Keratoacanthoma in the immunocompromised patient – Surgical concerns

Kathleen M Singleton MD, Steven F Morris MD MSc FRCSC, Arnis Freiberg MD FRCSC FACS

Department of Plastic Surgery, The Toronto Hospital, Western Division, University of Toronto, Toronto, Ontario

KM Singleton, SF Morris, A Freiberg. Keratoacanthoma in the immunocompromised patient – Surgical concerns. Can J Plast Surg 1994;2(3):108-112. It is well known that clinical and histological differentiation between keratoacanthoma and squamous cell carcinoma is often difficult. The two lesions share many common features, but have very different outcomes. Both occur with increased frequency in immunosuppressed patients. This report documents two cases of histologically confirmed keratoacanthoma in immunosuppressed patients. These lesions were excised but had frequent recurrences and in both cases underwent histologically proven malignant transformation. The purpose of this report is to demonstrate the potentially aggressive nature of keratoacanthomas in the immunocompromised patient.

Key Words: *Immunosuppression, Keratoacanthoma, Squamous cell carcinoma*

Kératoacanthome chez le patient immunocompromis : Préoccupations d'ordre chirurgical

RÉSUMÉ : Il est souvent difficile de différencier entre kératoacanthome et épithélioma spino-cellulaire sur les plans cliniques et histologiques. Les deux affections ont de nombreuses caractéristiques communes, mais évoluent fort différemment. Les deux apparaissent plus fréquemment chez les sujets immunodéprimés. Ce rapport présente deux cas de kératoacanthome confirmés à l'histologie chez de tels patients. Les lésions ont été excisées, mais ont connu de nombreuses récurrences et dans les deux cas, une transformation cancéreuse a été démontrée à l'histologie. Le but du présent article est de démontrer la nature potentiellement agressive des kératoacanthomes chez le patient immunocompromis.

Keratoacanthoma (KA) is generally considered to be a benign skin lesion with a characteristic appearance and natural course which has been well described in the past (1). Frequently, however, the histological and clinical differentiation between KA and squamous cell carcinoma (SCC) has been difficult. No histochemical assay has yet evolved to aid pathologists in this diagnostic dilemma (2-4), and although a number of histological criteria have been used to differentiate the two lesions, the use of these criteria varies among pathologists, with the final diagnosis often based on the patient's clinical history (5,6)

The difficulty in histological differentiation between KA and SCC becomes crucial when a diagnosed KA recurs or becomes invasive. Whether such growth represents a malignant transformation of a previous KA, a problem with the initial histological diagnosis, or accelerated growth of the KA

after excision remains controversial, and without reliable histochemical markers to differentiate KA from SCC, it is impossible to clarify this issue. Our interest in this controversy stems from two recent cases in which KAs were noted in immunocompromised patients. These lesions were difficult to eradicate surgically and had many clinical features of invasive SCC. The purpose of this paper is to report on these two cases, which exemplify some of the problems inherent in the surgical treatment of KA in the immunocompromised patient, and to review the available literature.

CASE REPORTS

Case 1

A 65-year-old white male had successfully undergone cadaveric renal transplant surgery in 1980. The etiology of his renal failure was familial polycystic kidney disease, initially diagnosed in 1973. Immediately following the transplant surgery, an immunosuppressive regime of azathioprine 1.75 mg/day and prednisone 12.5 mg and 10 mg on alternate days was instituted. This patient also had an eight-year history of hypertension, controlled by propranolol 40 mg bid. In

Correspondence and reprints: Dr Arnis Freiberg, Room 4-034 Edith Cavell Wing, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8. Telephone (416) 369 5691, Fax (416) 369 5297

Figure 1) Case 1. Parietal area of the scalp showing a recurrent lesion 1.5 cm in diameter

Figure 2) Histological section of tumour depicted in Figure 1. Diagnosis – keratoacanthoma

1988, he suffered an acute anterior myocardial infarction, from which he made a successful recovery.

