Keratoacanthoma as a postoperative complication of skin cancer excision

Leonard H. Goldberg, MD, FRCP,[a,b] Sirunya Silapunt, MD,[a]
Kathleen K. Beyrau, MD,[c] S. Ray Peterson, MD,[a] Paul M. Friedman, MD,[a] and
Murad Alam, MD[d]
Houston, Texas, Portage, Wisconsin; and Chicago, Illinois

Background: Keratoacanthomas usually occur spontaneously as a single rapidly growing tumor on sun-exposed skin. Multiple keratoacanthomas are rarely seen. Keratoacanthomas may also develop after trauma, laser resurfacing, radiation therapy, and at the donor site after skin grafting.

Objective: We report 6 cases of keratoacanthomas that developed in and around healing and healed surgical sites after treatment of skin cancer. These tumors developed 1 to 3 months after surgery and were sometimes multiple.

Methods: We performed follow-up examinations of patients' wounds after the treatment of skin cancer. Histological examination of nodules developing in the margins of healing wound sites and in the scars of healed wound sites after Mohs micrographic surgery revealed keratoacanthomas.

Results: The tumors presented as a rapidly growing nodule or nodules, with the typical morphology and pathology of keratoacanthoma. One patient developed multiple keratoacanthomas at surgical and nonsurgical sites. These nodules were treated by a combination of excision, curettage and electrodesiccation, and oral isotretinoin, 4 mg/d.

Conclusion: Keratoacanthoma must be considered in the differential diagnosis of a rapidly growing nodule within or around the surgical site after skin cancer surgery. (J Am Acad Dermatol 2004;50:753-8.)

Keratoacanthoma (KA) usually occurs spontaneously as a single rapidly growing tumor with characteristic morphology on the sun-exposed regions of middle-aged or older persons. Multiple KAs are also seen. These may be 1 of 3 types: multiple self-healing KA of Ferguson-Smith; eruptive KAs of Grzybowski; and multiple familial KAs of Witten and Zak.[1-4] KA may also develop after trauma, laser resurfacing, radiation therapy, and at the donor site after skin grafting.[5-9] We report 5 cases of KA that developed in wounds healing by second intention and in scars within 3 months after Mohs micrographic surgery (MMS) for squamous cell carcinoma (SCC), basal cell carcinoma, and lentigo maligna. These cases illustrate the potential role of second-intention healing and scarring in the development of postoperative KA.

From the DermSurgery Associates, Houston[a]; Department of Medicine (Dermatology), University of Texas, M. D. Anderson Cancer Center, Houston[b]; Davis Duehr Dean Clinic, Portage[c]; and Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago.[d]
Funding sources: None.
Conflicts of interest: None identified.
Reprint requests: Leonard H. Goldberg, MD, FRCP, DermSurgery Associates, 7515 Main St, Suite 240, Houston, TX 77030. E-mail: Goldb1@dermsurgery.org.
0190-9622/$30.00

doi:10.1016/j.jaad.2003.11.065

PATIENTS AND METHODS

Six cases were included in this study. We followed the clinical course of patients who had KA lesions that developed at their wound site after MMS. Patient No. 6 developed the KA after curettage and electrodesiccation for a SCC. These 6 patients were seen during a period of 4 years. During this time an average of 1500 patients per year were treated with MMS.

RESULTS

Case 1

A 72-year-old woman with a history of basal cell carcinoma of the nose presented with 1-cm lesions of SCC on the lower aspect of her left leg and middle

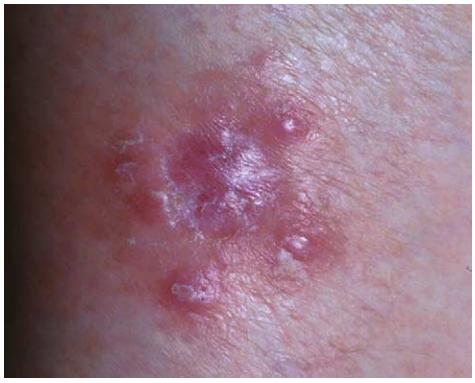

Fig 1. Multiple (6) 2- to 6-mm diameter nodules that developed in margins of scar from second-intention healing and surrounding normal skin after removal of squamous cell carcinoma. Patient developed further nodules in healing wound sites after excision of tumors.

