discussion

GEKA is a chronic and extremely rare variant of KA that affects the skin and mucous membranes.[1,7,16] The disease presents with small, pruritic and painful papules with keratotic centers which tend to coalesce.[12,13,15] It commonly presents in the fifth to seventh decade of life, mostly in white patients with no gender bias.[2,8,12]

The etiology of this disease is unknown with sporadic cases being identified having no genetic basis.[5] Recently, environmental factors such as exposure to sunlight or chemical carcinogens, thermal burns, tar, radiation therapy, and laser therapy were identified as factors which may predispose to its onset.[11] Immunological abnormalities such as interleukin-2 deficiency and genetic predisposition have been postulated as risk factors or mechanisms for the pathogenesis.[7,15] In recent years, DNA from human papillomaviruses (HPVs) has been found in KAs due to advancements in C-reactive protein.

However, the data on this association is conflicting. While HPV has been detected in many solitary KAs, including Witten and Zak variant tumors, GEKAs is likely independent of HPV.[14,17]

GEKA is characterized by a sudden onset of hundreds to thousands of small erythematous follicular papules of 1 to 5 mm size that contain a keratotic plug in the central umbilication that heals with pruritis forming a deep scar.[9,18] It is mostly distributed in areas exposed to the sun and leads to ectropion or masked facies if lesions are located in the periorbital region. Ectropion associated with GEKA, would need surgical management so as to prevent xerophthalmia, conjunctivitis, and, although extremely rare, blindness.[1,4,12,13] The lesions can appear over sun protected sites like the trunk and limbs with preference for intertriginous areas. It is less common over the palms and soles.[2,9,10] The oral mucosa, tongue and oropharynx may be involved causing dysphagia or hoarseness in some cases. [1,4,18]

Though there are no pathognomic signs for GEKA, diagnostic criteria based on constant and variable characteristics were proposed by Nofal *et al*.[6] The constant variables are: history of a few weeks or months, negative family history, progressive course, onset in adulthood typically in the fifth or seventh decade, persistent pruritus, generalized eruption of hundreds to thousands of small follicular papules with a keratotic center; and histopathology: consistent with solitary KA. Variable features include nodules with a central crater, solitary KA, mucosal lesions, and hyperpigmentation on the face around the eyes and may extend to the cheeks also called "fox mask" sign.[6,15,17,18]

The histopathological findings are similar in solitary and the multiple types of KAs.[1] The classic features include a central keratin-filled crater, symmetrical epidermal proliferation at the sides, eosinophilic hyaline keratinocyte and cellular atypia;[2,3] many keratinized horn pearls may also be observed. The dermis consists mainly of inflammatory cell infiltrate of lymphocytes and histiocytes.[8,15]

Differential diagnosis is includes itchy papular eruptions like lichenoid drug reactions, follicular lichen planus, pityriasis rubra pilaris and Kyrle disease.[8] The different variants of multiple KA have unique characteristics e.g. the Ferguson-Smith type presents during adolescence and includes fewer lesions that typically leave depressed scars.[2] Familial KAs of Witten and Zak and Muir–Torre syndrome are autosomal dominant genetic diseases.[10]

The treatment of GEKA is not clearly identified.[1] Topical preparations such as retinoids, 5-fluorouracil, podophyllin, imiquimod and intralesional regimen of corticosteroids, bleomycin, interferon alpha-2b and methotrexate have been tried but have limited efficacy due to the widespread nature of the disease.[8] Surgical interventions are also considered unsuitable.

Systemic therapy is the best way to manage this condition, although it often has disappointing results with significant adverse effects and high recurrence rates.[2,15] Oral retinoids acitretin in particular is preferred as the first line of treatment, because of the antikeratinizing effects result in the regression of lesions and prevent recurrences;[1,12] however, the use of acitretin can aggravate ectropion in some cases.

Grine *et al.* have considered cyclophosphamide for the resolution of the skin lesions in the short term. However, the adverse effects may not be tolerated by the patients including nausea, fatigue, diffuse alopecia, mild anaemia, macrocytosis and lymphopenia, therefore should

be used as last option.[8] Other drug alternatives, including methotrexate, aminopterin, cyclosporine, intravenous 5-fluorouracil, interferon gamma and alpha are also reported as therapeutic options with in efficiency response.[15] A few authors mentioned the use of photodynamic therapy as a partial control of disseminated eruptive keratoacanthoma, which can help to improve the quality of life.

Conclusion

The GEKA is a benign condition that predominantly affects individuals in their fifth decade of life. Although its exact cause is still unknown, the primary complications of this disease include ocular issues ranging from conjunctivitis to ectropion, significantly impacting the quality of life of patients. In this regard, we believe that actively researching this condition is crucial to expedite its diagnosis and treatment.

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