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Original Article

Intralesional Methotrexate Injection for the Treatment of Epithelial Crateriform Tumor

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ABSTRACT

Background: Intralesional methotrexate injection (IL-MTX) is an appropriate strategy for treating epithelial crateriform tumors (ECTs) when surgical excision can result in functional or cosmetic defects; however, not all ECTs are responsive to this treatment.
Objective: This study aimed to evaluate the effectiveness of IL-MTX for ECTs and to determine the differences in clinical response according to the pathological features.
Methods: The medical records of patients treated with IL-MTX for their ECTs were retrospectively reviewed. Effectiveness was evaluated in terms of size reduction and flattening.
Results: Twenty-five cases of ECTs with biopsy were included in this study. Eight cases of keratoacanthoma (KA) and 15 cases of squamous cell carcinoma (SCC) were identified, but 2 cases could not be clearly distinguished. Seventeen patients (68%) showed a response after injection, and response rate in KA and SCC were 75% (6/8) and 60% (9/15), respectively. Nine patients showed complete resolution with IL-MTX. Patients received 3 injections, and regression was observed in 7.56 weeks after the first injection. According to histopathological results, patients with KA and SCC received 2 and 3.33 injections, respectively, and complete resolution was observed after 7 and 7.67 weeks, respectively.
Conclusion: IL-MTX is safe and effective, and could be considered as a useful non-surgical treatment option for ECTs. Both KA and crateriform SCC showed good response; However, KA showed a better response.

Keywords: Keratoacanthoma; Methotrexate; Squamous cell carcinoma

INTRODUCTION

Epithelial crateriform tumor (ECT) is a group of cutaneous neoplasms characterized by a central keratin plug. Various epithelial skin tumors have a crateriform morphology. Ogita et al.[1] histologically classified ECTs into keratoacanthoma (KA) and 6 other types of tumors including crateriform squamous cell carcinoma (SCC). According to this study, KA is characterized by proliferation of large pale pink cells with a glassy appearance showing compact keratinization with a few layers of basophilic cells at the margins. In contrast, SCC shows atypical keratinocytes on whole lesion with less large pale pink cells. While pleomorphism is usually random in SCC, the early and well-developed stages of KA display a gradient of cellular pleomorphism with most of the pleomorphic keratinocytes at the periphery of the deep lobules. They also reported about 12% of ECT was KA with a conventional SCC component. Although KA is well known for its spontaneous involution, SCC exhibits aggressive behavior that leads to local tissue destruction. However, owing to the clinical and histological resemblances between these entities, distinguishing these is difficult[2]. Furthermore, the final size and resolution cannot be predicted during the initial stage[3]. Therefore, early ECT treatment is necessary.

Surgery remains the treatment of choice for both KA and SCC[3]. However, surgery can induce cosmetic or functional defects,

especially when the tumors are large or located in vulnerable areas like head and neck or hand. Therefore, effective non-surgical alternatives have been required for the treatment of ECTs. Previous studies have described the successful treatment of KA and SCC with intralesional methotrexate injections (IL-MTXs)[4,5], which suggests the possibility of IL-MTX as an alternative to the surgical treatment of ECTs.

However, not all ECTs are responsive to IL-MTX in clinical practice. Thus, understanding the exact effects of treatment and identifying the factors that might affect the therapeutic outcomes is important. Salido-Vallejo et al.[6] previously reported that a better response to IL-MTX is related to increased odds of occurrence of KA, rather than SCC.

We aimed to evaluate the efficacy of IL-MTX administration in the treatment of ECTs and to determine the differences in clinical response according to the pathological features.

MATERIALS AND METHODS

Medical records of patients treated with IL-MTX for ECTs were retrospectively reviewed. Data were collected from the electronic database of Korea University Medical Center. This study was approved by the Institutional Review Board (IRB) of Korea University Anam Hospital (IRB No. 2023AN0342) and informed consent was waived because of the retrospective nature of the study.

