Keratin and controversy:
A common cutaneous tumour that confounds classification

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CASE

A male patient, aged 65 years, presents for a routine skin check. Inspection reveals a solitary, dome-shaped lesion to his left forearm. It is firm, slightly tender, 1.5 cm in diameter and erythematous with a central keratotic plug (Figure 1). On history, the lesion developed rapidly over 2–3 weeks. The patient is otherwise well. Of note, he had a similar-appearing nodule to his right arm last year that resolved spontaneously after 6 months.

His past medical history includes type 2 diabetes mellitus, chronic venous insufficiency and multiple keratinocyte cancers. Excision of a basal cell carcinoma the previous year was complicated by wound breakdown and cellulitis.

QUESTION 1

What is the most likely diagnosis?

QUESTION 2

Which differential diagnoses would you consider?

QUESTION 3

Is the lesion benign or malignant?

QUESTION 4

Given the history of a similar-appearing lesion that spontaneously regressed, is intervention necessary?

ANSWER 1

Keratoacanthoma is the most likely diagnosis.

Solitary keratoacanthomas are common, rapidly growing epidermal tumours with a characteristic crateriform structure and keratotic core.[1] They tend to occur in sun-exposed, hair-bearing regions such as the head, neck and extremities, most typically in older, fair-skinned individuals.[2] Although their pathogenesis remains unclear, they are believed to originate from the pilosebaceous unit. As with cutaneous squamous cell carcinomas (SCCs), common risk factors include UV exposure, immunosuppression, fair skin and old age.[2] They can arise in areas of trauma (eg surgery, tattoos) and have an association with some drugs (eg BRAF inhibitors).[1]

One of the most striking features of keratoacanthomas is their capacity for spontaneous regression. Their clinical course typically follows three phases: proliferation, stabilisation and regression (Table 1).[2]

This triphasic progression is one of three key criteria in the diagnosis of keratoacanthoma,[2] the other two being: (1) the classical crateriform structure; and (2) typical features on histopathology.

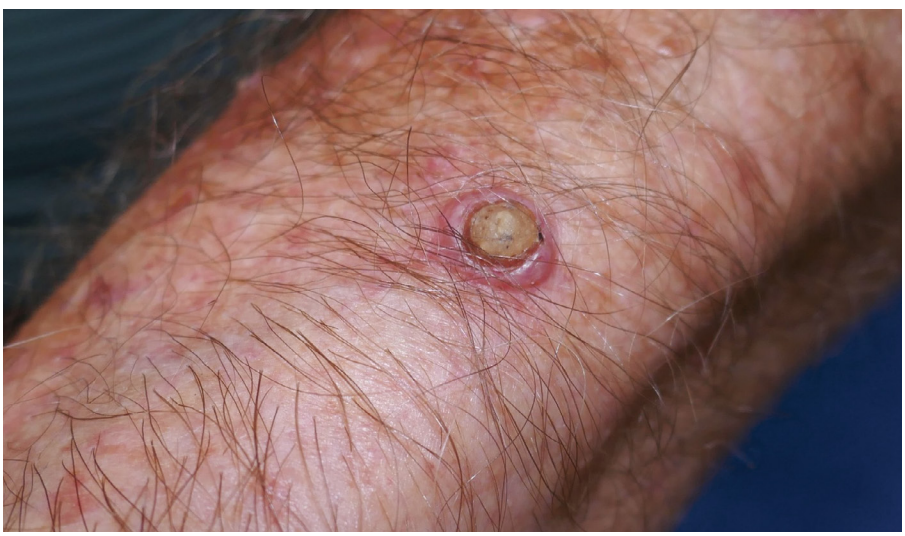

Figure 1. Lesion at presentation.

Dermoscopic features of keratoacanthoma include a structureless yellow-to-brown centre, white circles, white structureless regions and blood spots. Dermoscopy cannot reliably discriminate between SCC and keratoacanthoma.[2]

ANSWER 2

Table 2 lists the common differential diagnoses of keratoacanthoma.[1] Notably, keratoacanthomas are not the sole cause of keratin horns. They can also be produced by actinic keratoses, intraepidermal carcinomas, SCCs, viral warts, porokeratosis and seborrhoeic keratoses.

