

Management of Keratoacanthomas with Intralesional Methotrexate Injection

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Six cases of keratoacanthoma (KA) were treated successfully with intralesional methotrexate. The rapid involution and excellent cosmetic result suggests that intralesional methotrexate may play a beneficial role in the treatment of these difficult lesions in aesthetically important areas.

Key Words: Keratoacanthoma, intralesional, methotrexate.

Keratoacanthomas are rapidly growing benign cutaneous neoplasms, usually occurring on sun-exposed areas of the body¹ and believed to arise from the hair follicle.² The first description in English language of this lesion was by Mac Cormac in 1936, and they called it *molluscum sebaceum*, but the term Keratoacanthoma (KA) was first proposed by Freudenthain in 1950.³ A characteristic feature of keratoacanthoma is that it grows rapidly, usually attaining a size about 10 to 25 mm in approximately 6 weeks. This is followed by slow involution over a period of 2 to 6 months, but sometimes involution can take over a year. This initial rapid growth followed by regression is thought to reflect the cyclic history of hair follicle.^{2, 4, 5} The other theory is that this regression is achieved by immunologic mechanisms.⁶ Clinically six different types have been described,^{7, 8, 9} but the commonest one is of the solitary type. Whatever the type, KA shows a basic gross and microscopic appearance. The mature lesion is dome shaped and is skin coloured or slightly reddish in hue with a keratinous plug in the centre. Microscopically there is a keratin shell crater, with hyperplasia and dyskeratosis of the adjacent epithelium. We report our clinical experience with KA patients treated with intralesional methotrexate therapy on outpatient basis.

Patients and Methods

Our study included a group of six, consecutive patients presenting with lesions morphologically typical of keratoacanthoma (Table 1). The diagnosis was made on history and morphological appearance. All patients satisfied the following criteria to be included in the study:

Patients suffering with blood dyscrasias, hepatic disease, or renal disease were excluded from the study.

All the lesions were solitary

Although all of our patients were above the age of fifty, we do not recommend excluding patients who are pregnant or breast-feeding.

The lesions were injected on an outpatient basis, each patient receiving an intralesional injection of methotrexate (MTX), 25 mg/ml. The drug was injected in the centre, indurated base, and all four quadrants of the lesion including the shoulder of the lesion i.e. at the junction of the indurated skin with the lesion. No local anaesthetic was

required, as the procedure was virtually free from pain and discomfort.

In order to prevent contamination from any accidental spillage of the drug during its administration, necessary precautions were under taken. Patient's eyes were covered, and the surgeon wore an apron, mask and gloves. It was noted that during injection, almost 50% of the drug leaked away from the centre of the crater. A dry dressing was applied to cover the treated lesion, while the patient was instructed to avoid touching the lesion and keep the area dry.

Patients were followed up on weekly basis and if the lesion responded to the treatment by showing evidence of resolution, a further dose of methotrexate was administered, the dose depending on previous response and the size of the remaining KA. If no resolution was evident, the lesion was submitted for excision with a view of it being a squamous cell carcinoma.

Results

Six consecutive patients with solitary keratoacanthomas (KA) were treated with intralesional methotrexate (MTX). None of the patients had a preoperative biopsy and the diagnosis was made on history and classical morphological appearance. The ages ranged from 52 to 82 years with a mean age of 70.8 years. All lesions occurred on sun-exposed areas of the body.

All lesions responded to treatment, with complete regression occurring after 3 to 7 weeks. The biggest lesion 3.8cms was located on the cheek and took the longest to respond. Patients required a minimum of 2 and a maximum of 3 injections.

The intralesional injection was followed by necrosis of the lesion few days later (Figures 1 and 2). Total dose of MTX injected in a lesion ranged from 76.5 mg to 175 mg. No side effects were noted in our patients. We had not used any local anaesthetic during the procedure and they all tolerated the treatment very well. The lesions healed with minimal scarring and good cosmetic result (Figures 3 and 4). Patients have been followed up for a minimum period of 12 months to a maximum of 24 months. No local recurrences have been noted.