Patients treated with IL-MTX for ECTs between January 2015 and December 2022 were included in the study. Patients without biopsy result or whose treatment response could not be confirmed due to a lack of clinical photographs were excluded. Patient's age, tumor location, biopsy result, treatment interval, total treatment duration, and number of injections, and adverse reactions were collected from the medical records. Clinical photographs taken before and after the treatment were examined, and histopathological slides were reviewed. Tumor staging was done according to National Comprehensive Cancer Network guidelines® for squamous cell skin cancer (version 2. 2022) and computed tomography (CT) scan was taken if needed.

A 25-mg/ml solution of methotrexate (MTX) was injected directly into the tumor mass, until the tumor was filled with the solution and uniform blanching appears. The injections were repeated at 1- or 2-week intervals. The effectiveness of IL-MTX was evaluated in terms of size reduction and flattening of tumors. If a reduction in size or flattening was observed more than 20% change, we considered it was responsive and maintained therapy. Surgical removal was performed in the absence of changes or aggravation. If ECTs were completely or almost flattened, lesions were evaluated after 1- or 3-month interval. If flattening was maintained without exacerbation, we considered them as completely resolved. If ECTs were completely resolved by IL-MTX alone, the total duration of treatment and number of injections were calculated between the date of treatment initiation and that of confirmation of tumor disappearance. We switched to topical treatment with 5% imiquimod cream if lesions were much flattened and patients do not want injection therapy anymore. Surgical removal was performed if pathologic confirmation of clearance is needed after treatment.

Statistical analysis was done using SPSS software (version 23.0; IBM, Armonk, NY, USA). Fisher's exact test was used for comparing response rate. The p-values of <0.05 were considered statistically significant.

RESULTS

Overall, 25 patients were included in the study. The mean age was 75.44 (standard deviation [SD], 13.46) years. Thirteen (52%) were men. In 20 patients (80%), the tumors were located in the head and neck, and 4 tumors were located on the hands. The nose (n=5), and cheeks (n=6) were the most commonly affected regions.

Eight patients were diagnosed with KA, and 15 were diagnosed with SCC. In 2 cases, KA and well-differentiated SCC could not be clearly distinguished because 2 components of them are accompanied, and we defined them as "intermediate." Among the SCC cases, 13 were well-differentiated, one was moderately differentiated, and one was confirmed as verrucous SCC.

Patient demographics and tumor characteristics of every patients are summarized in **Table 1**.

KA

Eight cases were diagnosed as KA. The mean age of patients was 78.63 (SD, 7.21), and every tumor was located in head and neck area. The largest diameter of every case was less than 2 cm. Six patients (75%) showed a response after IL-MTX therapy. Two of them continued the therapy and complete resolution was shown with IL-MTX alone (**Fig. 1**). Two of the others completed a therapy with topical imiquimod after flattening following IL-MTX. The remaining patients stopped continuing further management after size reduction.

SCC

Fifteen cases were confirmed as SCC. The mean age of patients was 73.6 (SD, 15.37). Nine patients (60%) showed a response after IL-MTX therapy. Six of them continued the therapy and complete resolution was shown with IL-MTX alone (**Fig. 2**). In case of the other 3 responders, wide excision and topical imiquimod therapy were done in one case each. The remaining one stopped visiting the hospital after size reduction.

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Table 1. Demographics and tumor characteristics

