Keratoacanthoma

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Key Points

- Keratoacanthoma probably lies within the spectrum of intraepidermal keratinocyte neoplasia and is possibly related to squamous cell carcinoma. The majority of lesions regress spontaneously. There are both surgical and chemotherapeutic treatment options.
- Keratoacanthoma is a lesion that usually undergoes three phases: rapid growth, maturation and regression.
- There are several forms of solitary keratoacanthomas as well as syndromes involving multiple lesions. Some of these syndromes are familial.
- The major risk factor for developing this lesion is sun exposure.
- The specific aetiology of keratoacanthoma formation and regression, including the potential role of infectious, environmental and genetic factors, is not yet known.
- Keratoacanthoma shares several histologic features of squamous cell carcinoma. There are various features that usually distinguish keratoacanthoma from squamous cell carcinoma; however, no one architectural or histopathological marker clearly delineates between the two.

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Definition

Keratoacanthoma (KA) is an epidermal neoplasm of the skin and mucous membranes that exhibits rapid growth, maturation and regression. It occurs most often on the sun-exposed areas of fair-skinned adults and is thought to arise from cells in the hair follicle. The exact biologic behaviour of keratoacanthoma remains controversial. In the past it had been considered a reactive condition or pseudomalignancy which could be treated expectantly. Now the favoured view is that KA is a malignant tumour with low, but not negligible, metastatic potential, which in many cases will regress. Even those that ultimately involute can cause considerable

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destruction before they regress. The regression may be partially mediated by immunity, but takes the form of terminal differentiation. The exact course of these tumours is unpredictable. Recently, the clinical behaviour of KA was retrospectively reviewed in 445 cases published in 113 articles. In all cases follow-up and outcomes had been reported, and none of these resulted in death or distant metastases. Yet, in the immunosuppressed patient, any lesion with histologic features of keratoacanthoma should be managed as a squamous cell carcinoma, with complete eradication.

There are four types of keratoacanthomas: solitary, multiple, eruptive and keratoacanthoma centrifugum marginatum.

Epidemiology

The incidence of solitary keratoacanthoma is highest in fair-skinned individuals, and the majority of the lesions occur on sun-exposed areas of the body. In 1963, Ghadially documented that KA occurs twice as often in men than in women and that the most frequently affected age group was 60–65, while the average age was 56. From this group, 90 % of the lesions were on sun-exposed skin with the cheeks, nose and dorsa of the hands being most commonly affected. In 1984, Kligman and Callen noted that the majority of the lesions occurred on sun-exposed skin and were accompanied by actinic damage, including a "leathered" aged appearance, actinic keratosis, other cutaneous neoplasms, solar lentigines, poikilodermas or a combination of these findings.

The incidence of Japanese Hawaiians seeking care for KA between 1983 and 1987 was 22.1/100,000, while the incidence in white Hawaiians was 104/100,000 and the incidence in Japanese residing in Japan was approximately 0.1/100,000. Dufresne et al. in Rhode Island, an area with marked seasonal variation in temperature and daylight hours, noted a statistically significant increase in the presentation of keratoacanthoma during the summer months. More recently, other authors also found differences in the seasonal appearance of KA; the tumour occurred more frequently in the winter months in Houston, Texas, versus June, November and December in Minneapolis, Minnesota.

Multiple keratoacanthomas of the Ferguson-Smith variant are an autosomal dominant disorder in which lesions may be numerous (up to hundreds) and both men and women are equally affected. Although lesions can begin as early as infancy, the mean age of onset is 25.5 years for women and 26.9 for men (Schwartz 1994).

Basic Concepts of Pathogenesis

A single cause for keratoacanthoma is unknown. The lesion occurs most often on hair-bearing, sun-exposed skin, but can occur on non-hair-bearing, sun-protected skin as well. For instance, keratoacanthoma has been reported on the hard palate, tongue, gingiva, lip (Fig. 48.1), nasal mucosa conjunctiva, anal mucosa, vulva, palms and soles.