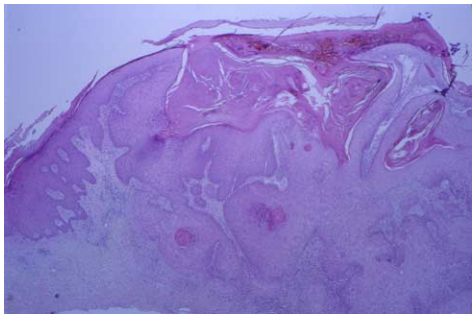

Fig 2. Keratoacanthoma characterized by keratin plug, overhanging epidermal lip, and invasion of dermis by masses of glassy epidermal cells. (Hematoxylin-eosin stain; original magnification ×20.)

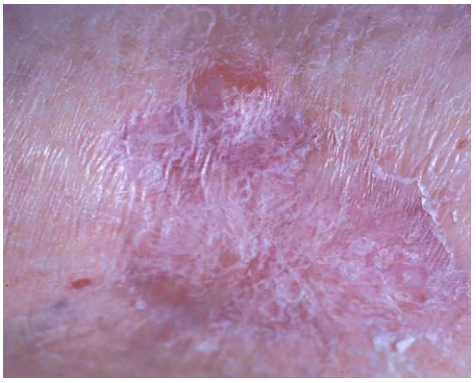

Fig 3. Same patient as Fig 1. Keratoacanthoma (6- × 6-mm) has developed in border of another healed wound site by second intention, after excision of squamous cell carcinoma.

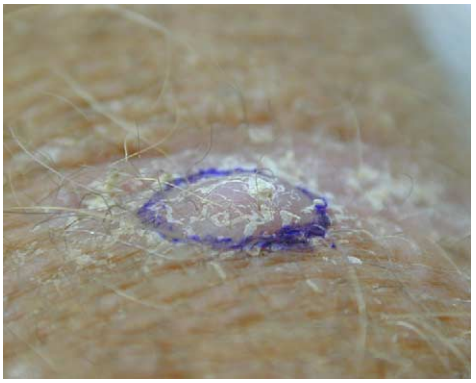

Fig 4. Rapidly growing 10- × 12-mm nodule developed in scar of previous surgical site from Mohs micrographic surgery excision of squamous cell carcinoma 4 weeks after operation. Histopathology was keratoacanthoma.

of her left finger. Histopathology showed well-differentiated SCCs. These SCC lesions were excised with MMS with histopathologically tumor-free margins. Six weeks after the operation, she developed 6 discrete KAs within the margin of the healed surgical site and the immediately surrounding skin of the left leg (Fig 1). The lesions were excised with MMS. Histopathology showed KA (Fig 2). In 2.5 months, she developed a KA on the margin of the surgical site from the previous excision of the 6 KAs on the lower aspect of her left leg. This lesion was treated with MMS and histopathologically confirmed as a KA. Then 8 weeks later, she developed another rapidly growing nodule within the margin of the healed wound on the lower aspect of her left leg (Fig 3). Biopsy specimen confirmed a KA. She was treated with isotretinoin (40 mg/d) for 1 month. The lesion regressed and disappeared.

During the next 3 years until the current time, she has developed 14 KAs within scars and de novo on the lower aspect of her left and right legs and 3 KAs de novo on the left and right hand and arms. These lesions were treated with the combination of operations and isotretinoin.

Case 2

A 69-year-old white man presented with a 1.0- × 2.0-cm diameter SCC on the left midforearm. The biopsy specimen showed a well-differentiated SCC. Histopathologically tumor-free margin was obtained after 1 stage of MMS. The defect was closed with a complex linear closure. At 4 weeks after operation, he developed a rapidly growing nodule 1.0- × 1.2-cm in diameter at the previous surgical site (Fig 4). Histopathology showed a KA. One stage of MMS was performed and clear margins were obtained. The tumor did not recur.