No.	Sex/Age	Location	Diagnosis	Differentiation	Response	Size >2 cm	LN	Staging
1	F/83	Forehead	KA		R	No		
2	M/64	Nose	KA		R	No		
3	M/74	Nose	KA		R	No		
4	M/86	Cheek	KA		R	No		
5	M/76	Lip	KA		R	No		
6	F/80	Neck	KA		R	No		
7	M/81	Temple	KA		NR	No		
8	F/85	Cheek	KA		NR	No		
9	M/81	Scalp	SCC	Well	R	Yes	(–)	II
10	F/91	Scalp	SCC	Well	R	Yes	(–)	II
11	F/44	Nose	SCC	Well	R	No	(–)	I
12	M/51	Nose	SCC	Well	R	No	(–)	I
13	F/53	Hand	SCC	Well	R	No	(–)*	I
14	M/73	Hand	SCC	Well	R	No	(–)	I
15	M/86	Hand	SCC	Well	R	No	(–)	I
16	F/75	Cheek	SCC	Moderate	R	Yes	(–)	II
17	M/60	Ankle	SCC	Verrucous	R	Yes	(–)*	II
18	F/89	Temple	SCC	Well	NR	No	(–)*	I
19	F/78	Cheek	SCC	Well	NR	Yes	(–)*	II
20	F/82	Cheek	SCC	Well	NR	Yes	(–)*	II
21	M/84	Cheek	SCC	Well	NR	No	(–)	I
22	F/91	Lip	SCC	Well	NR	No	(–)	I
23	F/66	Hand	SCC	Well	NR	Yes	(–)	II
24	M/93	Nose	Intermediate		R	No	(–)	
25	M/60	Lip	Intermediate		R	Yes	(–)	

LN: lymph node metastasis, KA: keratoacanthoma, N: non-responder, R: responder, SCC: squamous cell carcinoma.
*Computed tomography scan was done for evaluation.

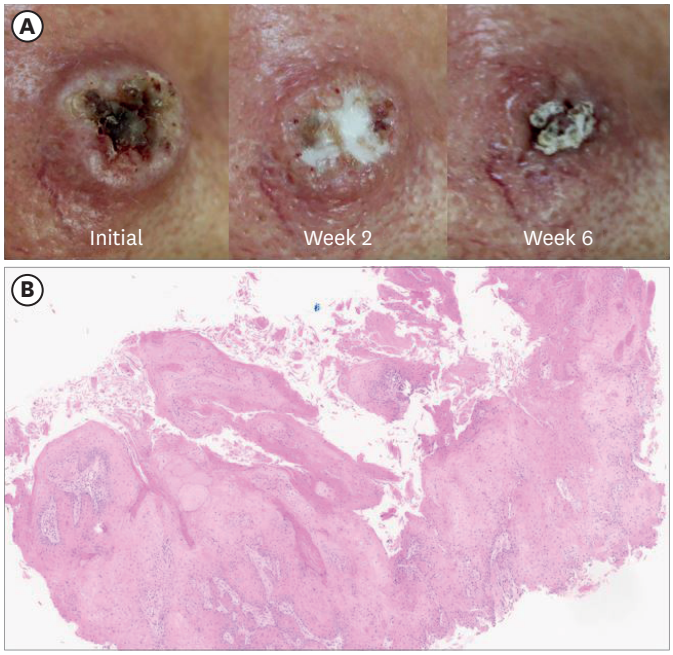

Fig. 1. Histopathologic findings and clinical response of keratoacanthoma completely resolved through intralesional methotrexate injection itself. (A) Clinical resolution after 2 injections. (B) Initial biopsy shows large pale pink cell proliferation with a glassy appearance and symmetrical crateriform architecture with peripheral collarette (hematoxylin and eosin, ×40).

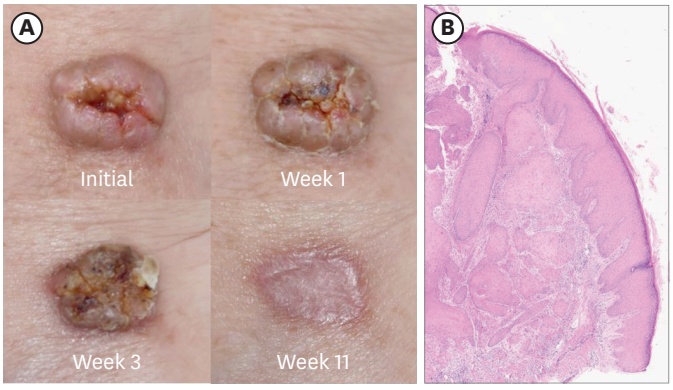

Fig. 2. Histopathologic findings and clinical response of well differentiated squamous cell carcinoma completely resolved through intralesional methotrexate injection itself. (A) Clinical resolution after 3 injections. (B) Initial biopsy shows tumor nests of atypical keratinocytes on whole lesion with less large pale pink cells compared to keratoacanthoma (hematoxylin and eosin, ×40).