Several proposed aetiologic mechanisms include:

Sun Exposure

The fact that most KAs occur on sun-exposed skin and occur more often in individuals who spend more time in the sun implies a connection between solar radiation and the lesion's pathogenesis. The

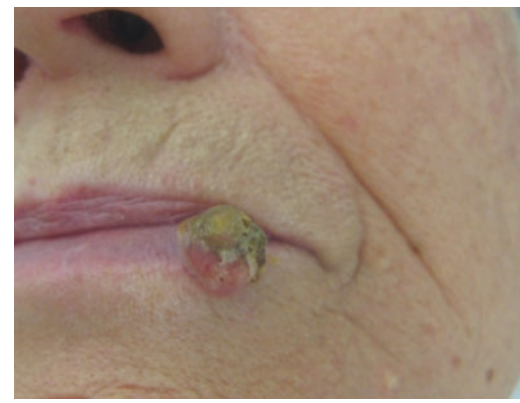

Fig. 48.1 Large keratoacanthoma of the lip

specific mechanism is unclear. Filipowicz et al. have demonstrated that the apoptotic mediator CD95 (Fas) is downregulated in two-thirds of keratoacanthoma lesions developing on sun-exposed skin. This data suggests that loss of the protective apoptotic mechanism may be one path to keratoacanthoma formation. A similar downregulation of CD95 was also seen in other lesions such as actinic keratosis, squamous cell carcinoma and basal cell carcinoma, and indeed these lesions have been described as occurring in the same patients and the same sun-exposed areas of the skin as KA.

Other Radiation-induced Forms

There have been case reports of keratoacanthoma occurring after cutaneous exposure to radiation therapy. Shaw et al. described the development of several keratoacanthomas on the face of a woman shortly after radiation therapy to her sinuses for a squamous cell carcinoma. There have also been case reports of psoralen and ultraviolet A (PUVA) therapy inducing keratoacanthoma. Brazzelli et al. reported keratoacanthoma arising in a vitiligo lesion after a prolonged course of UVB narrowband (UVB-NB) therapy.

Trauma

There have been numerous reports of keratoacanthoma developing at sites of skin trauma, even in young patients. Several specific case reports describe KA formation at the margins of excisions and skin grafts. Keratoacanthomas have also developed at the site of thermal burns and CO2 laser resurfacing. Kaptanoglu and Kutluay described a keratoacanthoma developing in previous cryotherapy sites for actinic keratosis.

Viral

There have been numerous studies suggesting a possible viral aetiology in the formation of keratoacanthoma. Specifically, HPV DNA has been demonstrated in several keratoacanthomas by various techniques including in situ hybridisation and PCR. Stockfleth et al. suggested that HPV infection does not cause KA formation in all people, but may be one predisposing factor in some patients and a cofactor for malignant transformation.

Hair Follicle Cycling

Ghadially proposed pathways by which keratoacanthomas develop from cells in the hair follicle. The cyclic nature of hair growth – anagen (growth phase), catagen (regression phase) and telogen (resting phase) – presents a similarity to the rapid growth, maturation and regression of most keratoacanthomas. The mechanism of formation of lesions on the mucosa and other non-hair-bearing skin is not known. It is also interesting to note that KA arising in the subungual area may arise from cells in the nail bed which grow constantly and do not cycle; thus, it seems logical that keratoacanthomas arising in this area would rarely show spontaneous regression. In fact keratoacanthomas of the subungual area often continue to grow, without regression, causing severe local tissue and bone destruction.

Immune Factors

Patel et al. demonstrated significant differences in the profiles of immune cells invading keratoacanthomas and squamous cell carcinomas. The infiltrates of KAs were demonstrated to be higher in CD3+ and CD4+ cells as well as cells expressing the interleukin-2 receptor and the adhesion molecule, CD36.

Keratoacanthomas tend to develop more frequently in immunosuppressed patients, and the lesions tend to be more locally aggressive in this population. These differences suggest that there is an immunologic role in KA regression, although a specific mechanism has not been elucidated.

Genetics

Several forms of keratoacanthoma express specific genetic patterns. KAs are found in conjunction

with sebaceous skin tumours and internal malignancies in Muir-Torre syndrome. This syndrome is a variant of the hereditary nonpolyposis colon cancer (HNPCC) syndrome and is inherited in an autosomal dominant pattern. Patients with Muir-Torre syndrome have germline mutations in their DNA mismatch repair genes. Several researchers have utilised microsatellite instability to document mutations in MSH-2 and MLH-1 mismatch repair genes in lesions from patients with both Muir-Torre syndrome and HNPCC (Machin et al. 2002).

DNA repair defects also characterise xeroderma pigmentosum, a syndrome in which keratoacanthomas are seen with actinic keratosis, basal cell carcinoma, squamous cell carcinomas and melanomas on sun-exposed skin.

