Successful treatment of a giant temporal keratoacanthoma with intralesional methotrexate

Gabrielė Jonauskaitė, MD[1], Agnė Vasiulytė, MD[1], Gintarė Kazbaraitė, MD[2], Tadas Raudonis, MD, PhD[2]

[1] Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2] Clinic of Infectious Diseases and Dermatovenereology, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Highlights

This case report demonstrates the complete resolution of a giant temporal keratoacanthoma in a high-risk elderly patient using intralesional methotrexate without surgical intervention. This approach serves as a highly effective, cosmetically favorable alternative to surgical excision, particularly for patients with fragile skin, advanced age, or other contraindications to surgery.

Introduction

Keratoacanthoma (KA) is a rare low-grade neoplasm, characterized by rapid growth, a squamoid appearance, and a tendency to occur in sun-exposed skin areas, particularly in elderly patients. The most common treatment modality for KA is surgical excision to avoid leaving potential malignant cutaneous squamous cell carcinomas (cSCC) untreated. However, KAs are known for their tendency to spontaneously regress, and surgery is often unnecessary when KA can be reliably distinguished from malignant lesions. Therefore, in high-risk scenarios, other less-invasive methods of treatment are preferable to prevent risks associated with surgery.[1] One possible non-surgical KA treatment method is intralesional methotrexate (MTX). MTX acts by inhibiting DNA synthesis by binding to dihydrofolate reductase, in turn reducing the formation of tetrahydrofolate and preventing the synthesis of thymidine.[2] Therefore, MTX primarily targets rapidly dividing tumor cells, leading to inhibition of cancerous growth or regression of malignant lesions.

We present a case report of an elderly patient with a giant KA, which was successfully treated using local MTX injections. Even after the initial MTX injection, significant improvement and shrinkage were noticeable. A total of 5 injections were administered, and no recurrence was observed.

Case Presentation

An 82-year-old woman presented with a large nodule on her face. Upon inspection, a nodule with central hyperkeratosis, up to 30 mm in diameter, was observed in the left temporal area (Figure 1). Digital dermoscopy of the keratotic nodule revealed a central keratin mass, white ring-like structures within the hair follicles, and white structureless areas. Subsequently, a 3-mm punch biopsy was taken from the nodule. Histopathological analysis results showed distinct epidermal hyperplasia, a moderate degree of keratinocyte atypia involving deep layers of the epidermis, and monomorphonuclear infiltration of the dermis (Figure 2). Considering the patient's clinical presentation, dermoscopic findings, and histopathological analysis results, which were consistent with KA, a diagnosis of KA was made.

Treatment with intralesional MTX injections was initiated. This treatment method was chosen owing to the patient's advanced age, concurrent use of anticoagulant medication, and the

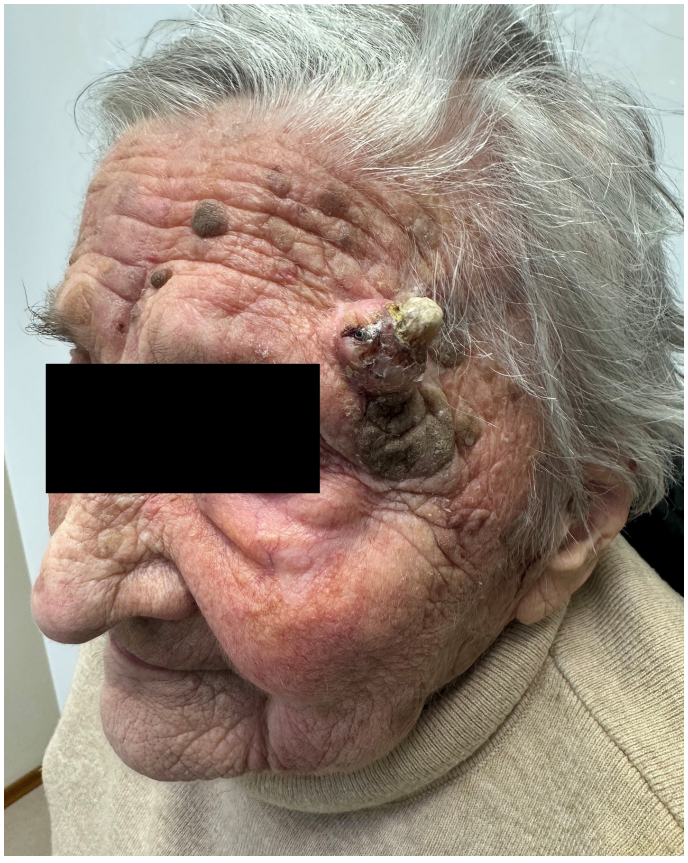

Figure 1. Giant keratoacanthoma with an eroded, irregular surface and a prominent central hyperkeratotic plug in the temporal area.