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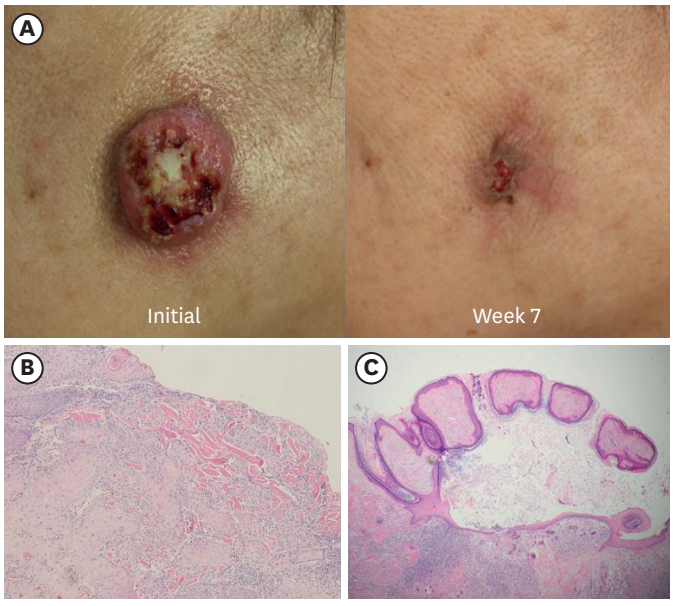

Fig. 3. Moderately differentiated squamous cell carcinoma completely resolved through intralesional methotrexate administration itself. (A) Complete resolution after 6 injections. (B) Initial biopsy shows pleomorphic atypical tumor nests invading deep dermal layer (H&E, ×100). (C) Complete resolution was pathologically confirmed after excision and cytologic atypia was not found in epithelial component (H&E, ×40).
H&E: hematoxylin and eosin.

Among 15 SCC cases, 7 cases had size over 2 cm, and 4 of them were responders (57.1%). Among the 8 tumors less than 2 cm, 5 of them were responders (62.5%). Significant difference in response rate according to tumor size was not shown in Fisher's exact test (p>0.05).

Remarkable lymph node involvement was not detected under palpation in most patients. CT scan was taken in 5 cases with suspicious lymph node enlargement and there was no evidence of lymph node involvement.

Other than 13 well-differentiated cases, one case of SCC with moderate differentiation and one case of verrucous SCC were included in our study, both of which showed a response to IL-MTX. For moderately differentiated SCC, the therapy was completed with wide excision, and complete resolution was confirmed pathologically (**Fig. 3**).

Overall response

Response rate to IL-MTX was higher in KA than SCC, but difference was not proven to be statistically significant (p>0.05). Regardless of pathologic diagnosis, 17 patients (68%) showed a response after IL-MTX therapy (6 KA, 9 SCC, and 2 intermediate). Patients with no significant response underwent surgical removal. No critical adverse events were observed during the treatment period.

ECTs on the head and neck showed a response rate of 65% and every patient with lesions located on the nose showed a response. ECTs on the hand showed a response rate of 75% (3/4).