Case 3

A 74-year-old white woman presented with a 3- × 2-cm nodule with central umbilication on the lower aspect of her right leg. Biopsy specimen showed a well-differentiated SCC. Histologic tumor-free margins were obtained after treatment with 1-stage MMS. She was placed on isotretinoin (40 mg/d) for 30 days and the 3.5- × 2.5-cm diameter defect was left to heal by second intention. Three weeks after stopping the isotretinoin, she developed 2 clinical KAs on the edge of the granulating wound (Fig 5). She was again given 40 mg of isotretinoin daily; the lesions flattened but had not completely cleared at 1 month and they were treated by curettage and desiccation. The histopathology showed KA. The isotretinoin was discontinued. Four weeks later the original wound was healing with heaped-up granulation tissue. A new KA had developed 6 cm away from the surgical site on the same leg (located separately from the original lesion). A third course of isotretinoin was prescribed for another 4 weeks. At the end of this period, the most recently diagnosed KA away from the surgical site had flattened and involuted. The KAs associated with the original operation site had disappeared.

Case 4

A 79-year-old man presented with a lentigo maligna on his right forearm. He had a history of previous lentigo maligna on the right neck and malignant melanoma on the right helix excised by MMS, which was performed on the lesion of the right forearm. At 1 month after operation, he developed a 10- × 8-mm diameter red nodule adjacent to the surgical scar of the right forearm (Fig 6). A deep shave excision was done and the histopathology showed KA (Fig 7). At 3 weeks after the excision, the wound had healed and there was no clinical evidence of tumor recurrence.

Case 5

A 71-year-old man presented with a histopathologically diagnosed superficial basal cell carcinoma on the right thigh. MMS was performed and the 2- × 3-cm resulting defect was allowed to heal by second intention. The patient developed a nodule on the superior margin of the granulating wound at 2 weeks after operation. The patient was seen at 3 weeks after the operation and KA was diagnosed. He was placed on isotretinoin (40 mg/d) for 1 month. The lesion resolved 13 days after starting the medication.

Case 6

A 75-year-old man presented with a 1-cm diameter verrucous nodule on the right forehead. Curettage and electrodesiccation was performed and histopathology confirmed an SCC. One month after the operation, he developed a rapidly growing nodule at the surgical site, which reached a size of 2.5 × 2.8 cm in diameter after 6 weeks (Fig 8). The tumor had the clinical and histologic features of KA (Fig 9). MMS was performed and tumor-free margins were obtained. He was placed on isotretinoin (40 mg/d) for 1 month. There was no recurrence.

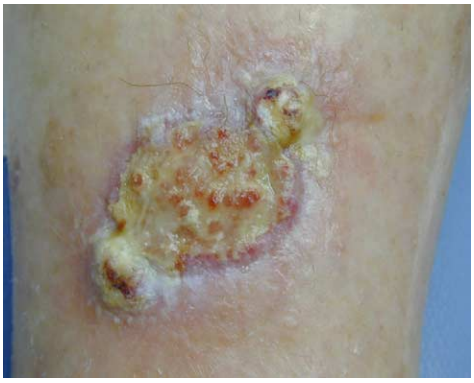

Fig 5. Two keratoacanthomas at margin of healing second-intention wound site after Mohs micrographic surgery for well-differentiated squamous cell carcinoma.

Six patients were identified, in the immediate 3-month postoperative period, who developed rapidly growing keratotic papules within the healing wound, epithelializing wound margin, scar, and immediate surrounding skin after the treatment of skin cancers. These papules and nodules were initially suggested as being recurrent tumors after operation for skin cancer. However, they were all KAs. Most of these KAs, once diagnosed, were treated with a combination of deep shave excision, MMS, curettage and desiccation, and oral isotretinoin. In case No. 1, the postoperative KA was the initial tumor in an ongoing series of new KAs, which developed during the next 7 years on lower aspects of both legs. This pattern of multiple KAs was seen in earlier case reports.[10-12] Patient No. 3 also developed a single nonsurgical related KA on the same leg at a distance from the original surgical site.

