

High Efficacy of 15 Mg Intralesional Methotrexate in Solitary Large Keratoachantoma Lesions: A Cases Series of 5 Subjects

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Abstract

Intralesional methotrexate (IL-MTX), at the dose of 20-25 mg per injection, could be a very effective and safe alternative treatment of keratoacanthoma (KA), especially for lesions not amenable to surgical removal. Here, we report a fast clinical efficacy of 15 mg IL-MTX injections performed for the treatment of 5 large solitary KA lesions. We report the clinical outcome of 5 subjects (three men and two women, mean age 79 years; range 56 to 92) with large KA lesions. For all lesions, a 3-mm punch biopsy confirmed the diagnosis of "squamous cell carcinoma, KA type". Lesions were located on the face (4 lesions) and one in the dorsal part of the hand. Lesions dimension area ranged from 2 to 28 cm² (average: 9 cm²; mean tumour diameter: 3.2 cm with a range from 1.5 to 6 cm). Due to the volume and locations of the lesions, treatment with IL-MTX was proposed to the patients. One intralesional MTX injection of 15 mg each was performed and repeated 1 week apart for up to four treatments. A complete resolution (clearance of the lesions=100%) was observed at the end of the IL-MTX cycle, and documented with high-resolution colour pictures, in 4 subjects (80% of the treated lesions). In a subject with a very large lesion (28cm²) located in the dorsal part of the hand a regression of >50% after IL-MTX was observed. After this volume reduction, surgical removal of the residual lesion was performed. The treatment was very well tolerated in all subjects. No local or systemic side effects were observed. This five-cases report suggests and confirms that 15 mg of intralesional MTX could be considered an effective and safe treatment of solitary KA located in difficult-to-treat areas.

Keywords: Case report; keratoacanthoma; Methotrexate intralesional

Introduction and Objectives

Keratoacanthoma (KA) is a skin cancer with in general a fast-growing behaviour [1]. KA generally occurs as solitary lesion [2]. KA is generally considered a well-differentiated squamous cell carcinoma, and it is characterized by rapid growth and possible spontaneous involution [3,4]. Even if commonly these skin lesions have a very low metastatic risk, some KAs could have an aggressive evolution leading to spreading and death [5]. Surgical excision, Mohs excision, curettage, and electrodesiccation represent first-choice treatment options [6]. However, invasive procedures could have several contraindications or limitations, mainly in the very old subjects. Several case reports and retrospective studies have demonstrated that intralesional methotrexate (MTX) could be a very effective and safe alternative treatment of KA, mainly in patients with multiple comorbidities [7-9] such as elderly people. Intralesional MTX could be also a therapeutic option in difficult to treat area for example the lips [10]. Della Valle and Milani [11] reported the high efficacy of intralesional MTX injections (total dose 40 mg) in a 99-year-old woman. Intralesional methotrexate (IL-MTX), at the dose of 20-25 mg per injection, could therefore considered to be a very effective and safe alternative

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treatment of KA, especially for lesions not amenable to surgical removal [12]. Here, we report a fast clinical efficacy of 15 mg IL-MTX injections performed for the treatment of 5 large solitary KA lesions.

Materials and Methods

We report the clinical outcome of 5 subjects (three men and two women, mean age 79 years; range 56 to 92) with large KA lesions. For all lesions, a 3-mm punch biopsy confirmed the diagnosis of "squamous cell carcinoma, KA type". Lesions were located on the face (4 lesions) and one in the dorsal part of the hand. Lesions' dimension area ranged from 2 to 28 cm² (average: 9 cm²; mean tumour diameter: 3.2 cm with a range from 1.5 to 6 cm). One intralesional MTX injection of 15 mg each was performed and repeated 1 week apart for up to four treatments. At each treatment session the KA lesion was infiltrated with a 0.38 ml pre-filled syringe containing 15 mg of MTX (Velos™; Cantabria Labs Difa Cooper, Italy). The total amount of MTX injected at each session was divided between five separate injection sites as follows: the shoulder of the lesion was injected at a depth of 2 to 8 mm (depending on lesion size) in all four quadrants in such a way as to blanch the entire rim of the lesion. All injections were performed with a 30-gauge needle. No local anaesthesia was necessary. All subjects were evaluated clinically and by blood tests 6 weeks after the last IL-MTX treatment to evaluate safety and tolerability profile of the treatment.