In April 1989 he was seen by a dermatologist to evaluate a 3 cm raised skin lesion in the right parietal area of the scalp. A diagnosis of KA was made and the lesion was removed by curettage. The pathology report confirmed the diagnosis of KA. Three weeks later the lesion had recurred and was 1.5 cm in diameter (Figure 1). The patient was referred to the senior author and the lesion was locally excised and closed using a Limberg transposition flap. The pathology report stated that "...although there was cellular atypia and prominence of mitotic figures, a diagnosis of KA was favoured" (Figure 2). The margins were reported to be free of tumour. Three weeks later the patient returned with yet another recurrence of the lesion, located near the incision line. Again, the lesion was excised and the pathological diagnosis of KA was favoured, although there were many histological features of SCC. The presence of elastic fibres was considered to be more indicative of KA.

The patient returned three months later with a 1.5 cm diameter subcutaneous, firm, tender mass in the right

Figure 3) Histological section of subcutaneous tumour from the postauricular area appearing three months following excision of the lesion described in Figures 1 and 2. Pathology report – "metastatic keratinizing SCC"

postauricular area. An enlarged lymph node was suspected and removed from the site. The pathologic diagnosis was metastatic SCC (Figure 3). No lymphatic tissue was seen. Two months later the patient presented with another KA in a different location on the scalp, 3 cm from the initial site. This lesion was excised and reported as a KA. Another two months later he developed yet another firm subcutaneous mass just inferior to the previous postauricular mass. This lesion also was removed and also reported as metastatic SCC. Quadrosopic examination was performed in order to search for a primary, without success. A right modified radical neck dissection was performed followed by radiation therapy for SCC. One year later, suboccipital nodes appeared which required a block excision and skin flap closure. The patient has been lost to follow-up.

Case 2

A 65-year-old white male underwent cadaveric renal transplant surgery in 1975 for chronic renal failure. Postoperatively he was started on prednisone 10 mg/day for immunosuppression.

Figure 4) Case 2. Recurrent lesion on the dorsal aspect of the first web space of the hand

Figure 5) Case 2. Second recurrence, three months following excision of lesion shown in Figure 4

Figure 6) Case 2. Third recurrence, six months following radiation

He was seen in February 1989 by a dermatologist regarding a 2 cm diameter lesion which had been present for approximately three months on the dorsum of his right hand. A clinical diagnosis of KA was made and the lesion was removed by curettage. The pathology report confirmed the diagnosis of KA. One month later, the lesion had recurred (Figure 4) and the patient was referred to the senior author. The lesion was excised with a margin of 1 cm. The pathology report stated that, although there were features of SCC, the diagnosis of KA was favoured. Three months later the lesion had again recurred (Figure 5) and, due to the possibility of SCC, was excised with a wider margin, and the 6 cm diameter defect was reconstructed using a split thickness skin graft. The pathology report again favoured KA. The patient was referred to the oncology service for radiation therapy. The hand remained healed for six months when yet another recurrence was noted (Figure 6), one year after the initial appearance. A thumb and index finger ray amputation was performed. The patient has remained well without evidence of local or regional recurrence.

Figure 7) Anatomic distribution of keratoacanthoma

DISCUSSION

Keratoacanthoma (molluscum sebaceum) is a lesion which usually begins as a firm erythematous papule. The typical natural history includes a two- to eight-week period of rapid growth during which the KA reaches a maximum size of 1 to 2 cm. The central area typically becomes umbilicated and fills with a thick keratinous plug. The lesion then undergoes a quiescent period of two to eight weeks, after which, in most cases, it begins to regress spontaneously. It may, however, still cause local tissue destruction (7). As the tumour regresses, the keratin plug is shed and a puckered scar is left at the site. Three clinical types of KA are recognized: solitary, multiple and eruptive, of which the solitary KA is the most common (7).

The anatomic distribution of the lesion (Figure 7) suggests an affinity for sun-exposed areas (1). The KA usually arises in previously healthy skin, but has also been known to arise in existing dermatoses or traumatized skin (7). In the case of KAs which are very large, persistent, cosmetically disfiguring or multiple, nonoperative treatments include: radiation (600-

TABLE 1: Histologic criteria of keratoacanthoma and squamous cell carcinoma

Histologic feature	% patients KA	% patients SCC
Invaginating keratin-filled crater	98	17
Collarette	73	8
Epidermal proliferation deep and lateral to lesion	98	12
Extension to and not beyond sweat glands	79	28
Extension more lateral than downward	58	42
Invasion of dermis beyond sweat glands	5	23
Anaplasia or marked pleomorphism of invading cells	5	81
Parakeratosis, dyskeratosis and single cell keratinization	31	90
Abnormal or numerous mitoses (>2 per HPF)	1	37
Associated actinic changes	5	23

HPF High power field; KA Keratoacanthomata; SCC Squamous cell carcinoma. Adapted from Kern et al (2)

1000 rads); topical or intralesional 5-fluorouracil; oral retinoic acid and systemic methotrexate.

