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Original Article

Chronic involuting relapsing keratoacanthoma with grouping tendency of lesions in seven staggering cases

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Abstract

Background There are case reports in the medical literature showing some patients have recurrent keratoacanthoma in selected regions and given different names such as chronic keratoacanthoma serpiginous, eruptive keratoacanthoma centerifugum and involuting keratoacanthoma.

Objective To report seven patients with keratoacanthoma who had recurrent relapsing and involuting keratoacanthoma in selected body regions and to suggest a covering reprehensive name for this specific medical condition.

Methods This is a cross sectional descriptive study that was carried out during the period from 2013-2020 where all patients with keratoacanthoma were collected and from among them the recurrent involuting keratoacanthoma were isolated. Full demographic and clinical examination was done. Skin biopsies were performed for histopathological evaluation.

Results Forty-five patients with keratoacanthoma were described with Fitzpatrick skin type III, IV among them seven (15.5%) male patients with chronic involuting relapsing keratoacanthoma (CIRKA) were detected, their ages ranged from 25-60 years with a mean of 50 years, with negative family history. All had chronic picture with 3-4 years duration. Patients gave history of old and new lesions appearing on the sites. The sites of lesions were on the dorsa of hands in three patients with one patient with addition of chest involvement. The other four patients had their lesions on the legs and one patient also had lesion on the face. All patients ahd lesions on the sun exposed sites including face, hands and legs. All patients on all sites showed different stages of lesion maturation, early umblicated papules and nodules, small and large plaques, and large tumor size some with characteristic keratoacanthoma with crateriform. All patients had grouping of their lesions in well selected sites. In addition, some had atrophic areas which were the sites of involution. Histopathological evaluation demonstrated a picture of keratoacanthoma in all patients.

Conclusion All patients showed features of recurrent involuting relapsing keratoacanthoma on well-defined areas. The histopathology was that of keratoacanthoma and all cases are not part of syndrome. As literature described this entity by different names; hence we suggest the name chronic relapsing involuting keratoacanthoma (CIRKA) as a representative, new and informative name.

Key words
Involuting; Relapsing; Keratoacanthoma; Chronic; CIRKA.

Introduction

Keratoacanthoma is a rapidly evolving skin tumor that has been postulated to come from the hair follicle and has a three phase nature of quick proliferation, stabilization, and regression, resembling cycles of hair follicles. Major signaling pathways that were thought to be engaged in the etiopathogenesis of KAs include Wnt/retinoic acid signaling, B-Raf, H-ras,

hedgehog, and p27. Several precipitating factors might be involved with these lesions like trauma, immunosuppression/ immunodeficiency, chemicals, radiation, foreign bodies and cell cycle-modulating medications. Historically, keratoacanthomas are considered to be a variant of cutaneous SCC and were often recorded as KA-type cSCC. However; the tendency for regression had led many to categorize KAs as biologically benign tumors with distinctive pathophysiological mechanisms from malignant SCC.[1,2]

A typical presentation of mature KA is skin-color similar to skin or red papule or nodule with keratinous plug in the center of lesions and superficial telangiectasia mostly on sun-exposed areas. KAs may present as a solitary lesion (which is the most common presentation) or multiple lesions. Solitary KA are typically sporadic, and their size ranges from 1 to 2cm. Giant KAs are single lesions more than 20cm in diameter most commonly seen on nose or eyelid.

There many syndromes that encourage the progression of multiple KAs including: xeroderma pigmentosum, Muir-Torre syndrome Ferguson-Smith, and Grzybowski. It is of importance to focus on the two latest genetic syndromes, since they involve eruptive, multiple KAs. Ferguson Smith syndrome is an autosomal dominant condition characterized by spontaneously multiple regressing KAs on sites of sun light exposure, that usually develop during the third decade of living.[3] Eruptive generalized keratoacanthomas of Grzybowski is a non-familial case, presenting as eruption of thousands of KAs during adut life, they develop rapidly and may slowly resolve over a period of months.[4] Witten-Zac syndrome is an autosomal dominant condition that appears in children and has a characteristic picture by the presence of features common to both Ferguson-Smith syndrome and Grzybowski syndrome, including multiple milia, ulcerated small nodules, and large self-healing lesions.[5]

Another variant of multiple KAs are the multiple persistent KAs, which are slowly healing and non-familial. The conjunctivae, soles, penis and palms have been involved. In one patient, the KAs kept developing for thirty-five years and changed into a mass that was painful and extended to the underlying tendon.[6] In addition, multiple KAs can develop in the setting of immunosuppression, the use of immunosuppressive drugs and following radiation therapy.[7,8]

Most KAs resolve spontaneously over weeks or months and mostly all cases regress or are treated and are not relapsing. However; in some cases, KAs tend to persist for a longer period of time, an example is Keratoacanthoma centrifugum marginatum, which is a unique picture of KA, most commonly observed on surfaces of sunlight exposure and presented with peripheral progressive expansion and hyperkeratotic raised borders. Clearing of the center with atrophy are other clinical characteristics. The size is variable in KCM, with reported cases ranging from 5cm×5cm to as large as 20cm×14cm. Spontaneous resolution might not occur, or it might heal in 6 to 12 months rather than 2-6 months as seen in the common KA. There is also a report of multiple keratoacanthoma centrifugum mariginatum in literature.[6,9,10]