Ferguson-Smith keratoacanthomas also demonstrate an autosomal dominant pattern of inheritance, and KAs of the Witten-Zak type have been reported in families.

Activated ras genes have been detected in several tumours including keratoacanthoma. RAS is a family of proteins involved in cell signal transduction that normally cycle between active and inactive states. Mutations in the ras gene can lead to proteins that are disproportionately active and thus tumorigenic. In a study by Peng et al., rabbits were altered to express human EJras, a RAS mutant, and all of these transgenic rabbits developed keratoacanthomas approximately 3 days after birth. Additionally, nearly all of these lesions spontaneously regressed. Clearly, mutations in this family of RAS proteins have the potential to explain KA formation in humans.

Vemurafenib, a fibrosarcoma kinase B (BRAF) inhibitor, is the first molecularly targeted therapy for the treatment of advanced-stage melanoma licensed in the USA and Europe. Its mechanism of action involves selective inhibition of the mutated BRAF V600E kinase that leads to reduced signalling through the aberrant mitogen-activated protein kinase (MAPK) pathway. Vemurafenib use can be associated with the development of cutaneous neoplasms such as squamous cell carcinoma and keratoacanthoma as a side effect. These lesions often arise weeks after initiation of therapy often in sun-exposed areas. The precise mechanism by which BRAF inhibition promotes the appearance of keratinocyte neoplasms is not yet fully understood (Fig. 48.2). However, the prevailing hypothesis is that in the context of a hyperactive mutant RAS gene and a normal BRAF gene, BRAF inhibitors, including vemurafenib, paradoxically activate ERK signalling by promoting the formation of CRAF-containing dimers, leading to hyperproliferation and tumour formation. Su and colleagues provide evidence supporting such a mechanism by showing that 60 % of the cSCCs and KAs in vemurafenib recipients had RAS mutations (mostly in HRAS) – a rate higher than the 3–40 % usually seen in sporadic cutaneous squamous cell carcinomas. Furthermore, cells overexpressing mutant RAS hyperproliferated in the presence of the drug, and skin tumours developed sooner in mice with Hras mutations induced by a vemurafenib analogue.

Clinical Presentation

Keratoacanthoma is a lesion that undergoes three phases: proliferation, maturation and regression. These phases correlate with both its clinical and histological appearances. In the early proliferative phase, KA appears as a flesh-toned to pink bud, dome- or berry-shaped papule that grows rapidly over the course of several weeks into a firm nodule that often has scale on top. During the maturation phase, a central, firmly embedded keratin plug develops (Figs. 48.1 and 48.2). This plug may appear verrucous, may grow to resemble a cutaneous horn (Fig. 48.2) or may become more darkly pigmented with the appearance of a necrotic centre. The firmly embedded keratinous plug cannot be dislodged with ease. The periphery of the lesion is often erythematous and slopes down to merge with the surrounding normal skin.

The tumour is usually not fixed to deeper structures. In the regression phase, the lesion involutes and eventually expels its keratinous centre. Regression usually results initially in a saucer-shaped depression when the plug is dislodged; this evolves into an atrophic, hypopigmented, depressed scar. KA often traverses its entire lifecycle within 2–6 months.