Table 2. Treatment response of overall cases and completely resolved cases

Cases	Total No. of cases	No. of responders (rate)	Injection (times)	Duration (wk)
Overall cases				
Total	25	17 (68%)		
Diagnosis				
Keratoacanthoma	8	6 (75%)		
Squamous cell carcinoma	15	9 (60%)		
Intermediate	2	2 (100%)		
Completely resolved cases				
Total	9		3	7.56
Diagnosis				
Keratoacanthoma	2		2	7
Squamous cell carcinoma	6		3.33	7.67
Intermediate	1		3	8

Analysis of completely resolved cases

Nine cases that showed complete resolution with IL-MTX administration itself. They were confirmed as KA (n=2), SCC (n=6), or intermediate (n=1) through biopsy. The patients underwent 3 sessions of IL-MTX administration (mean; SD, 1.5), and complete resolution was observed at 7.56 weeks (mean; SD, 3.00) after the first day of injection.

Based on histopathological diagnosis, patients with KA and SCC underwent 2 (mean) and 3.33 (mean; SD, 1.75) times of injections, and complete resolution was observed after 7 (mean; SD 1.41) and 7.67 (mean; SD, 3.72) weeks, respectively. In one intermediate case, complete resolution was confirmed after 8 weeks and 3 injections were administered.

Treatment response of overall cases and completely resolved cases are summarized in **Table 2**.

DISCUSSION

In our patient group, 92% (23/25) of the patients with ECTs who underwent histological confirmation were diagnosed with KA or well-differentiated SCC. In the case of KA, although the wait-and-see approach until spontaneous regression can be considered, the final size until regression is unpredictable. SCC shows aggressive behavior, which leads to local tissue destruction and even metastasis. Therefore, treatment is required as soon as possible for ECTs, regardless of the histological diagnosis. Furthermore, 96% (24/25) of the ECTs were located on the head, neck, or hand, which is cosmetically and functionally important anatomical areas. These findings highlight the need for treatment modalities other than surgical resection.

MTX is an effective strategy for rapidly growing tumors

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because it prevents the synthesis of deoxyribonucleic acid nucleotides via competitive inhibition of folate reductase[7]. Intralesional application enables the direct delivery of MTX without systemic toxicity, and previous studies have described successful results of IL-MTX administration on KA and SCC[5].

Annest et al.[8] and Smith et al.[9] reported that IL-MTX for KA achieved treatment success in 83% and 95.7% of cases, respectively, in a retrospective analysis. In the case of SCC, the effect of neoadjuvant IL-MTX has been studied because complete surgical excision remains the treatment of choice. These studies reported tumor size reduction or better outcomes in the neoadjuvant IL-MTX group[10-13]. Bergón-Sendín et al.[12] confirmed that 92.5% of SCC cases showed a reduction in tumor thickness on ultrasound measurements after neoadjuvant IL-MTX. However, data on a SCC treated with IL-MTX alone are limited. Only one case of successful IL-MTX treatment has been reported, and the patient showed complete resolution after 3 monthly-interval sessions[14].

Most previous studies have separately investigated the effects of IL-MTX administration on KA and SCC. However, in clinical practice, when an epithelial tumor with a crateriform morphology is encountered, distinguishing between KA and SCC without total excision of the tumor is difficult, which leads to disfiguring scars. Less invasive biopsy techniques such as a punch or an incisional biopsy can be attempted; however, they do not guarantee precise diagnosis. Although some pathological features of KA such as an epithelial lip around the periphery with an extension over the crater and dermal islands of glassy eosinophilic hyaline keratinocytes have been reported[1,15], clearly distinguishing KA from SCC is challenging. The "intermediate" cases in our study correspond with this well-known fact. Therefore, a systematic study of all ECTs is necessary.

In this study, most ECTs were KA or well-differentiated SCC through histological analysis, which can provide a supportive background for the application of IL-MTX to ECTs. The overall response rate of ECTs to IL-MTX administration was 68% (17/25). The complete resolution with IL-MTX administration was confirmed in 9 patients. In previous studies, a systematic review showed 74%–100% of success rate in KA[5], and neoadjuvant IL-MTX in SCC showed size reduction in 93% of the cases[10].