Surgical treatment is indicated in cases in which the KA fails to resolve with nonoperative treatment or becomes large and destructive, and in cases in which there is a significant suspicion of SCC. Some authors recommend surgical removal for all KAs, in order to permit an accurate pathological diagnosis, and to ensure a cure (8). Surgical methods include shave excision with local curettage and electrodesiccation or complete excision with reconstruction (9,10).

It is well known that the immunosuppressed renal transplant recipient is at increased risk for development of de novo carcinomas and at a significantly younger age (6,11,12). Penn estimates that these patients have a 100-times increased risk for development of a cutaneous malignancy (13). Approximately two-thirds of these lesions are epithelial, of which the majority are SCC (14,15). Cutaneous malignancies in the immunosuppressed patient usually start with hyperkeratosis which can progress to KA or to SCC, which, in these patients, have a tendency to become rapidly invasive (11). Therefore, early and adequate treatment is essential to prevent metastases and death (16).

Cohen et al (6) found 59 malignant skin lesions in a review of 580 renal transplant recipients over a 16-year period. The majority of these lesions were SCC. However, the authors experienced difficulty in distinguishing KA from SCC. Of the five KAs initially reported in the pathological files of these authors, two were reclassified as SCCs due to cyto-atypia in the adjacent epithelium. Hardie et al (17) described a lesion which was initially thought to be a KA, but which recurred, metastasized and subsequently resulted in the death of the patient. Poleksic et al (18) reported the rapid transformation of a KA to SCC in a patient who was being treated with intensive chemotherapy for Hodgkin's disease. Other authors

have suggested that KA can undergo spontaneous transformation to SCC (19,20). Whimster (19) proposed that KA acts as a co-carcinogen with solar damage to produce SCC. It has been suggested previously that these lesions may have been misdiagnosed from the beginning (5). Kern et al (5) examined the reproducibility of the pathological diagnosis of 100 KAs and 100 SCCs (Table 1). Conclusions were based on the presence or absence of 10 histological features generally considered to be characteristic of either KA or SCC. They felt that the most important aspect in arriving at a diagnosis of SCC was the presence of anaplasia and mitotic activity, and that the presence of these characteristics should lead to treatment appropriate for an aggressive neoplasm. They found that in 81% of KAs and 86% of SCCs, the original diagnosis was confirmed. This suggests, however, that almost 20% of KAs are misdiagnosed initially. Based on these results, it appears that misdiagnosis may occur frequently. Iverson et al (21) concluded that the term 'self healing' in relation to KA is a fallacy and suggested treating all KAs as premalignant lesions.

Recurrences of KA have been documented in the past. In a review of several different patient groups, Rook et al (19) found a recurrence rate of 4 to 5%, with the majority being KAs of the fingers, hands and lips. They also found that KAs tended to become multiple in immunosuppressed patients, but did not find any which underwent malignant transformation. Ghadially et al (1) noted eight recurrences in 238 patients. Kingman (7) reported seven recurrences in 78 patients. Muir-Torre, an autosomal dominant syndrome, is characterized by multiple KAs and sebaceous hyperplasia in association with visceral malignancies. It has been recognized that patients with this syndrome treated by immunosuppression have developed exacerbations of the syndrome's cutaneous manifestations (22). The incidence of SCC arising from KA is unknown, however it has been previously recognized that SCC may arise from old scars, immunization sites or chronic lesions (19). As previously stated, KA also has been known to arise from damaged skin.

In the cases presented here, the KAs appear to be aggressive, with recurrences and possibly malignant transformation. Although the biological basis for these events is not currently understood, these cases serve as an indicator that KA in the immunologically compromised patient may present a significant surgical challenge. We recommend early excision with close follow-up, in much the same way as one would treat SCC.