Histologically, mature KAs have a crater filled

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with keratin, pale, eosinophilic, glassy, differentiated proliferation of epidermis often with lips extending over both side of the craters, often with squamous eddies or keratin pearls and sometimes neutrophilic microabscesses within the epidermis. Cytologic atypia of keratinocytes is usually mild. Perivascular or lichenoid infiltrate of lymphocytes, sometimes with eosinophils or plasma cells may be present.[11]

Most tumors regress spontaneously leaving a scar but this is rarely recognized in clinical practice. KA is a rapidly growing tumor that might cause local severe destruction and behave like SCC, especially when the tumor is located near important organs like the nose and eyes, hence its treatment is mandatory. Simple topical curative therapy was used by Sharquie using podophyllin 25% in benzoin.[12] Surgical removal with conventional excision or Mohs micrographic surgery are the standard of treatment. Destructive therapies, radiation, topical and systemic treatments, and observation have also been suggested.

Methods

This is a cross sectional study that was carried out from 2013-2020 where all patients with recurrent involuting relapsing keratoacanthoma were gathered. Full demographic and clinical evaluation was done. Skin biopsies were performed from multiple areas and processed and stained by Hematoxylin Eosin for histopathological assessment.

Results

A total of forty five patients with keratoacanthoma were described with Fitzpatrick skin type III and IV among them seven (15.5%) male patients with chronic involuting relapsing keratoacanthoma were detected with ages ranged from 25-60 years with a mean of 50 years with negative family history. All had chronic picture with around 3-4 years duration.

Patients gave history of small umbilicated lesions that gradually enlarge in size and then stayed static for weeks and months then started to involute leaving atrophic scars and this process was repeated in cycles. The sites of lesions were on the dorsum of both hands in three cases with one patient showing additional chest involvement. While the other four patients had their lesions on the legs with one patient with lesions on the face.

On examination, in all patients the lesions were located on the sun exposed sites including face, hands and legs. Also all patients, on all sites showed different stages of lesion maturation, early umblicated papules and nodules, small and large plaques, and large tumor size some with characteristic keratoacanthoma with crateriform configuration. All patients had grouping of their lesions in well selected sites. In addition, some had atrophic areas which were sites of involution. Histopathological evaluation demonstrated features of keratoacanthoma in all patients, mainly a crater filled with keratin, pale, eosinophilic, glassy, epithelial differentiated proliferation often with lips extending over both side of the crater, but in many other patients these features were combined with severe pseudoepithelial hyperplasia, lacking shouldering features. In addition, keratin pearls were frequently seen but no atypia or increased mitotic features were observed **(Table 1), (Figures 1-4)**.

Discussion

KA is a relatively common low-grade tumor that originates in the hair follicles and simulates squamous cell carcinoma pathologically. Strong controversy essentially confirms classifying

Table 1 showing the demographic, clinical and histopathological characteristics of each patient.

Patient number	*Age*	*Gender*	*Skin type*	*Site*	*Grouping of lesions or not*	*Number of lesions*	*Duration since 1st attack*	*Histopathological evaluation*
1	60	male	IV	Dorsa of the hands	Yes	10	3 years	Typical picture of KA
2	25	male	III	Legs	Yes	5	3 years	Typical picture of KA
3	55	male	IV	Face+ legs	Yes	12	4 years	Typical picture of KA
4	55	male	IV	Chest+ dorsa of the hands	Yes	13	3 years	Typical picture of KA
5	30	male	III	Legs	Yes	16	3 years	Typical picture of KA
6	50	male	III	Dorsum of the right hand	Yes	4	4 years	Typical picture of KA
7	48	male	IV	Legs	Yes	9	4 years	Typical picture of KA

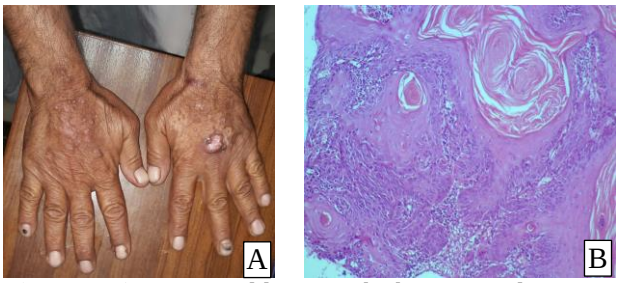

Figure 1 A) 60 years old man with chronic involuting relapsing eruptive keratoacanthoma centrifugum with grouping configuration. B) the same patient showing histopathological features of keratoacanthoma. HE stain x 40.

keratoacanthoma as a variant of invasive SCC. The behavior of clinical KA is hardly predictable and the differential diagnosis of keratoacanthoma and other conditions with keratoacanthoma-like pseudocarcinomatous epithelial hyperplasia is challenging, both histopathologically and clinically.[11]

There are very few population-based studies describing the clinical features of KA as most reports are single institution studies featuring small numbers of patients.[13,14] The present study is the only one describing seven cases of chronic involuting relapsing keratoacanthoma, which constituted around 15.5% of the total cases of keratoacanthoma that were collected over 7 years' time. These group of patients are not part of familial syndrome unlike previously reported cases.