According to clinical response, a larger ratio of KA to SCC was observed in the responder group than in the non-responder group (75% vs. 60%). This is accordant to a previous study with 89 patients, which showed that the well-responsive group had 10.5-fold increased odds of having KA[6]. Furthermore, we could know KA showed a better response to IL-MTX in terms of the number of injections and the duration until complete resolution was achieved in this study (**Table 2**). Therefore, differences in pathological features seem to exist according to the clinical response to IL-MTX, and we speculate that the response may help discriminate between KA and SCC, as a previous study implied[6].

In the case of SCC, previous studies have applied IL-MTX as a neoadjuvant aspect[10-13], followed by surgical excision. Our results show 20% of low-grade SCC was resolved by multiple IL-MTX, and unnecessary surgery can be avoided in some patients. This implies the possibility of IL-MTX administration as an early therapeutic option for some SCC rather than an auxiliary treatment. Moreover, one case of moderately differentiated SCC showed complete resolution with IL-MTX administration. Although further research should be done, pre-surgical IL-MTX administration can also be an option for patients with SCC of an unfavorable pathological type. However, it should be noted that all of our SCC cases were limited to stage I or II. There was no patient with tumor more than 4cm or lymph node involvement. We considered IL-MTX as first line therapy only for low grade localized lesions with small size.

To the best of our knowledge, this is the first study to analyze the effects of IL-MTX on tumors with a crateriform morphology independent of pathology, which may contain both KA and SCC. In contrary to previous studies reported effectiveness of IL-MTX for individual tumors, this study shows 68% of crateriform tumors were responsive to IL-MTX therapy regardless of pathologic diagnosis and KAs responded more favorably than SCCs. This study presents a useful treatment guide for ECTs for real-world practice. It can be considered affirmatively as early intervention for ECT in terms of as a treatment option or as a neoadjuvant therapy.

Although considering ethnic differences is important when dealing with various skin cancers, data on ECTs in Asian patients are insufficient. Yoo and Kim[16] confirmed that Korean patients with KA required more IL-MTX treatment sessions despite a short interval. The pharmacogenomics of MTX may influence the effect of IL-MTX[17], which requires further evaluation for each ethnic group. Although success rate showed some differences, IL-MTX administration may be a useful treatment option for Asian patients with crateriform tumors.

This study had several limitations other than its retrospective nature and small number of cases. First, considering the mechanism of action of IL-MTX[7], ECTs in the non-proliferative stage might not respond well. Furthermore, because there was no control group, we could not exclude the spontaneous regression effect of each tumor, and further studies are necessary to evaluate the predictive value of tumor stage, and large controlled trials are warranted. Moreover, additional study comparing the effect and prognosis of IL-MTX with those of excision-only or excision with neoadjuvant IL-MTX would further elucidate the significance of IL-MTX. Finally, IL-MTX is not approved officially as a treatment for cutaneous SCC yet, although there are many studies reporting the benefit of this treatment. Further research with many patients under randomized control to evaluate the efficacy and safety of IL-MTX for ECTs are required.

In conclusion, we suggest that IL-MTX administration is a safe and effective method and could be considered as a therapeutic or neoadjuvant option for epithelial tumors with crateriform morphology. Although IL-MTX was effective for both KA and crateriform SCC, it was more effective for KA.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

The data supporting the findings of this study are available from the corresponding author upon request.