DISCUSSION

In our study, the first patient continued to develop keratotic papules and nodules at the sites of treatment for skin cancers. Repeated MMSs were unsuccessful in controlling the recurrence of SCC, KA type, in spite of substantial clear margins. Because SCC and KA are so similar histopathologically, the decision was made to try isotretinoin, based on the presumption that the recurring lesions were actually newly formed KAs growing at the traumatized skin margins of the MMS.

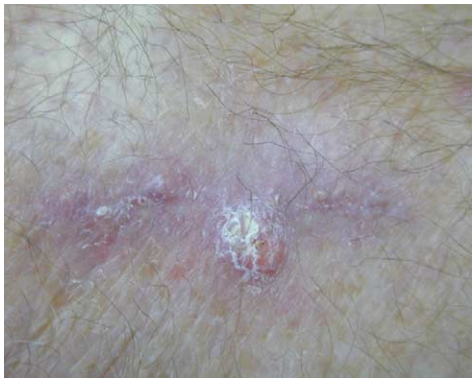

Fig 6. Keratotic papule (10- × 8-mm) that developed 1 month after operation for lentigo maligna on forearm was keratoacanthoma.

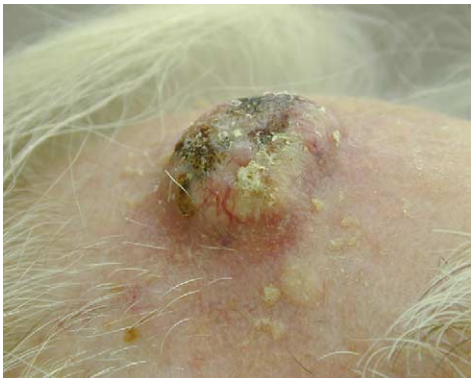

Fig 8. Nodule (2.5- × 2.8-cm) developed 1 month after curettage and electrodesiccation for squamous cell carcinoma on forehead and grew rapidly for 6 weeks.

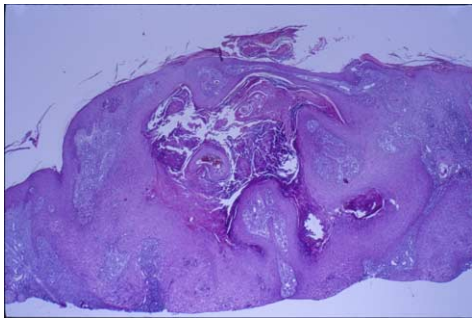

Fig 7. Keratoacanthoma (KA) showing central keratin plug surrounded by acanthotic epidermis consisting mainly of glassy looking keratinocytes. Nests of epidermal cells infiltrating dermis. Overall appearance is that of KA with well-defined margins. (Hematoxylin-eosin stain; original magnification ×20.)

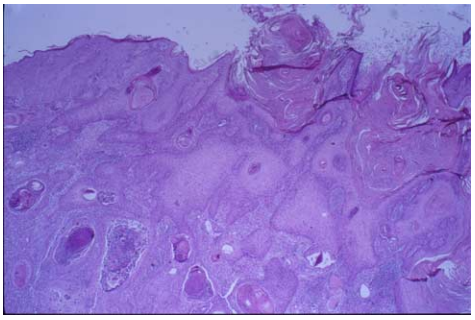

Fig 9. Keratin plugs, overhanging lip of epidermis, and infiltration of dermis by glassy looking nests of keratinocytes. Nests produce keratin pearls and some have neutrophilic abscesses. (Hematoxylin-eosin stain; original magnification ×20.)

Clinically, KA is a very characteristic tumor presenting as a painless rapidly growing nodule on the sun-exposed skin of the face and the extremities. Lesions may present from small up to several centimeters. In contradistinction to the SCC, the lesion grows during a period of weeks. It is a nodule with sharply demarcated margins very often presenting on the surface almost as an endoexophytic mass. It very soon develops a central keratinous plug. This lesion is painless and may grow to a large size. At this stage they may resolve, but have a strong predisposition to form SCC. It has been said that the KA has 3 stages: rapid growth; stabilization; and resolution. KA may present as single or multiple nodules and has various clinical manifestations including variants (Table I).