SUMMARY

KA is generally considered to be a benign skin lesion; however, it can be difficult to make a histological differentiation between KA and SCC. Two case studies have been presented which demonstrate that, in the immunocompromised patient, KA may become an aggressive skin tumour with a much higher than normal incidence of recurrence and possibly malignant transformation. It is recommended that in immunocompromised patients, the KA should be excised completely, early in its course, and close follow-up should be maintained.

REFERENCES

1. Ghadially FN. Keratoacanthoma. In: Fitzpatrick TB, ed. *Dermatology in General Medicine*, 3rd edn. New York: McGraw Hill Inc. 1987;766-72.
2. Ariano MC, Wiley EL, Ariano L, Coon JS, Tetzlaff LH. Peanut lectin receptor, and carcinoembryonic antigen distribution in keratoacanthomas, squamous dysplasias, and carcinomas of skin. *J Dermatol Surg Oncol* 1985;11:1076-83.
3. Graham RM, MacFarlane AW, Curley RK, Nash JRG. β_2 microglobulin expression in keratoacanthomas and squamous cell carcinoma. *Br J Dermatol* 1987;117:441-9.
4. Smoller BR, Kwan TH, Said JW, Banks-Schlegel S. Keratoacanthoma and squamous cell carcinoma of the skin: Immunohistochemical localization of involucrin and keratin proteins. *J Am Acad Dermatol* 1986;14:226-34.
5. Kern WH, McCray MK. The histopathological differentiation of keratoacanthoma and squamous cell carcinoma of the skin. *J Cut Path* 1980;7:318-25.
6. Cohen EB, Komorowski RA, Clowry LJ. Cutaneous complications in renal transplant recipients. *Am J Clin Pathol*. 1987;88:32-7.
7. Kingman J, Callen JP. Keratoacanthoma. *Arch Dermatol* 1984;120:736-40.
8. Stal S. Keratoacanthoma. *Clin Plast Surg* 1987;14:425.
9. Stewart RG, Petti GH, Heustis DG. Multiple keratoacanthomas involving the head and neck. *Otolaryngol Head Neck Surg* 1988;99:55-8.
10. Pagani WA, Lorenzi G, Lorusso D. Surgical treatment for aggressive giant keratoacanthoma of the face. *J Dermatol Surg Oncol* 1986;12:282-4.
11. Marshall V. Premalignant and malignant skin tumors in immunosuppressed patients. *Transplantation* 1974;17:272.
12. Koranda F, Dehmel EM, Kahn G, Penn I. Cutaneous complications in immunosuppressed renal homograft recipients. *JAMA* 1974;229:419.
13. Penn I. Chemical immunosuppression and human cancer. *Cancer* 1974;34:1474.
14. Penn I. Cancer in immunosuppressed patients. *Transpl Proc* 1975;7:553 (Suppl 1).
15. Divakar D, Bailey RR, Lynn KL, Robson RA. Long term complications following renal transplantation. *NZ Med J* 1991;104:352-4.
16. Penn I. Depressed immunity and the development of cancer. *Clin and Exp Immun* 1981;46:459-74.
17. Hardie JR, Strong RW, Hartley LC, Woodruff PWH, Clunie GJA. Skin cancer in caucasian renal allograft recipients living in a subtropical climate. *Surgery* 1980;87:177-83.
18. Poleksic S, Yeung KY. Rapid development of keratoacanthoma and accelerated transformation into squamous cell carcinoma of the skin. *Cancer* 1978;41:12-6.
19. Rook A, Whimster I. Keratoacanthoma – A thirty year retrospective. *Br J Dermatol* 1979;100:41-7.
20. Burge KM, Winkelmann RK. Keratoacanthoma – Association with basal and squamous cell carcinoma. *Arch Dermatol* 1969;100:306-11.
21. Iverson RE, Vistnes LM. Keratoacanthoma is frequently a dangerous diagnosis. *Am J Surg* 1973;126:359-65.
22. Stone MS, Duncan C, McGavran MH. Torre's syndrome: Exacerbation of cutaneous manifestations with immunosuppression. *J Am Acad Dermatol* 1986;15:1101-3.