Corresponding Author: Gabrielė Jonauskaitė, MD, Faculty of Medicine, Vilnius University, M. K. Čiurlionio st. 21, LT-03101, Vilnius, Lithuania, Tel: +370-523-98700, Email: gabrielejon01@gmail.com
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presence of delicate, atrophic skin surrounding the tumor. Ten mg injections of MTX (0.2 ml; 50 mg/ml) were administered into the nodule, followed by 5 mg of oral folic acid the next day. Multiple MTX injections were administered at progressively increasing time intervals: 1 week, 1 month, 2 months, and 3 months.

A significant reduction in tumor size was evident just 1 week after treatment with only a single MTX injection. The lump in the left temporal area had shrunk, and the central hyperkeratosis had resolved (Figure 3). At the 1-month follow-up, after 2 intralesional MTX injections, the nodule had become barely noticeable. After 3 intralesional injections, the nodule had fully resorbed; only atrophy and erythema remained. A total of 5 injections were administered to conclude treatment, and no recurrence was observed 2 months after the final injection (Figure 4).

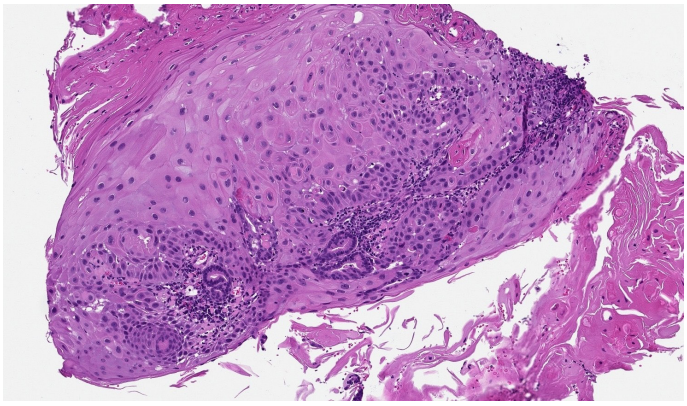

Figure 2. Histological image of the tumor showing pronounced epidermal hyperplasia, central hyperkeratotic plug, and a dense mononuclear dermal infiltrate, consistent with keratoacanthoma (hematoxylin-eosin, original magnification ×200).