ANSWER 3

Classification of keratoacanthomas has long been debated because of their similarities with SCCs. Many experts consider them to be a low-grade variant of SCC.[1,2] Others regard them as a diagnostic entity in their own right.[3] For its part, Cancer Council Australia characterises keratoacanthomas as tumours of intermediate malignant potential.[4]

Regardless, without clear evidence of spontaneous regression, keratoacanthomas and SCCs can be clinically indistinguishable. Although most keratoacanthomas follow a benign course, up to 10% show aggressive features including perivascular or perineural invasion, and there are rare (but not definitive) reports of metastatic spread.[3] Interestingly, perineural invasion does not appear to have an adverse impact on prognosis as it does with frank SCC.[3] The challenge of differentiating keratoacanthomas from SCCs has significant implications for management.

ANSWER 4

A wait-and-see approach for any presumptive keratoacanthoma is problematic unless clear involution or plateaued growth is evident. Treatment is typically warranted because of unpredictable progression. Even if a lesion is a true keratoacanthoma, continued enlargement may cause local damage and crenelated scarring requiring revision.[1] Additionally, spontaneous regression may produce an undesirable scar, and the lesions are often symptomatic and alarming for patients. The primary concern, however, is the difficulty of excluding SCC without histopathology.

CASE CONTINUED

The patient requests a confirmatory biopsy before committing to definitive treatment.

QUESTION 5

Why might a partial biopsy be unhelpful?

QUESTION 6

What are the reasonable management strategies?

ANSWER 5

Given the difficulties of distinguishing between keratoacanthomas and SCCs clinically, Cancer Council Australia recommends early excision of the entire lesion.[4] Partial biopsies should be avoided as they may miss key architectural features. Keratoacanthomas can include SCC-like areas, and vice versa.[1] Therefore, pathologists require the whole lesion to make a firm diagnosis.

ANSWER 6

Standard surgical excision and shave biopsy immediately followed by curettage and cautery are two commonly used approaches.[5] The latter relies on good lesion selection and technique for optimal outcomes. Although guidelines on surgical margin selection in keratoacanthomas are lacking, it would be reasonable to employ the clinical margin of 4 mm recommended for low-risk SCCs.[4] Other modalities include cryotherapy, intralesional chemotherapy and radiation. The relative advantages and disadvantages of each strategy are summarised in Table 3.

Conclusion

The lesion is treated with shave biopsy followed immediately by curettage and cautery to the resultant surgical defect. This modality is selected as the lesion is a small, typical keratoacanthoma on the severely sun-damaged skin of a patient with a long history of skin

Table 1. The three phases of keratoacanthoma progression

Phase	Clinical features	Duration	Histopathology
Proliferation	A period of rapid growth, with evolution of minute pink or skin-coloured papules into 1- to 2-cm nodules	6–8 weeks	• Keratin-filled invaginations coalescing in a symmetrical pattern • Infiltration into the surrounding stroma
Stabilisation	Maintenance of the crateriform architecture	Weeks to months	• Exo-endophytic architecture with a central keratin-filled crater • Peripheral 'collarette' of overhanging epithelial rims • Squamous lobules extending to the level of the sweat glands composed of large, pale pink keratinocytes with a 'glassy' eosinophilic cytoplasm
Regression	Spontaneous involution, frequently leading to hypertrophic or atrophic scarring	Highly variable; overall lifespan, from development to regression, usually lasts 4–6 months	• Shallow, cup-shaped keratin plug with thinned epithelium • Fibrosis and inflammatory changes in the underlying dermis

malignancy and multiple previous excisions and curettes at other sites. The procedure is performed by a practitioner trained in the technique. From the patient's perspective, this allows for same-day treatment, a high chance of cure and no need for a second appointment for suture removal. Histopathology is consistent with keratoacanthoma (Figure 2A). There is no recurrence in the 3 years following. The appearance at 3-month review is shown in Figure 2B.

Key points

- Keratoacanthomas are rapidly growing epidermal tumours characterised by a crateriform architecture with a central keratotic plug, often developing in sun-exposed areas.
- Although keratoacanthomas may undergo spontaneous regression, their potential for aggressive behaviour and similarities to SCC support definitive treatment rather than observation.
- Treatment options are many and include surgical excision, curettage and cautery, cryosurgery, intralesional chemotherapy and radiation.

