Clinical Letter

Clinical utility of intralesional methotrexate to distinguish crateriform keratinocytic tumors before surgery

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Dear Editors,

Keratoacanthoma (KA) and cutaneous squamous cell carcinoma (CSCC) may adopt an identical crateriform morphology. Nowadays, the debate about whether KA is a distinct entity, or a low-grade variant of cutaneous squamous cell carcinoma (CSCC) still persists. Since CSCC is a more aggressive neoplasm, misdiagnosing crateriform lesions may have a negative impact on the patient's prognosis. Evaluating a partial biopsy is extremely challenging to confidently distinguish KA from CSCC [1]. No distinctive gene expression profiles have been identified and no pathognomonic criteria to unequivocally differentiate between KA and CSCC exist [2]. Consequently, the surgical approach remains the gold standard in the management of crateriform tumors, especially those arising on the face.

With intralesional methotrexate (il-MTX) in monotherapy, neoadjuvant to surgery or administered with palliative intent [3], a remarkable reduction in the size of tumors could be shown, both for KA and for CSCC. Nevertheless, the response of KA to il-MTX appears higher than that of CSCC [4, 5]. In the absence of reliable diagnostic tools to clinically discriminate between KA and CSCC, the aim of this study was to evaluate whether crateriform tumors can be accurately classified as KA or SCC according to the reduction in tumor size occurring after a single il-MTX infiltration.

A retrospective cohort study was conducted from 2014 to 2019 at Reina Sofía University Hospital (Spain). The study protocol was approved by the Pharmacy and Therapeutics Institutional Review Board of this institution.

We included immunocompetent adults ≥ 18 years with a primary solitary crateriform tumor with no regressing features treated with il-MTX prior to conventional surgery. Exclusion criteria were history of glomerular filtration < 30 mg/mL, bone marrow or hepatic failure, hypersensitivity to methotrexate, pregnancy or breastfeeding and genetic disorders associated with cancer.

Neoadjuvant intralesional MTX was administered during the waiting period ahead of the scheduled surgery after informed consent was obtained. A diagnostic punch-biopsy was performed before administration of il-MTX in all tumors. Syringes pre-filled with MTX (25 mg/mL) were injected intralesionally using a 30-gauge needle until the tumor blanched. All lesions were excised by the same surgeon (R.S.V.).

The primary outcome was the reduction of tumor area defined as the difference between the initial area (before il-MTX) and the final area (pre-surgery).

We used logistic regression to estimate odds ratios (OR) and 95 % confidence intervals (95 % CI) for KA comparing groups of relative area lesion change after il-MTX, adjusting for age, sex, and location of tumor. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the power of relative area lesion change after il-MTX to discriminate between patients with KA and CSCC. *P* values < 0.05 indicated statistical significance.

Table 1 displays baseline characteristics of CSCC and KA groups. The average volume of MTX infiltrated was 0.57 ml (95 % CI: 0.51–0.62). The mean time between diagnosis and surgery was 18.4 days (95 % CI: 16.2–20.7) for CSCC patients and 21.9 days (95 % CI: 18.1–25.8) for KA patients (P = 0.119). The mean initial major diameter was 1.9 cm (95 % CI: 1.7–2.1) in CSCC and 1.4 cm (95 % CI: 1.2–1.6) in KA (P = 0.001). The mean initial area was 2.6 cm^2 (95 % CI: 2.0–3.1) in CSCC and 1.7 cm^2 (95 % CI: 1.0–2.3) in KA (P = 0.038).

After il-MTX infiltration, a reduction in tumor lesion area was observed in 31 CSCC patients (68.9 %) and 42 KA patients (95.5 %) (P = 0.001). No area variation was observed in three CSCC patients (6.7 %) and one KA patient (2.3 %). An area increase was observed in eleven CSCC patients (24.4 %) and in one KA patient (2.3 %). The mean values of final greatest diameter in the CSCC and KA patients were 1.76 cm (95 % CI: 1.53–1.99) and 0.71 cm (95 % CI: 0.50–0.92), respectively (P < 0.001).

The average percentage of area lesion change after il-MTX in KA (mean: –63.4 %; 95 % CI: –75.2 to –51.5) differed significantly from that in CSCC (mean: –11.5 %; 95 % CI: –22.3 to –0.6) (P < 0.001). Some examples are shown in Figure S1 (online supporting information). We estimated that for a one-percentage point reduction in lesion area after il-MTX, a statistically significant 3.96 % (95 % CI: 2.22–5.72 %) increase in the odds of having KA would be expected. Patients were categorized into two groups according to relative area lesion change (median = –36.2 %). When comparing with the group of patients in the lowest category (relative lesion area reduction lower than 36.2 %), patients in the highest category (relative area reduction greater than or equal to 36.2 %) showed a 10.5-fold increased odds of having a KA (95 % CI: 3.8–28.0). This association remained after adjusting for age, sex, or tumor location (Table 2).