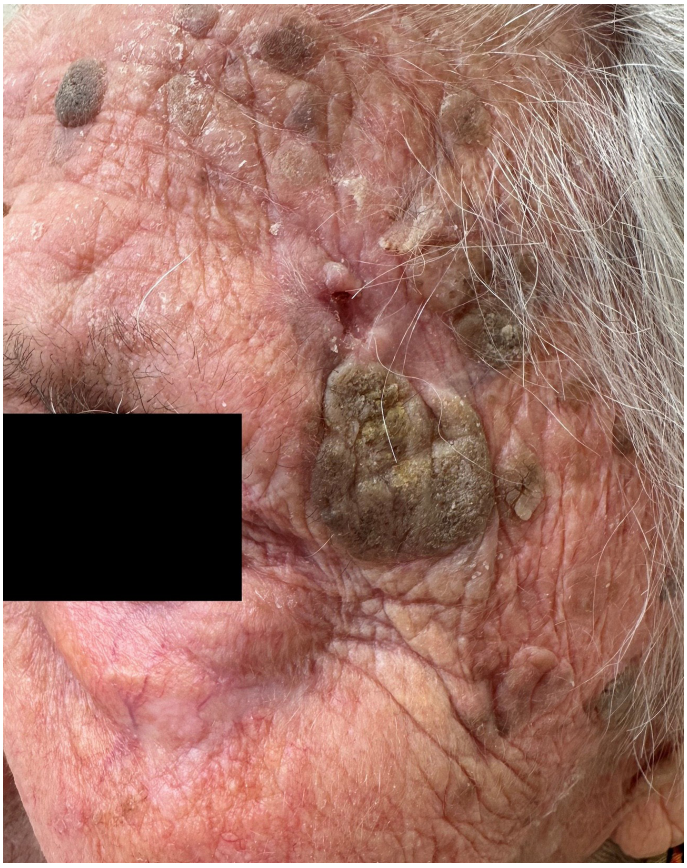

Figure 3. Keratoacanthoma regression after 2 methotrexate injections 1 month into treatment.

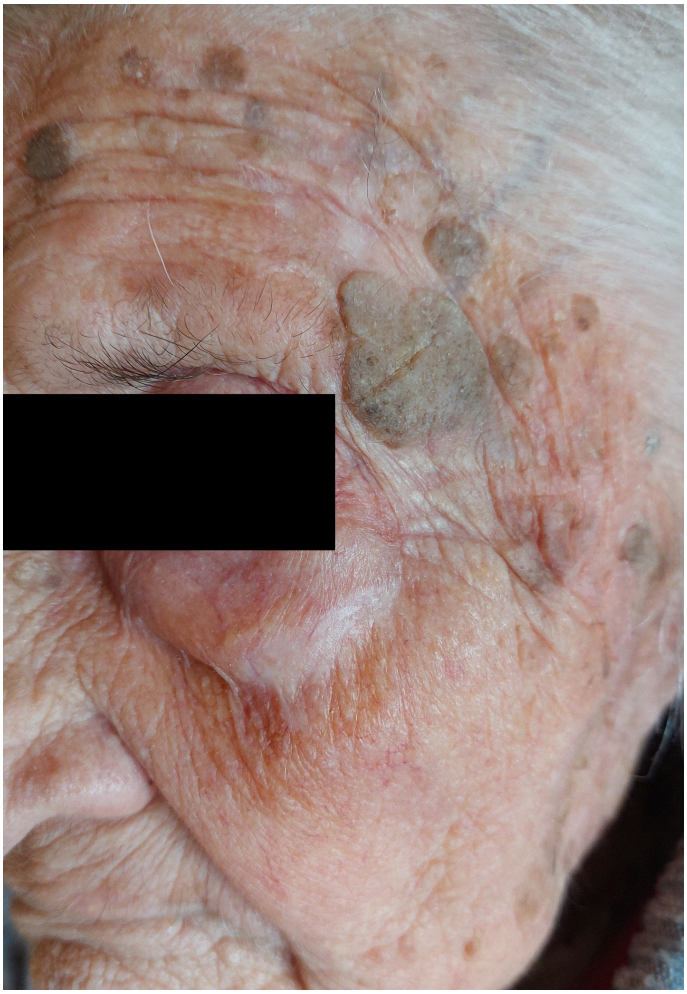

Figure 4. Total regression of the tumor 2 months after the final injection.

Discussion

KA arises from follicular infundibular or isthmic keratinocytes and most commonly develops in sun-exposed areas of the body, such as the face.[3] Only rarely, solitary lesions may be identified on mucous membranes, such as within the oral cavity.[4] Owing to the close pathohistological and clinical resemblance between KA and well-differentiated cSCC, as well as the absence of a definitive distinguishing marker, the true incidence of KA remains difficult to determine. Reported estimates range from 100 to 150 cases per 100,000 individuals, but the actual figure is likely much higher. As with cSCC, the major risk factors for KA development include ultraviolet exposure, immunosuppression, chronic wounds, radiation, and human papillomavirus infection.[1] Other commonly associated variables are older age, male sex, fair skin, smoking, certain medications, and genetic diseases.[5] KA is

also associated with cutaneous trauma, as lesions often develop at the sites of tissue injury, such as following laser therapy, cryotherapy, surgical procedures, or tattooing.[6,7] It is likely that the reported patient developed KA after laser ablation treatment of verrucous epidermal hyperplasia.