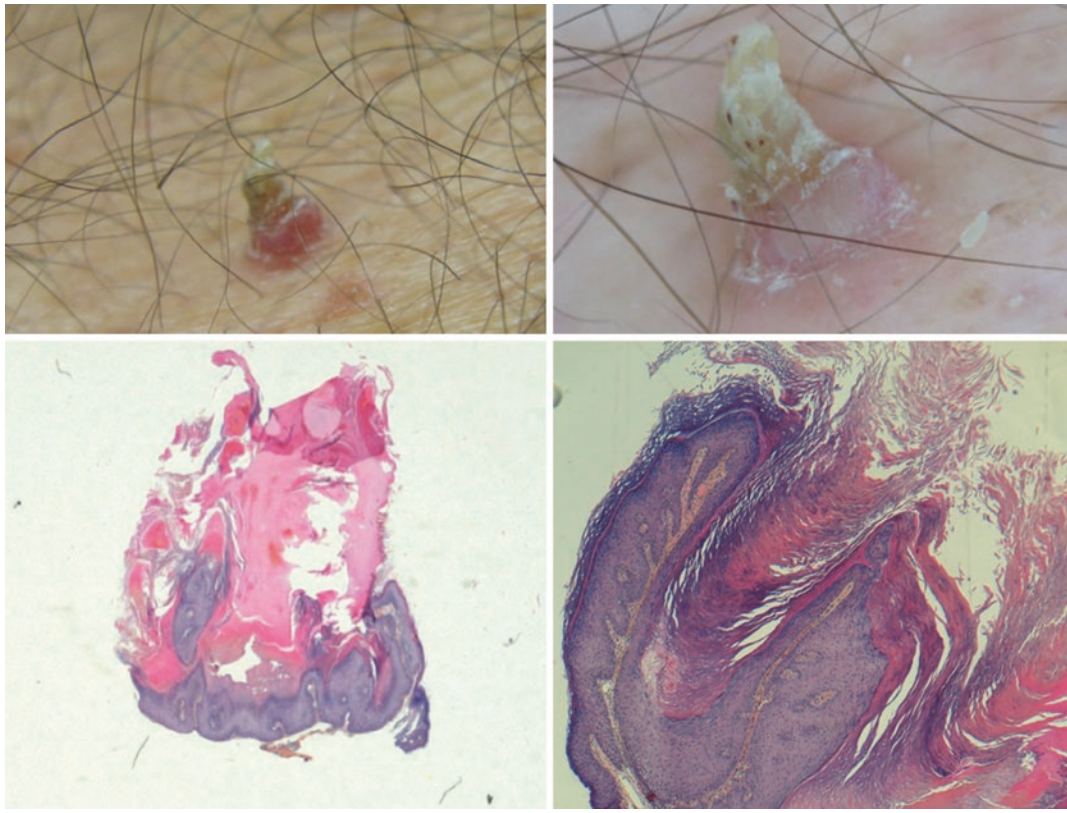

Fig. 48.2 Clinical (*upper left*) and dermoscopy (*upper right*) images of a keratinasing tumour induced during treatment with BRAF inhibitor. Clinically the lesion shows a bright pink elevated tumour with a central horn. Dermoscopy shows a lesion filled by keratin, hair pin vessels and blood spots. The histologic diagnosis is based on the architectural pattern of the lesion at scanning magnification (*down left*). The centre of the lesion shows a crater filled with eosinophilic keratin. Over the sides of the crater, a "lip" or "marginal buttress" of epithelium extends over the keratin-filled crater. At the base and sides of the crater (*down right*), the epithelium is acanthotic and composed of keratinocytes which are highly keratinised and have an eosinophilic, glassy cytoplasm with mild cytologic atypia

Under dermoscopy classical mature KAs are characterised by the presence of hairpin vessels surrounding the centre of the lesion filled by keratin. Hairpin vessels are surrounded by a whitish halo as in other keratinising tumours (Figs. 48.2 and 48.3). Recently, Rosendal et al. described the main dermoscopic criteria present in keratoacanthomas and squamous cell carcinomas, adding to the classical criteria the presence of white circles and blood spots. Central keratin was more common in keratoacanthoma than in SCC (51.2 % vs 30.0 %, $P=0.03$) with highest sensitivity for keratoacanthoma SCC (79 %), and white circles had the highest specificity (87 %). In a multivariate model, white circles, keratin and blood spots were independent predictors of SCC and keratoacanthoma.

Solitary Keratoacanthoma

Solitary keratoacanthoma is the most common form of this tumour. It occurs most often on the sun-exposed, hair-bearing skin, especially the face and dorsal hands, of adults with fair complexion. Solitary keratoacanthoma has the classic appearance of a rapidly growing hemispheric nodule (2–6 weeks) with a central keratin-filled crater that spontaneously regresses over a period of months. Lesions tend to be single, but there