The percentage of area lesion change showed a good ability to discriminate between KA and CSCC [AUC (95 % CI): 0.84 (0.76–0.92), P < 0.001] (Figure 1). We used two

Table 1 Baseline characteristics of eligible patients with crateriform keratinocytic tumors.

Patients	Total (n = 89)			CSCC (n = 45)			KA (n = 44)			P value
	n (%)	Mean (95 % IC)	Median (range)	n (%)	Mean (95 % IC)	Median (range)	n (%)	Mean (95 % IC)	Median (range)	
Age (years)		76.4 (73.6 to 79.3)	79 (40 to 103)		80.2 (76.9 to 83.4)	83 (54 to 95)		72.7 (68.0 to 77.4)	74.5 (40 to 103)	0.010
Men	52 (58.4)			31 (68.9)			21 (47.7)			0.043
Phototype										0.251
I–II	23 (25.8)			14 (31.1)			9 (20.5)			
III–IV	66 (74.2)			31 (68.9)			35 (79.5)			
Tumor lesions										
Sun-exposed location	66 (74.2)			38 (84.4)			28 (63.6)			0.025
Tumor evolution time (months)		2.8 (2.0 to 3.6)	2.0 (0.5 to 24.0)		3.5 (2.1 to 5.0)	2.0 (0.5 to 24.0)		2.1 (1.5 to 2.6)	2.0 (0.5 to 12.0)	0.066
Initial major diameter (cm)*		1.6 (1.5 to 1.8)	1.5 (0.5 to 4.2)		1.9 (1.7 to 2.1)	1.8 (0.7 to 4.0)		1.4 (1.2 to 1.6)	1.2 (0.5 to 4.2)	0.001
Initial minor diameter (cm)*		1.4 (1.2 to 1.5)	1.3 (0.5 to 4.2)		1.6 (1.4 to 1.8)	1.5 (0.5 to 3.0)		1.2 (1.0 to 1.4)	1.0 (0.5 to 4.2)	0.007
Initial area (cm^2)**		2.1 (1.7 to 2.6)	1.4 (0.2 to 13.9)		2.6 (2.0 to 3.1)	2.1 (0.4 to 9.4)		1.7 (1.0 to 2.3)	0.9 (0.2 to 13.9)	0.038
Time to surgery (days)		20.0 (17.9 to 22.1)	18.0 (7.0 to 60.0)		18.4 (16.2 to 20.7)	15.0 (7.0 to 37.0)		21.9 (18.1 to 25.8)	20.0 (7.0 to 60.0)	0.119
MTX infiltrated (ml)		0.57 (0.51 to 0.62)	0.50 (0.15 to 1.20)		0.64 (0.56 to 0.71)	0.60 (0.20 to 1.20)		0.49 (0.42 to 0.57)	0.50 (0.15 to 1.20)	0.008

Abbr.: 95 % CI, 95 % confidence interval; CSCC, cutaneous squamous cell carcinoma; KA, keratoacanthoma. *Tumor diameters were meticulously measured with a standardizer ruler by two board-certified physicians. **Tumor area measurements were calculated using the formula π x r x s [largest (r) and smallest (s) radius] after assuming a circular or elliptical morphology for all tumors.

Table 2 Estimated odds ratios for KA by level of relative lesion area change after il-MTX.

Relative area lesion change category	Less than 36.2 % reduction			Greater than or equal to 36.2 % reduction			
Relative area lesion change (%)	Mean	Median	Range	Mean	Median	Range	
	−0.5	−9.4	73.8 to −35.3	−72.9	−75.0	−36.2 to −100	
KA cases (%)	22.7			75.6			*P* value
Model 1: OR (95 % CI)*	1 (reference)			10.5 (3.9 to 28.0)			< 0.001
Model 2: OR (95 % CI)**	1 (reference)			10.5 (3.8 to 29.1)			< 0.001
Model 3: OR (95 % CI)***	1 (reference)			16.9 (5.1 to 55.7)			< 0.001
Model 4: OR (95 % CI)****	1 (reference)			15.1 (4.9 to 46.8)			< 0.001

Abbr.: 95 % CI, 95 % confidence interval; KA, keratoacanthoma; OR, Odds ratio.
*Not adjusted. **Adjusted for age ***Adjusted for sex. ****Adjusted for tumor anatomical location (sun-exposed or unexposed area).

alternative methods to explore the estimation of cut-points for relative area reduction after il-MTX with potential clinical usefulness to discriminate between KA and CSCC (Table 2).