The classification of KA is a topic of active discussion in the scientific community. Given the often self-resolving nature of the lesions, KA is generally regarded as benign. However, some sources classify it as a low-grade cSCC, since rare cases of KA-associated metastasis and even death have been documented, and histologic differentiation between the 2 entities can be exceptionally challenging. Additionally, although KA itself is benign, it may transform into cSCC, suggesting that KA may be regarded as a subtype or precursor of cSCC.[8] Conversely, some studies have demonstrated that KA and cSCC exhibit distinctive gene expression profiles, supporting their differentiation as separate conditions.[9]

Clinically, KA manifests as a crater-like nodule, pink in color, with a keratotic plug in the center.[8] The most common form of KA is the solitary type, which typically measures up to 2 cm.[10] The lesion in our case was larger, and at 30 mm it can be classified as a giant KA.[11] Other forms of this tumor include KA centrifugum marginatum, subungual KA, multiple KA, mixed eruptive and self-healing type. KA progresses through 3 main histological phases: proliferation, maturation, and regression. During the proliferation phase, the central keratotic plug has not yet formed. In the maturation phase, the lesion develops more typical histopathological characteristics, including a central keratotic plug, overhanging epithelial lips, compact keratinization, and presents with an exo-endophytic squamous proliferation. During the regression phase, the characteristic central plug starts to clear out, while the epithelium starts to thin.[12]

To confirm the diagnosis of KA, a biopsy and a subsequent histopathological examination are performed. Hallmark features include a central keratotic plug; linear, dotted, or hairpin-shaped vascular patterns; a smooth, elevated, rolled border; a homogeneous pink or white rim; yellowish areas within the lesion; and regular architectural patterns.[13] The main challenge of managing KA and choosing the right treatment option is reliable differentiation between KA and cSCC—histologically, the latter is more invasive, exhibits more cytologic atypia and mitotic figures, as well as ulceration and a random distribution of pleomorphic cells.[12] Some sources also cite the predominance of white structures, including white circles, as a distinguishing feature more typical of cSCC than KA.[13]

The most common treatment modalities for KA remain Mohs micrographic surgery or standard surgical excision with 4 mm margins.[11] However, emerging alternative treatment possibilities are being explored to minimize the need for unnecessary invasive procedures. These include ionizing radiation, topical therapies with 5-fluorouracil and imiquimod, destructive techniques like electrodesiccation and curettage or cryotherapy, and laser-based treatment (eg, Argon or YAG lasers). Additionally, photodynamic therapy, systemic therapy (such as oral retinoids, cyclophosphamide, and other medications), and intralesional treatment, including 5-fluorouracil, corticosteroids, or MTX, are being used.[14] The focus of this article is intralesional MTX, which was selected as a less-invasive alternative to surgery.

The decision was made to avoid surgery because of the patient's advanced age, fragile skin, use of anticoagulants, as well as large size and facial location of the nodule, potentially complicating a radical surgical excision. This case report further supported the findings that intralesional MTX is an effective and safe treatment option for poor surgical candidates, especially with large KAs in cosmetically sensitive areas. It can be challenging to reliably distinguish KA from cSCC, for which surgical excision remains the gold standard treatment. However, according to a Korean study by Cho et al,[15] intralesional MTX is an effective and safe treatment modality for both KA and well-differentiated cSCC. The efficacy of this treatment method is discussed in the literature; for example, Moss et al[16] compared surgical treatment and intralesional MTX for KA and found that intralesional MTX has a cure rate of 88% with a minimum of 6 weeks without recurrence or further complications. Smith et al[17] reported an even higher treatment success rate of 95.7% for KA using intralesional MTX. Multiple intralesional MTX injections can also be used to achieve complete tumor involution, not only in solitary KAs,[18] but also, although rarely reported, in giant KAs.[19]

Our case report demonstrates that intralesional MTX can serve as an effective alternative treatment for giant KAs, especially in high-risk patients who are poor surgical candidates. Nonetheless, given the challenges of distinguishing KA from well-differentiated cSCC, detailed clinical and histopathological evaluation and careful selection of appropriate patients are essential when considering non-surgical therapies. Although the findings are promising, MTX currently remains an alternative treatment option for KA, and larger, long-term studies are necessary to validate its safety and efficacy.

Potential Conflicts of Interest: The authors declare no conflicts of interest.

Patient Consent: Written informed consent for the publication of clinical information and images was obtained from the patient.

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