A case of multiple KAs after a severe sunburn was reported in 1939.[13] Oil and tar products have been associated with certain cases of isolated KA.[14] There are reports of KAs that developed in patients receiving psoralen-UVA treatment and radiation therapy.[7,8,15,16] In 1997, Hamilton et al[5] reported a case of KA developing in a split-skin graft donor site of a patient with a burn injury. Recently, a case of multiple KAs after carbon-dioxide laser resurfacing has been reported.[6] Trauma seems to act as a trigger for the formation of a KA.

KA poses diagnostic and therapeutic dilemmas. If left untreated, KAs may spontaneously regress in 4 to 24 weeks or longer. However, the rapid growth phase is very disconcerting for both the patient and the physician. During this phase, the tumor may be destructive to the surrounding tissue and may become very large. In addition, a certain percentage of the tumors may behave like invasive SCC. It is not known which tumors will fall into this group. Metastasizing KA have been reported.[17] Large KAs may metastasize to the draining lymph nodes.[17]

Because of the difficulty in accurately differentiating which KA will spontaneously resolve and which KA may grow to a very large size and destroy surrounding tissue, solitary KAs are usually treated as SCC. Multiple KAs have been successfully treated

with oral isotretinoin.[10-12,18] A more aggressive approach to the treatment of KAs has evolved. In the past, many people did not treat KA or treated it only because of cosmetic reason.

Excision is the standard treatment for solitary KAs. Standard margins of 3 to 4 mm are used, as with SCC. This yields a complete specimen for histology and is efficient and rapid. MMS provides tissue sparing with complete histologic margin verification, and should be used when available. Curettage and electrodesiccation has also been successfully used in the treatment of KA. Curettage and electrodesiccation is used only for smaller tumors when the site is not cosmetically important. Recurrence is around 3.6%, a figure consistent with other treatment modalities that have a recurrence rate averaging between 3% to 5%.[19]

Radiation therapy is an excellent treatment for KA when operation can not be performed. This usually means older patients unfit for operation because of severe major illness. Good cosmesis and excellent results can be obtained with radiation therapy.[20,21] The major drawback is the need for multiple treatments in a hospital or treatment center setting. Radiation therapy is not used in younger patients because of its carcinogenic properties. Donahue et al,[21] in 1990, found radiation to be an effective treatment for KAs that had recurred after surgical excision.

Intralesional 5-fluorouracil (5-FU) for the treatment of KAs was reported by Goette and Odom,[22] and Parker and Hanke.[23] Lesions that do not respond promptly to intralesional 5-FU must be considered to potentially behave like SCC.

Methotrexate has been used for the treatment of KA by weekly doses of a 25-mg intramuscular injection for 5 to 8 weeks.[24] Melton et al[25] successfully used intralesional methotrexate to treat 9 patients with large or strategically located KAs. Grob et al,[26] in 1993, used intralesional interferon alfa-2a to treat 6 large KAs, with regression in 5 of the 6 lesions noted after 3 to 7 weeks.

Vitamin-A deficiency results in epithelial squamous metaplasia that can be reversed with vitamin-A supplements. Both the synthetic retinoids and natural forms of vitamin A have been used for the treatment of keratinizing disorders and KAs.[27] The synthetic retinoids, isotretinoin and etretinate, have been used to treat both multiple and single KAs. In 1980, Heydey et al[28] reported the use of isotretinoin (2 mg/kg/d) in a patient with Ferguson-Smith type KAs. With aging, this patient developed many KAs at sites of minor skin trauma and previous surgical excision sites. Levine et al,[11] in 1984, described a female patient with SCC who, after surgical excision of a primary lesion, developed multiple KAs and SCCs during the next several years. She was treated successfully with isotretinoin (2 mg/kg/d) with adjunctive surgical excision of 1 refractive lesion.[11] Shaw and White[12] used isotretinoin (1.5 mg/kg/d) to treat a male patient with multiple KAs that were refractive to surgical excision and intralesional 5-FU. He was eventually treated successfully with oral isotretinoin with total regression of pre-existing lesions and prevention of new ones. In 1990, Street et al[10] reported 2 patients with multiple KAs. The first patient was refractive to 5-FU and isotretinoin, but was treated successfully with etretinate (1 mg/kg/d). In the second patient, multiple KAs regressed completely with isotretinoin; however, many small papules did remain recalcitrant to treatment. Goldberg et al,[29] in 1990, treated 12 patients with solitary KAs. In 9 patients, isotretinoin (0.5-1 mg/kg/d) led to regression of the lesions.[29] In 1993, Watson[30] used etretinate to treat solitary KAs. Of 19 patients, 15 were successfully treated within 2 weeks by etretinate (1 mg/kg/d).[30]