Results

This cases series has been collected between January 2019 and June 2020. All patients had typical solitary KA lesions on sun-exposed surfaces. In consideration of clinical aspects, the volume and localization of the lesions an intralesional treatment with methotrexate was proposed. IL-MTX was administered as described in the Material & Methods section. A complete resolution (clearance of the lesions=100%) was observed at the end of the IL-MTX cycle, and documented with high-resolution colour pictures (see figure), in 4 subjects (80% of the treated lesions). In a subject with a very large

lesion (28cm²) (case 3 in the Figure 1) located in the dorsal part of the hand a regression of >50% after IL-MTX was observed. After this volume reduction, surgical removal of the residual lesion was performed. The treatment was very well tolerated in all subjects. No local or systemic side effects were observed. No alterations of blood cells formula or hepatic and renal functions were detected. Pictures of the all 5 subjects are reported at baseline and after IL-MTX treatment.



Discussion

KAs are skin cancer lesions classified as well-differentiated squamous cell carcinoma [13]. The most common clinical presentation is a rapidly growing, well-demarcated nodular lesion [14]. These kinds of skin tumors are common in elderly subjects, with a peak incidence between 60 and 70 years of age, especially in sun-exposed areas [15].

Typical locations are the face, nose, neck, and dorsal hands [16]. The lesion evolves rapidly, and it is often tender. The rapidly growing phase could be followed by an involution phase [17]. KAs were believed in the past, to be benign lesions. KA are now considered as a variant of well-differentiated squamous cell carcinoma [18]. Even if it could be a very infrequent event, some KAs could have aggressive behaviour, leading to metastasis and possible death [19]. For this reason, KAs should be treated as squamous cell carcinoma. The option of surgical excision could be limited or contraindicated in some cases by the high morbidity associated with the procedure and the required extensive surgical reconstruction [20]. Radiotherapy is also a suitable therapeutic choice for KA; however, the risk of recurrence could be high. KA are skin lesions frequently detected in elderly subjects. In this population concomitant diseases or concomitant pharmacological treatments could represent relative or absolute contraindications to invasive treatment strategies such as surgery, Mohs surgery, and curettage. Topical 5-fluorouracil and intralesional MTX have been successfully used when invasive strategies are contraindicated or when cosmetically sensitive areas are involved [21]. In scientific literature, several case reports and retrospective studies have demonstrated that intralesional MTX could be a very effective and safe alternative treatment of KA [22]. Intralesional MTX could be also a therapeutic option in difficult to treat area for example the lips. Della Valle and Milani [23] reported the high efficacy of intralesional MTX injections (total dose 40 mg) in a 99-year-old woman. Intralesional methotrexate (IL-MTX), at the dose of 20-25 mg per injection, could therefore considered to be a very effective and safe alternative treatment of KA, especially for lesions not amenable to surgical removal [24]. The pharmacological background for the use of this molecule is that MTX is able to inhibit DNA synthesis in dividing cells [25,26]. There are several clinical contraindications for the use of MTX, for example active infections, liver diseases, blood dyscrasias and pregnancy [27]. The use of intralesional MTX in KA has been reported in several scientific publications involving more than 50 subjects aged between 53 and 90 years. In these patients, MTX was in general use with an average of 2.1 injections with an average cumulative dose of 38.2 mg. In this group of patients, a complete response was obtained in 80% of the treated subjects. In general, the treatment was well tolerated. Two cases of pancytopenia have been reported in these case series, but they have been observed in subjects with concomitant renal diseases [28]. Pancytopenia could be observed soon after the first MTX injection. The average age of subjects treated with intralesional MTX in these reports of the literature was 72 years (range 44-90). In our cases series no safety concerns regarding blood cells count and formula or hepatic and renal functions were detected.

Conclusion

This five-case report confirms that 15 mg of intralesional MTX could be considered an effective and safe treatment of solitary KA located in difficult-to-treat areas.

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