These CIRKA cases are rarely diagnosed and rarely reported and after extensive reviewing of literature we found only a single case report of a similar condition.[13] This series includes a total of seven male patients, all of them have chronic picture of multiple recurrent lesions on sun-

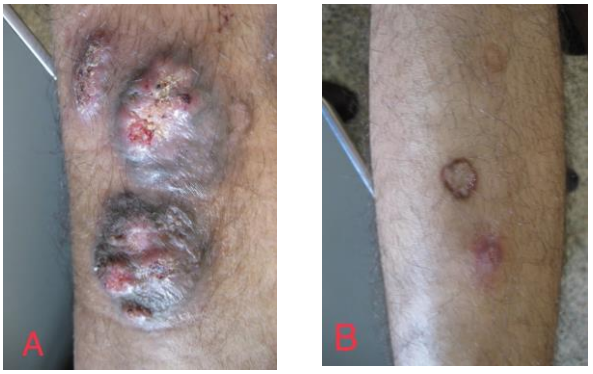

Figure 2 A, B showing 25 years old male with chronic involuting relapsing keratoacanthoma on the leg with grouping configuration. Note the involuting lesions in figure 2B.

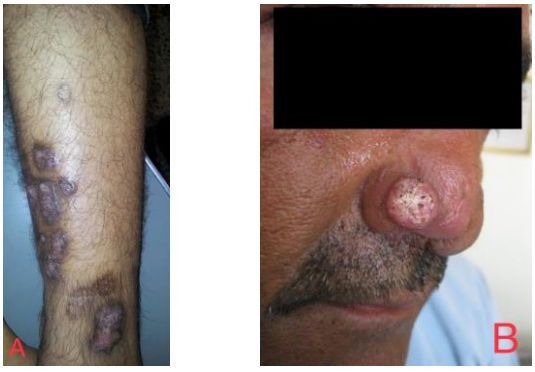

Figure 3 A) 55 years old male with chronic involuting relapsing keratoacanthoma of the leg with tendency for grouping. B) the same patient with single keratoacanthoma on the right nasal ala.

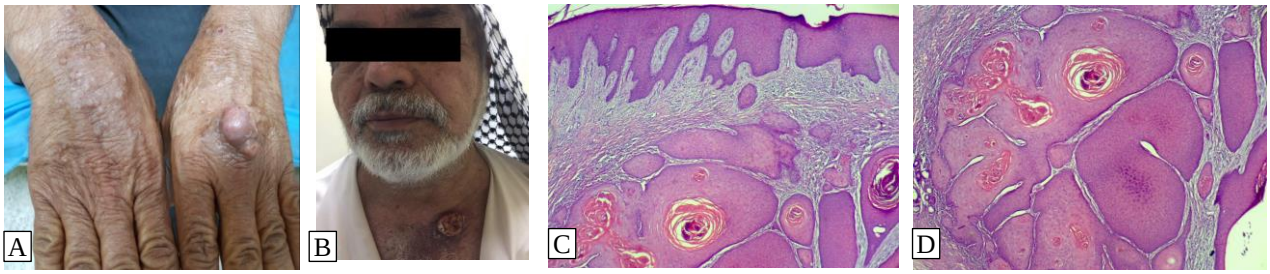

Figure 4 A) 55 years old male with chronic involuting relapsing keratoacanthoma on the hands with grouping behavior. B) the same patient with single lesion of keratoacanthoma on the chest. C,D) the same patient showing histopathological features of chronic relapsing keratoacanthoma. C: HE stain x 10, D: HE stain x 40.

exposed sites (face, chest, dorsa of hands and legs). These lesions grow rapidly, then remain static for a certain period of time and then involute spontaneously leaving atrophic scars, this process is repeated periodically. None of the patient had a family history of similar lesions. On examination, these lesions have multiple stages of development, some are umblicated papules and nodules, some are large plaques and some are tumors with crateriform configuration with grouping tendency in well recognized sites. And to the best of our knowledge this is the first work describing this grouping behavior. Histopathology of theses lesions showed full picture of keratoacanthoma.

After extensive review of literature and from our observation, we suggest to consider the patients in the present work as special variant of keratoacanthoma named CIRKA disease.

Conclusion

This the first study describing this special new variant of keratoacanthoma named CIRKA**.** All patients showed features of chronic involuting relapsing keratoacanthoma on well-defined areas with grouping tendency. All lesions were detected on sun exposed sites mainly hands and legs. The histopathological features support the diagnosis of keratoacanthoma.

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