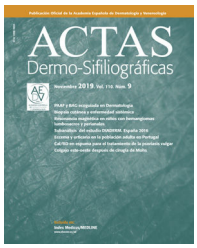
ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



LETTER TO THE EDITOR

[Translated article] Differentiating Keratoacanthoma From Squamous Cell Carcinoma: Are We Losing the Battle or Our Bearings? — Comment on ''Intralesional Methotrexate for Keratoacanthomas: A Case Series''

Diferenciación del queratoacantoma del carcinoma epidermoide cutáneo: ¿estamos perdiendo la batalla o perdiendo el norte? Comentario sobre *Tratamiento intralesional de queratoacantomas con metotrexato: serie de casos*

To the Editor,

We read with great interest the article ''Intralesional methotrexate for keratoacanthomas: A case series'' authored by Silvestre Torner et al.[1] and published in *Actas Dermosifilográficas*. We would like to share our thoughts on the management of keratoacanthomas, with a special focus on its diagnosis and treatment.

Since it was first described by Sir Jonathan Hutchinson back in 1888,[2] keratoacanthoma (KA) has been a challenging type of skin cancer for pathologists and dermatologists alike regarding its proper diagnosis and management. KA not only shares morphological and clinical similarities with the well-differentiated cutaneous squamous cell carcinoma (SCC),[3] but also controversies surrounding the malignant potential of KA, which fuel the debate on whether it should be considered an independent entity or part of a wider spectrum in which KA would represent benignity at one end and SCC malignancy at the other.[4] For this reason, KA is often treated like SCC and eventually excised with tumor-free resection margins.

The diagnosis of KA is based on 3 main characteristics:[2] a typical clinical presentation of a crateriform tumor, rapid growth with a 3-phase course over weeks or months (proliferation, stabilization, and regression), and a histopathological examination of a sufficiently representative biopsy sample. However, the final diagnosis and differentiation from SCC could depend on subtle architectural and cytological features leading to subjective interpretations among pathologists. In fact, a survey conducted among 17 anatomic pathology labs from Great Britain and Ireland, which studied a total of 11 718 biopsy samples coded as KA or SCC, found extreme variability in their final diagnoses, with SCC:KA ratios ranging from 2.5:1 to 139:1.[3]

In the immunohistochemistry setting, several attempts have been made to identify markers to distinguish KA from SCC. Most are associated with inflammatory infiltrates, cell cycle regulators (apoptosis and cell death), cell proliferation, cell surface proteins (related to adhesion, migration, and differentiation), and cell signaling.[2] Although the study of these markers has provided interesting data for understanding the pathogenesis of both entities, none of them has been capable of consistently defining the diagnosis of KA vs SCC.[5] This should not be surprising, because if there is considerable variability in the early diagnoses, there should also be a certain classification bias in these studies, thus leading to incorrectly attributing the results to one diagnosis or another right from the beginning.

In a world where life expectancy continues to increase, a growing incidence of age-related tumors such as KA and SCC among the elderly population can be expected. To avoid invasive procedures such as disfiguring surgeries, in this population, therapeutic trends should change and focus on finding balance among the 4 pillars of medical ethics: beneficence, non-maleficence, autonomy, and justice.[6]

In this regard, there is growing evidence on the efficacy profile of non-invasive procedures to treat KA and SCC.[7] Intralesional therapy with drugs such as methotrexate and 5-fluorouracil has demonstrated good results in the curative treatment of both KA,[8] and SCC, thus reducing the need for complex surgical reconstructions,[9] and even becoming curative.[10]

However, questions remain on what to do with KAs that remain unresponsive to intralesional therapy: could we, actually, be dealing with SCCs? Are there any markers to predict their response, regardless of the initial diagnosis? Although immunohistochemical markers have been widely

DOI of original article:
https://doi.org/10.1016/j.ad.2023.08.010

https://doi.org/10.1016/j.ad.2024.01.010

studied as a diagnostic tool in the management of both KA and SCC, they have not been evaluated as predictors of response to intralesional therapy regardless of diagnosis. As a matter of fact, such evaluation would require getting rid of the recurrent subjective classification bias, thus serving as a practical tool for therapeutic decision-making in our routine clinical practice.

Giving a specific name to a tumor may not be as important as predicting its biological behavior. Maybe time has come to accept that we may have actually lost the battle of trying to distinguish KA from SCC. Maybe we should start to reconsider our strategy and focus on potential new markers to predict the tumor's response to non-invasive therapies.

References

1. Silvestre Torner N, Gruber Velasco F, Romero Jiménez B, Vargas Laguna E. Intralesional methotrexate for keratoacanthomas: A case series. Tratamiento intralesional de queratoacantomas con metotrexato: serie de casos. Actas Dermosifiliogr. 2023;114:279–81, http://dx.doi.org/10.1016/j.ad.2022.04.021.
2. Kwiek B, Schwartz RA. Keratoacanthoma (KA): An update and review. J Am Acad Dermatol. 2016;74:1220–33, http://dx.doi.org/10.1016/j.jaad.2015.11.033.
3. Carr RA, Houghton JP. Histopathologists' approach to keratoacanthoma: A multisite survey of regional variation in Great Britain and Ireland. J Clin Pathol. 2014;67:637–8, http://dx.doi.org/10.1136/jclinpath-2014-202255.
4. Mandrell JC, Santa Cruz D. Keratoacanthoma: Hyperplasia, benign neoplasm, or a type of squamous cell carcinoma? Semin Diagn Pathol. 2009;26:150–63, http://dx.doi.org/10.1053/j.semdp.2009.09.003.
5. Nagarajan P. Differentiating keratoacanthoma from squamous cell carcinoma-In quest of the holy grail. J Cutan Pathol. 2020;47:418–20, http://dx.doi.org/10.1111/cup.13640.
6. Ovaitt AK, Hughley BB, McCammon S. Ethical considerations for elderly patients with cutaneous malignancy. Otolaryngol Clin North Am. 2021;54:415–23, http://dx.doi.org/10.1016/j.otc.2020.11.013.
7. 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.
8. Bosch-Amate X, Mancinelli C, Morgado-Carrasco D. RF - Non-surgical Treatment of Keratoacanthomas FR - Tratamiento no quirúrgico de los queratoacantomas. Actas Dermosifiliogr. 2022;113:192–4, http://dx.doi.org/10.1016/j.ad.2020.02.019.
9. 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, http://dx.doi.org/10.1111/dth.15233.
10. Gil-Lianes J, Morgado-Carrasco D. RF - Intralesional 5-Fluorouracil in the Treatment of Nonmelanoma Skin Cancer FR - Tratamiento intralesional del cáncer cutáneo no melanoma con 5-fluorouracilo. Actas Dermosifiliogr. 2023;114:255–6, http://dx.doi.org/10.1016/j.ad.2021.07.029.

P. López Sanz[a,*], M. Fernández-Parrado[b], E. Escario Travesedo[a]

[a] *Servicio de Dermatología, Hospital General Universitario de Albacete, Albacete, Spain*
[b] *Servicio de Dermatología, Hospital Universitario de Navarra, Pamplona, Spain*

* Corresponding author.
E-mail address: lopezsanzpablo@gmail.com (P. López Sanz).