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Table 2. Differential diagnoses[1,6]

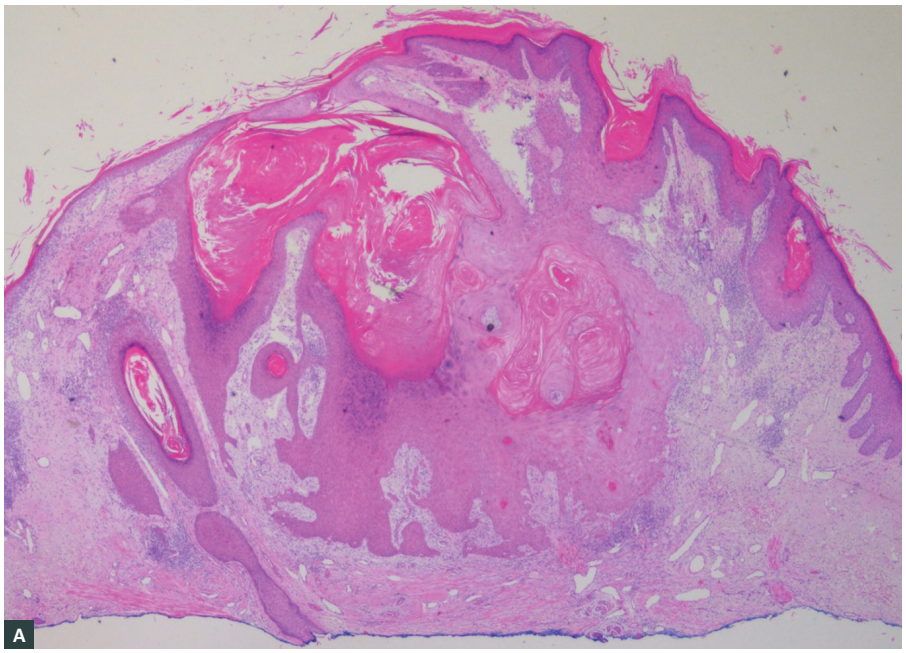
Differential	Points in favour	Points against
Well-differentiated squamous cell carcinoma	• Rapidly growing lesion, often on sun-exposed sites • Can present with a central keratin-filled crater • Common in older adults • Central mass of keratin and white structureless areas on dermoscopy	• Usually grows persistently with no evidence of regression • White circles more common on dermoscopy than for keratoacanthomas
Nodular basal cell carcinoma	• Occurs in sun-exposed areas, typically in older individuals • May present as a raised lesion with central ulceration	• Slower growth • Rarely includes a central keratotic plug • Arborising vessels, ulceration, blue-grey globules, leaf-like areas and buck-shot scatter dots on dermoscopy
Amelanotic melanoma	• May appear as a rapidly growing nodule, sometimes with ulceration	• Rarely features a keratin-filled crater • Polymorphic vessels, milky-red areas and blue-white veils on dermoscopy
Molluscum contagiosum	• Can present as dome-shaped papules with central umbilication • Often develops in sun-exposed regions	• More common in children or immunosuppressed individuals • Lesions tend to be clustered and smaller, usually <5 mm (giant molluscum contagiosum is a rare exception, presenting as a 0.5–1-cm nodule) • Central pore, polylobular white-yellow structures and peripheral linear vessels on dermoscopy
Verruca vulgaris (common warts)	• May present as a keratotic nodule • Often affects sun-exposed sites	• Lacks rapid growth and a central crater • Punctate haemorrhages, whitish halo and papillomatous surface on dermoscopy
Merkel cell carcinoma	• Presents as a rapidly growing nodule on sun-exposed areas • Usually occurs in older individuals	• Appears shiny and purple-red, without a keratin-filled crater • Polymorphic vessels and milky-red structures on dermoscopy
Metastatic cutaneous deposit	• Rapidly growing nodule(s)	• No known history of malignancy • Typically presents as multiple nodules • Serpentine vessels and pink background on dermoscopy
Prurigo nodularis	• Presents as firm nodules that can occur in sun-exposed areas • Nodules may become hyperkeratotic over time • White structureless areas and hyperkeratosis on dermoscopy Note: keratoacanthomas can arise in association with prurigo nodules	• Usually involves multiple lesions • Slow development and persistence rather than rapid growth • Brown-yellowish crusts and white starburst patterns on dermoscopy