Table 1 Keratoacanthoma patients treated with intralesional methotrexate

Age / Sex	Diameter (cm)	Location	Duration (months)	Injections	Week to heal	Total MTX (mg)
76/F	3	Cheek	3	3	5	110 mg
68/F	1.5	Forehead	8	2	3	76.5 mg
82/F	2.7	Hand	10	3	4	115 mg
76/F	3.2	Chest	11	4	5	125 mg
52/F	3.8	Cheek	4	4	7	175 mg

Discussion

About 72% to 97% of KAs are located on the face,^{10,11} cheeks, nose, eyelids, ears and lips being the most frequent locations. Because keratoacanthomas often involute spontaneously, some believe that they should merely be observed.¹² This involution is a slow process, extending over a period of 2-6 months, but sometimes involution can take over a year. Thomson found that the average regression time of the 48 keratoacanthomas he studied was 17 weeks.¹³ The decision to wait for spontaneous regression involves frequent patient follow-ups over a long period of time, a source of continuous anxiety to the patient and relatives and the resulting scar might be cosmetically less acceptable. At the same time there is always a possibility that the lesion might actually be a squamous cell carcinoma, and sitting idle on a suspicious lesion is not recommended. Hence for cosmetic and practical reasons it is always advisable to treat these lesions.

Different modalities of treatment include excision, radiotherapy, topical and intralesional 5-Fluorouracil, curettage and cautery, systemic retinoids, intralesional injection of methotrexate and Moh's micrographic surgery. Although surgical excision is currently the treatment of choice, occasionally however, the size and location of these lesions preclude complete excision without extensive reconstruction and/or scarring.

One of the various non-surgical modalities useful in managing KAs is radiotherapy. Most of the KAs are radiosensitive and response favourably to small doses of x-rays (600-1000 r).¹⁴ But the treatment requires expensive equipment, frequent hospital visits and there is always a risk of development of a malignant lesion within the treatment field in later years.¹⁵

Parker and Hanke have also used Intralesional 5-FU for the treatment of KAs with considerable success.¹⁶ But they did mention that the treatment might be ineffective in non-rapidly proliferating lesions. Kurtis and Rosen reported that the pain associated with intralesional injection of 5-FU required the addition of lidocaine.¹⁷

Intralesional and systemic methotrexate has been used in the past with encouraging results.¹⁸ Methotrexate most probably works by inhibiting DNA synthesis by inhibition of folate and dihydrofolate reductase.¹⁹ Systemically administered methotrexate has been found to be very useful in treating multiple keratoacanthomas and the larger, more aggressive keratoacanthomas.^{20,21}

In our study, six consecutive patients presenting with

keratoacanthoma were treated with intralesional methotrexate injections. It took between 3 to 7 weeks (with a mean of 4.8 weeks) for our patients to show complete resolution of their lesions. Melton et al have reported a quicker response to methotrexate.¹⁸ But the average size of KA in their patients was 1.8 cm while it was larger (2.4 cm) in our patients.

We found that no local anaesthetic was required, as the procedure was virtually pain free. The patient compliance was extremely good with no side effects.

We feel that the possible advantages of MTX over 5-FU as an intralesional agent include decreased number of patient visits and injections required greater efficacy, and decreased pain. The drug can be administered in lesions involving critical areas, where excision would require a skin graft or a flap cover, which would only compromise the final aesthetic result not to mention a surgical procedure, possible hospitalisation and an increase in treatment cost.

The main concern in treating KAs with MTX is the possibility that the lesion might be a squamous cell carcinoma.

Differential diagnosis between keratoacanthoma and a squamous cell carcinoma is extremely difficult and is not always easy to perform.²² Keratoacanthomas (KA) resembles squamous cell carcinomas (SCCs) except that, unlike SCCs, after a period of rapid growth over a few months they involute completely. Although it is a common belief that keratoacanthomas are squamous cell carcinomas which regress as a result of external (host) influence, results of a study carried out by Warring et al²³ rather suggests that KAs and SCCs are different de nove. Although we did not carry out pre-operative biopsies on our patients and the lesions were diagnosed on clinical appearance, all the patients responded with the treatment confirming our clinical diagnosis. But we do recommend that if the patient does not show a good response to first two injections, the lesion should be excised and submitted for histology.

Conclusions

The hastening of regression time and healing process, no side effects and cosmetically acceptable results suggest that intralesional injection of methotrexate is a good alternative to surgical excision in the management of keratoacanthomas (KA). But if the lesion fails to show response after two injections, excision biopsy is recommended in order to rule out squamous cell carcinoma.



Fig. 1.



Fig. 2



Fig. 3



Fig. 4

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