Table I. Clinical presentations of keratoacanthoma

1. Solitary keratoacanthoma
2. Giant keratoacanthoma
3. Subungual keratoacanthoma
4. Keratoacanthoma centrifigum marginatum
5. Keratoacanthoma dyskeratoticum and segregans
6. Ferguson-Smith type (multiple self-healing keratoacanthoma)
7. Grzybowski type (generalized eruptive keratoacanthoma)
8. Witten and Zak type (multiple familial keratoacanthoma)

Other variants

9. Aggressive keratoacanthoma
10. Verrucous keratoacanthoma

Patients with KAs refractory to a single method of treatment present a diagnostic and therapeutic dilemma to the treating physicians. In these patients, the underlying possibility that the lesion will behave like a SCC must be borne in mind. The serial use of different treatments or the combination of excision, curettage and electrodesiccation, radiation therapy, intralesional chemotherapy, or oral retinoids is in order. Treatment options for KA are shown in Table II.

CONCLUSION

KA may develop in postoperative healing wounds or surgical scars after the removal of skin cancers. In the clinical setting of a rapidly growing nodule after operation for a previous skin cancer, the possibility should be kept in mind that this lesion

Table II. Treatments for keratoacanthoma

1. Surgical treatment: yields a histopathological report
   a. Curettage and desiccation
   b. Deep shave excisional biopsy
   c. Excision with wide margin
   d. Mohs micrographic surgery
2. Medical treatment: no histopathology obtained
   a. Oral administration: retinoids
   b. Intralesional injection: 5-fluorouracil, methotrexate, interferon 2alfa, bleomycin
3. Cryosurgery with local anesthesia
4. Radiation therapy
5. Observation only

may be a KA. KA may, therefore, be considered a postoperative complication of cancer operation in a predisposed individual. Our experience is that biopsy and a course of isotretinoin (1-2 mg/kg/d) for 1 month is an appropriate initial approach to this problem. Because these lesions have the potential to behave like a SCC, clinical judgement and pathology reports help determine the best treatment for recurrent lesions. The presence of cytokines and genetic mutations may stimulate the growth of KA locally and at distant sites after excision of skin cancers, especially SCC. Excision of the newly formed lesions restimulates the area, ultimately leading to renewed growth of the lesions at the surgical margins.