Intralesional methotrexate has been shown to be a successful treatment for keratinocytic tumors. However, effectiveness rates vary considerably depending on which tumor is treated [4–6]. Successive il-MTX infiltrations have shown higher resolution rates in KA. Moss et al. reported that of the 64 KA that resolved after il-MTX, 70 % of cases needed > 1 infiltration [5]. We used a single dose of il-MTX as neoadjuvant therapy to surgery rather than as a main treatment, which may explain our lower response rates. Thus, when a significant reduction in size of a crateriform keratinocytic

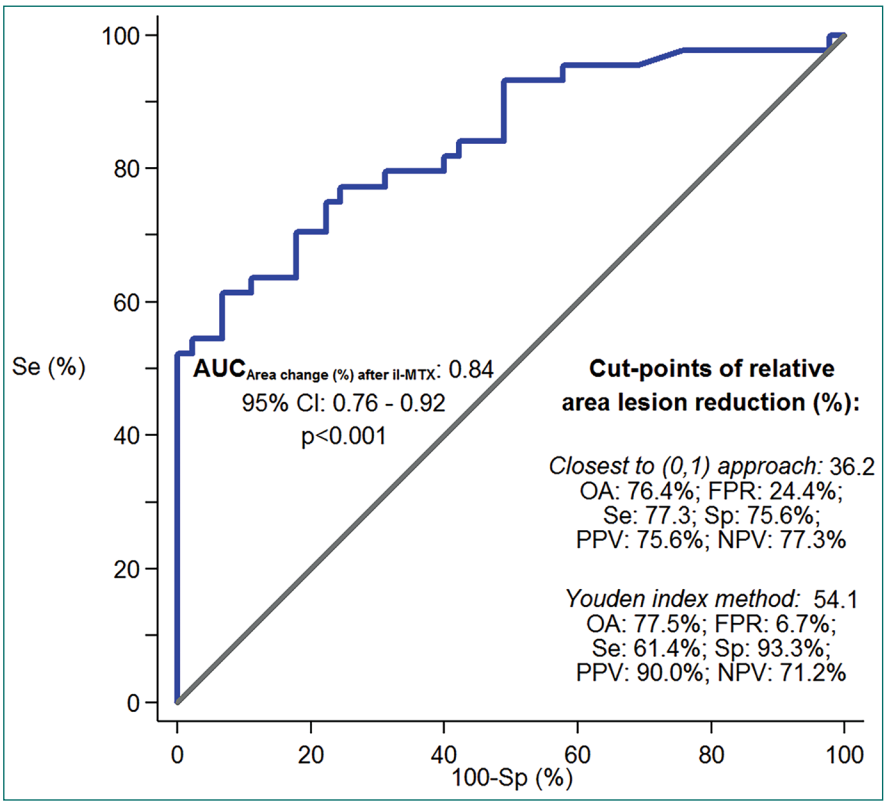

Figure 1 Receiver operating characteristic (ROC) curve for relative area lesion change after il-MTX treatment to discriminate KA tumors. Two criteria were used to estimate potential cut-points of relative area lesion change after il-MTX to discriminate KA tumors. Compared to the cut-point estimated with the closest to (0,1) criteria, the Youden index method cut-point showed higher Sp and PPV, and lower FPR and Se.
Abbr.: 95 % CI, 95 % confidence interval; AUC, area under the ROC curve; FPR, false positive rate; il-MTX, intralesional methotrexate; KA, keratoacanthoma; NPV, negative predictive value; OA, overall accuracy; PPV, positive predictive value; Se, sensitivity; Sp, specificity. Please replace "p<0.01" in the figure with "P < 0.01".

tumor occurs after il-MTX, a second administration could be appropriate given the high probability of an existing KA.

Our study is the first to use a standardized clinical practice protocol and to assess the response to il-MTX in KA and CSCC. We observed that relative area lesion change after il-MTX may be a potential indicator for clinical discrimination between KA and CSCC.

Misdiagnosis of CSCC as KA may be considered the worst scenario. However, the rate of false positive cases in our study was relatively low. Since il-MTX treatment can easily be performed during the pre-surgery waiting times found in the majority of hospitals, the procedure might not cause additional delay. If a complete response is not achieved, or a minimal reduction in size or even growth is observed, surgical excision should be performed as scheduled.

Our results suggest that a single MTX infiltration could help to predict the nature of the keratinocytic tumors before histopathological analysis. This may contribute to conservative management and allow surgery to be avoided in cases showing a significant response to il-MTX. These preliminary findings should be corroborated by additional, larger studies.

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Conflict of interest

None.

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