Table 3. Overview of treatment modalities for solitary keratoacanthomas

Treatment approach	Advantages	Disadvantages	Recurrence rate[A]
Surgical excision[2,7,8]	• Aims at complete removal of tumour • Permits histopathological assessment for diagnostic confirmation	• May not be suitable for all lesion sizes or anatomical regions given extent of tissue loss • Requires surgical expertise and access to appropriate facilities	0–8%
Mohs micrographic surgery[8,9]	• Suitable for larger lesions or those in sensitive areas where tissue preservation is vital	• Needs highly trained personnel and specialised equipment • Often time intensive • More expensive	0–2.4%
Curettage and cautery (electrodesiccation)[2,7,8]	• Frequently used for lesions not involving cosmetically sensitive regions • Same-day treatment • Cost effective • Minimal equipment requirements	• Produces an open wound	3.6%
Cryotherapy alone[2,10]	• Minimal equipment requirements • Cost effective	• May result in significant local injury, including secondary ulceration • May be uncomfortable/painful for patients • Does not produce histopathology	12.5–33.3%
Cryosurgery (cryotherapy combined with curettage and cautery +/– punch biopsy)[2,10]	• Minimal equipment requirements • Cost effective	• Generally limited to lesions <20 mm in diameter	2.2%
Intralesional chemotherapy (5-fluorouracil [5-FU], methotrexate [MTX], bleomycin, interferon alfa)[2,5]	• Useful for non-surgical candidates • May be used neoadjuvantly to decrease lesion size prior to surgery	• Typically requires multiple sessions over 1–6 weeks • Lack of histopathological confirmation	0–8%
Ionising radiation[4,5]	• Avoids surgery • Potentially useful for inoperable cases in cosmetically sensitive areas (though rarely employed)	• Unsuitable for patients aged <60 years • Requires several sessions • May induce eruptive keratoacanthomas • Lack of histopathological confirmation	Limited data
Laser/photodynamic therapy[2,5]	• Potentially effective for small lesions in inoperable regions • May produce favourable cosmetic outcomes	• Limited evidence and long-term data • Lack of histopathological confirmation	Limited data
Oral retinoids (acitretin, isotretinoin) [1,5]	• Potential option for multiple or eruptive lesions not conducive to surgery • Inexpensive • Generally well tolerated • Prophylactic retinoids can reduce the development of new keratoacanthomas	• Often requires long-term treatment to sustain clinical response • Adverse effects including dyslipidaemia and hepatotoxicity • Lack of histopathological confirmation	Limited data

[A]Cure rates from available studies for all modalities vary considerably. Operator technique and lesion size will affect results.

With any procedure, there is a small risk of keratoacanthomas developing at the surgical site via the Koebner phenomenon.



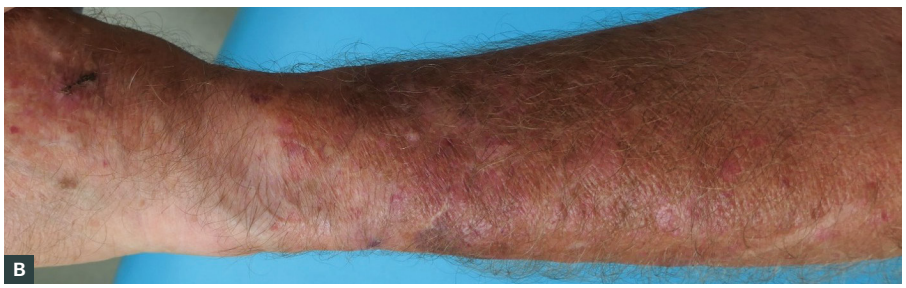


Figure 2. (A) Histopathology demonstrating exo-endophytic architecture with keratin-filled invagination and squamous lobules (haematoxylin and eosin, 40× total magnification). **(B)** The affected site 3 months after shave excision followed immediately by curettage and cautery.

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