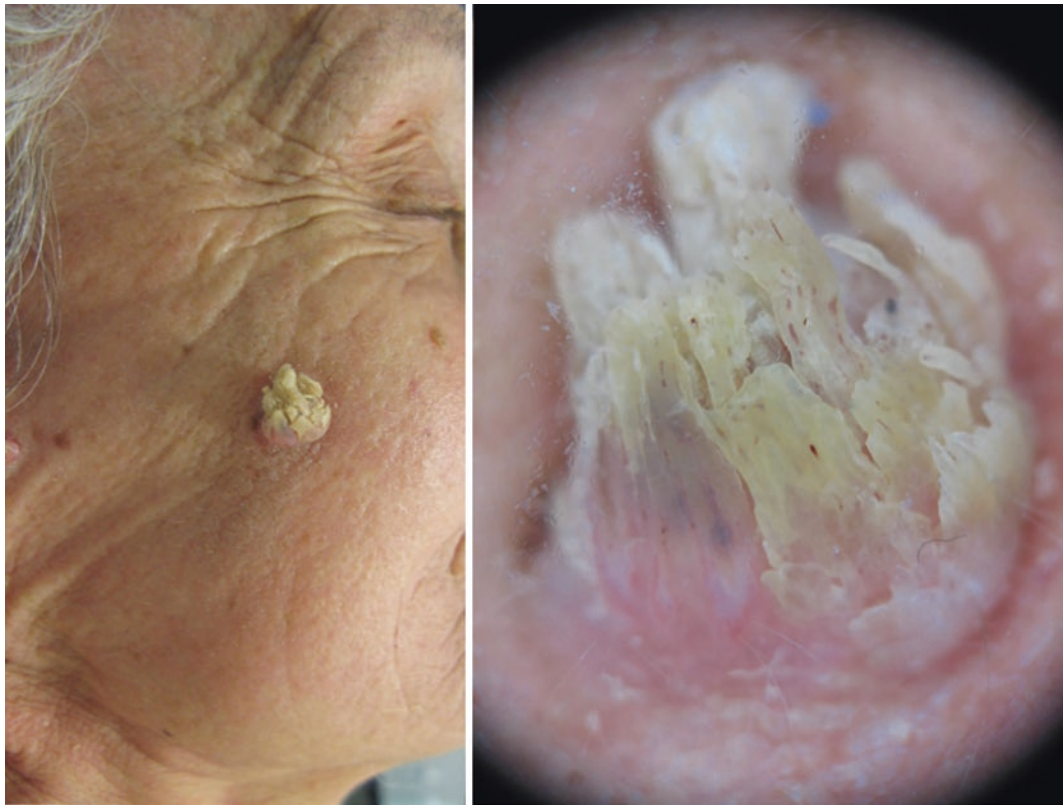

Fig. 48.3 Clinical (*left*) and dermoscopy (*right*) images of a keratinasing tumour induced during treatment with BRAF inhibitor. Clinically the lesion shows a bright pink elevated tumour with a central horn. Dermoscopy shows a lesion filled by keratin, hair pin vessels and blood spots

can be several lesions or additional lesion formation over the course of the patient's lifetime. It has been estimated that some 5 % of treated lesions recur. Invasion along nerve trunks has been documented and may result in recurrence after a seemingly adequate excision.

Giant Keratoacanthoma

A KA is considered giant if it grows larger than 3 cm in diameter. Giant keratoacanthoma may be locally invasive and disfiguring or may remain superficially situated. In spite of its size, it can still demonstrate complete, spontaneous regression.

Keratoacanthoma Centrifugum

Keratoacanthoma centrifugum marginatum is a rare, most commonly solitary, large lesion demonstrating a plaque-like appearance with central clearing and scarring. The diameter is similar to or larger than giant KA, but the proportions have changed so that the lesion is flat and atrophic in the centre with a raised rim that grows outwards and demonstrates keratin production. The dorsum of the hands and pretibial regions are favoured sites. Keratoacanthoma centrifugum marginatum often does not regress and can pose a significant therapeutic challenge.

Subungual Keratoacanthoma

Subungual keratoacanthoma is a rare tumour derived from the nail bed. It causes significant tissue destruction and does not regress. These lesions, classically, cause cup-shaped osteolysis without periosteal reaction in the underlying distal phalanx due to pressure erosion. Other

symptoms include local swelling, erythema, pain, nail bed deformity and in some cases bacterial superinfection. It may occur on the proximal nail fold and may involve nails of the fingers or toes, although they are seen most often on the thumb, index and middle fingers of patients in the third through seventh decades.

Multiple Keratoacanthoma Syndromes

Ferguson-Smith-Type Keratoacanthomas

Multiple KAs of the Ferguson-Smith type are an autosomal dominant disorder seen most commonly in males (3:1 predominance) with an onset in the second and third decades of life. The lesions occur first in small crops and are self-healing with scar formation. Sun-exposed sites are favoured, especially the ears and nose, and in most cases scalp lesions occur. The lesions tend to recur periodically throughout life, and later developing lesions have a lower tendency to spontaneously regress.