REFERENCES

1. Ferguson Smith J. Multiple primary, self-healing, prickle cell epithelioma of the skin. Br J Dermatol Syph 1948;60:315-8.
2. Grzybowski M. A case of peculiar generalized epithelial tumours of the skin. Br J Dermatol Syph 1950;62:310-3.
3. Jaber PW, Cooper PH, Greer KD. Generalized eruptive keratoacanthoma of Grzybowski. J Am Acad Dermatol 1993;29:299-304.
4. Agarwal M, Chander R, Karmakar S, Walia R. Multiple familial keratoacanthoma of Witten and Zak–a report of three siblings. Dermatology 1999;198:396-9.
5. Hamilton SA, Dickson WA, O'Brien CJ. Keratoacanthoma developing in a split skin graft donor site. Br J Plast Surg 1997;50: 560-1.
6. Gewirtzman A, Meirson DH, Rabinovitz H. Eruptive keratoacanthomas following carbon dioxide laser resurfacing. Dermatol Surg 1999;25:666-8.
7. Sina B, Adrian RM. Multiple keratoacanthomas possibly induced by psolarens and ultraviolet A photochemotherapy. J Am Acad Dermatol 1983;9:686-8.
8. Shaw JC, Storrs FJ, Everts E. Multiple keratoacanthomas after megavoltage radiation therapy. J Am Acad Dermatol 1990;23: 1009-11.
9. Pattee SF, Silvis NG. Keratoacanthoma developing in sites of previous trauma: a report of two cases and review of the literature. J Am Acad Dermatol 2003;48(Suppl):S35-8.
10. Street ML, White JW, Gibson LE. Multiple keratoacanthomas treated with oral retinoids. J Am Acad Dermatol 1990;23:862-6.
11. Levine N, Miller RC, Meyskens FL. Oral isotretinoin therapy. Arch Dermatol 1984;120:1215-7.
12. Shaw JC, White CR. Treatment of multiple keratoacanthomas with oral isotretinoin. J Am Acad Dermatol 1986;15:1079-82.
13. Poth DO. Tumor like keratosis: report of a case. Arch Dermatol Syph 1939;39:228-38.
14. Ghadially FN. A comparative morphological study of the keratoacanthoma of man and similar experimentally produced lesions in the rabbit. J Pathol Bacteriol 1958;75:441-53.
15. Hofmann C, Plewig G, Braun-Falco O. Bowenoid lesions; Bowen's disease and keratoacanthoma in long-term PUVA treated patients. Br J Dermatol 1979;101:685-92.
16. Hönigsmann H, Wolff K, Gschnait F, Brenner W, Jaschke E. Keratosis and nonmelanoma skin tumors in long-term photochemotherapy (PUVA). J Am Acad Dermatol 1980;3:406-14.
17. Hodak E, Jones RE, Ackerman AB. Solitary keratoacanthoma is a squamous cell carcinoma: three examples with metastases. Am J Dermatopathol 1993;15:332-42.
18. Wong W, Kolbusz RV, Goldberg LH, Guana A. Treatment of a recurrent keratoacanthoma with oral isotretinoin. Int J Dermatol 1994;33:579-83.
19. Nedwich JA. Evaluation of curettage and electrodessication in treatment of keratoacanthoma. Australas J Dermatol 1991;32: 137-41.
20. Goldschmidt H, Sherwin WK. Radiation therapy of giant aggressive keratoacanthomas. Arch Dermatol 1993;129:1162-5.
21. Donahue B, Cooper JS, Rush S. Treatment of aggressive keratoacanthomas by radiotherapy. J Am Acad Dermatol 1990;3:489-93.
22. Goette DK, Odom RB. Successful treatment of keratoacanthoma with intralesional fluorouracil. J Am Acad Dermatol 1980;2:212-6.
23. Parker C, Hanke CW. Large keratoacanthomas in difficult locations treated with intralesional 5-fluorouracil. J Am Acad Dermatol 1986;14:770-7.
24. Kestel JL, Blair DS. Keratoacanthoma treated with methotrexate [letter]. Arch Dermatol 1972;108:723-4.
25. Melton JL, Nelson BR, Sough DB, Brown MD, Swanson NA, Johnson TM. Treatment of keratoacanthomas with intralesional methotrexate. J Am Acad Dermatol 1991;25:1017-23.
26. Grob JJ, Suzini F, Richard MD, Weiller M, Zarour H, Noe C, et al. Large keratoacanthomas treated with intralesional interferon alfa-2a. J Am Acad Dermatol 1993;29:237-41.
27. Hay RJ, Champion RH, Greaves MW. Systemic therapy. In: Champion RH, Burton JL, Ebling FJD, editors. Textbook of dermatology. Vol 4. 5th ed. Boston: Blackwell; 1992. p. 2938-40.
28. Haydey RP, Reed ML, Dzubow LM, Shupack JL. Treatment of keratoacanthomas with oral 13-cis-retinoic acid. N Engl J Med 1980; 303:560-2.
29. Goldberg LH, Rosen T, Becker J, Knauss A. Treatment of solitary keratoacanthomas with oral isotretinoin. J Am Acad Dermatol 1990;23:934-6.
30. Watson AB. Etretinate therapy of solar-related keratoacanthoma. Australas J Dermatol 1993;34:9-11.