REFERENCES

1. Ogita A, Ansai SI, Misago N, Anan T, Fukumoto T, Saeki H. Histopathological diagnosis of epithelial crateriform tumors: keratoacanthoma and other epithelial crateriform tumors. J Dermatol 2016;43:1321-1331. PUBMED | CROSSREF
2. Beham A, Regauer S, Soyer HP, Beham-Schmid C. Keratoacanthoma: a clinically distinct variant of well differentiated squamous cell carcinoma. Adv Anat Pathol 1998;5:269-280. PUBMED | CROSSREF
3. Kwiek B, Schwartz RA. Keratoacanthoma (KA): an update and review. J Am Acad Dermatol 2016;74:1220-1233. PUBMED | CROSSREF
4. Gualdi G, Caravello S, Frasci F, Giuliani F, Moro R, Fargnoli MC, et al. Intralesional methotrexate for the treatment of advanced keratinocytic tumors: a multi-center retrospective study. Dermatol Ther (Heidelb) 2020;10:769-777. PUBMED | CROSSREF
5. Searle T, Ali FR, Al-Niaimi F. Intralesional methotrexate in dermatology: diverse indications and practical considerations. Dermatol Ther 2021;34:e14404. PUBMED | CROSSREF
6. Salido-Vallejo R, Sanz-Cabanillas JL, Núñez-Córdoba JM, González-Menchen A, Vélez A, Redondo P. Clinical utility of intralesional methotrexate to distinguish crateriform keratinocytic tumors before surgery. J Dtsch Dermatol Ges 2022;20:102-105. PUBMED | CROSSREF
7. Olsen EA. The pharmacology of methotrexate. J Am Acad Dermatol 1991;25:306-318. PUBMED | CROSSREF
8. Annest NM, VanBeek MJ, Arpey CJ, Whitaker DC. Intralesional methotrexate treatment for keratoacanthoma tumors: a retrospective study and review of the literature. J Am Acad Dermatol 2007;56:989-993. PUBMED | CROSSREF
9. Smith C, Srivastava D, Nijhawan RI. Intralesional methotrexate for keratoacanthomas: a retrospective cohort study. J Am Acad Dermatol 2020;83:904-905. PUBMED | CROSSREF
10. Bergón-Sendín M, Pulido-Pérez A, Nieto-Benito LM, Barchino-Ortiz L, Díez-Sebastián J, Suárez-Fernández R. Effectiveness of neoadjuvant intralesional methotrexate in cutaneous squamous cell carcinoma: a prospective cohorts study. Dermatol Ther 2022;35:e15233. PUBMED | CROSSREF
11. Bergón-Sendín M, Parra-Blanco V, Pulido-Pérez A, Nieto-Benito LM, Rosell-Díaz ÁM, Suárez-Fernández R. Histological findings after intralesional methotrexate treatment in cutaneous squamous cell carcinoma. Dermatol Ther 2020;33:e14377. PUBMED | CROSSREF
12. Bergón-Sendín M, Pulido-Pérez A, Carretero López F, Díez-Sebastián J, Suárez-Fernández R. Cutaneous ultrasound for tumor thickness measurement in squamous cell carcinoma: the effect of neoadjuvant intralesional methotrexate in 40 patients. Dermatol Surg 2020;46:530-536. PUBMED | CROSSREF
13. Salido-Vallejo R, Cuevas-Asencio I, Garnacho-Sucedo G, González-Menchen A, Alcántara-Reifs C, De la Corte-Sánchez S, et al. Neoadjuvant intralesional methotrexate in cutaneous squamous cell carcinoma: a comparative cohort study. J Eur Acad Dermatol Venereol 2016;30:1120-1124. PUBMED | CROSSREF
14. Vega-González LG, Morales-Pérez MI, Molina-Pérez T, Sereno-Gómez B. Successful treatment of squamous cell carcinoma with intralesional methotrexate. JAAD Case Rep 2022;24:68-70. PUBMED | CROSSREF
15. Kiss N, Avci P, Bánvölgyi A, Lőrincz K, Szakonyi J, Gyöngyösi N, et al. Intralesional therapy for the treatment of keratoacanthoma. Dermatol Ther 2019;32:e12872. PUBMED | CROSSREF
16. Yoo MG, Kim IH. Intralesional methotrexate for the treatment of keratoacanthoma: retrospective study and review of the Korean literature. Ann Dermatol 2014;26:172-176. PUBMED | CROSSREF
17. Kremer JM. Methotrexate pharmacogenomics. Ann Rheum Dis 2006;65:1121-1123. PUBMED | CROSSREF