Generalised Eruptive Keratoacanthomas of Grzybowski

Grzybowski first described a very rare and sporadic form of eruptive keratoacanthomas in which thousands of small 1–5 mm KAs appear simultaneously or progressively. The lesions are more concentrated on sun-exposed skin, but also involve the oral mucosa, larynx and intertriginous areas. The lesions can appear in groups or clusters and demonstrate Koebnerization. Because of the severe facial involvement and resultant scarring, patients exhibit masked facies and ectropion. This variant has been reported in white, Asian and black patients with equal incidence in men and women.

Witten and Zak-Type Keratoacanthomas

In Witten and Zak-type keratoacanthomas, there is a combination of both Ferguson-Smith-type lesions and the smaller eruptive Grzybowski-type lesions. This variant has been reported in multiple siblings of the same family.

Histology

The histologic diagnosis is based on the architectural pattern of the lesion, which is best evaluated at scanning magnification (Fig. 48.2). This is true at each stage of the lesion's evolution.

The centre of the lesion shows a crater filled with eosinophilic keratin, with orthokeratotic and parakeratotic cells. Over the sides of the crater, which seems to have been formed by the invagination of the epidermis, a "lip" or "marginal buttress" of epithelium extends over the keratin-filled crater. At the base and sides of the crater, the epithelium is acanthotic and composed of keratinocytes which are highly keratinised and have an eosinophilic, glassy cytoplasm. Mild cytologic atypia is common. Mitotic figures, necrotic and dyskeratotic keratinocytes and acantholytic keratinocytes are prominent. Microabscesses of neutrophils often admixed with eosinophils are noted within the hyperplastic epidermis.

The surrounding dermis has a moderately dense perivascular or lichenoid mixed inflammatory infiltrate composed of lymphocytes, eosinophils and plasma cells.

The most definitive histologic feature is evidence of terminal differentiation, where the scalloped outer border of the tumour has lost its infiltrative character and is reduced to a thin rim of keratinising cells lining a large keratin-filled crater.

There are no histologic findings proven to predict biologic behaviour. The number of mitotic figures, perineural invasion and extension into subcutaneous tissue do not appear to differentiate between those lesions that will involute spontaneously and those that will persist.

Some reported metastases of keratoacanthoma to the lymph node have retained the architectural and cytologic features of the primary fully developed lesion.

The differential diagnosis with well-differentiated squamous cell carcinoma is sometimes difficult. Unfortunately, there is no single diagnostic marker study to date that can reliably differentiate KA from SCC.

Interestingly, recently a study was carried out to assess syndecan-1 (CD 138) and Ki-67 expression to differentiate keratoacanthoma

(22 samples) from squamous cell carcinoma (17 samples). Syndecan-1 is an adhesion molecule whose expression appears to be inversely correlated with tumour invasiveness. Elevated Ki-67 expression is indicative of a high proliferation index, a feature of malignant tumours. According to the results of this study, syndecan-1 expression is markedly diminished, and Ki-67 expression is significantly increased in SCC compared to KA.

General Principles of Treatment

Although keratoacanthomas usually spontaneously involute, it is impossible to predict how long this will take. If no therapeutic intervention is implemented, the patient may be faced with a destructive growth of a tumour which has a limited tendency to metastasise. More importantly, SCC cannot always be ruled out. Therefore, excisional biopsy should be considered in most cases. Surgery limits the progression and invasion of the lesion and allows for definitive diagnosis. Mohs micrographic surgery has also met with good success in removal of lesions from the head and neck and of recurrent lesions.

Nonsurgical therapy may also be considered in certain anatomical sites to preserve function or to improve cosmetic outcome.

Preferred treatment options vary depending on size and location of the lesion, as well as experience by the physician with each modality.

Intralesional injection of 5-FU solution, 50 mg/mL at weekly intervals; bleomycin 0.5 mg/mL; or methotrexate 25 mg/mL can be effective. For a typical lesion four injections along the base at each pole are recommended.

Topical photodynamic therapy with delta aminolevulinic acid has been successful for solitary and giant KA.

Low-dose systemic methotrexate may be considered if there is no response to intralesional injection or if multiple lesions are present and there is no contraindication.

Both etretinate and isotretinoin in oral doses of 1 mg/kg/day have been reported with good outcome in the treatment of recurrent and multiple KA syndromes.

Topical 5 % imiquimod has been reported as another successful alternative for the treatment of keratoacanthoma.

Excision is recommended if there is not at least 50 % involution of the lesion after 3 weeks.

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