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LETTER

Two birds with one stone: Successful treatment with methotrexate in a patient with generalized eruptive keratoacanthoma of Grzybowski and rheumatoid arthritis

Generalized eruptive keratoacanthoma (GEKA) is an extremely rare variant of multiple keratoacanthoma (KA) affecting the skin and mucous membranes, described for the first time by Grzybowski in 1950.[1] So far, approximately 30 cases are reported worldwide.[2]

Middle-aged adults in the fifth to seventh decades of life are typically affected, without sex predilection, and most of the reported patients are white. No familial tendency has been observed and all cases were sporadic.[3]

The etiology remains unknown; a viral pathogenesis was postulated by Grzybowski[2] with the addiction of ultraviolet radiation as a triggering factor,[4,5] supported by the predilection for sun-exposed sites and the reported initiation and exacerbation of lesions following sun exposure.

The course of the disease is chronic and often demonstrates a poor response to therapy. Although oral retinoids represent the most frequently used therapeutic approach, several alternative treatments are reported for patients refractory to this regimen, with often discouraging results.[6]

We report the case of a patient with GEKA who went into remission with methotrexate treatment.

A 70-year-old woman presented with a 6-month history of widespread itching scaly papules and nodules, with sudden onset. Personal medical history revealed a history of sun exposure, hypertension, and a recent diagnosis of early rheumatoid arthritis. There was no family history of any type of cancer, including non-melanoma skin cancer.

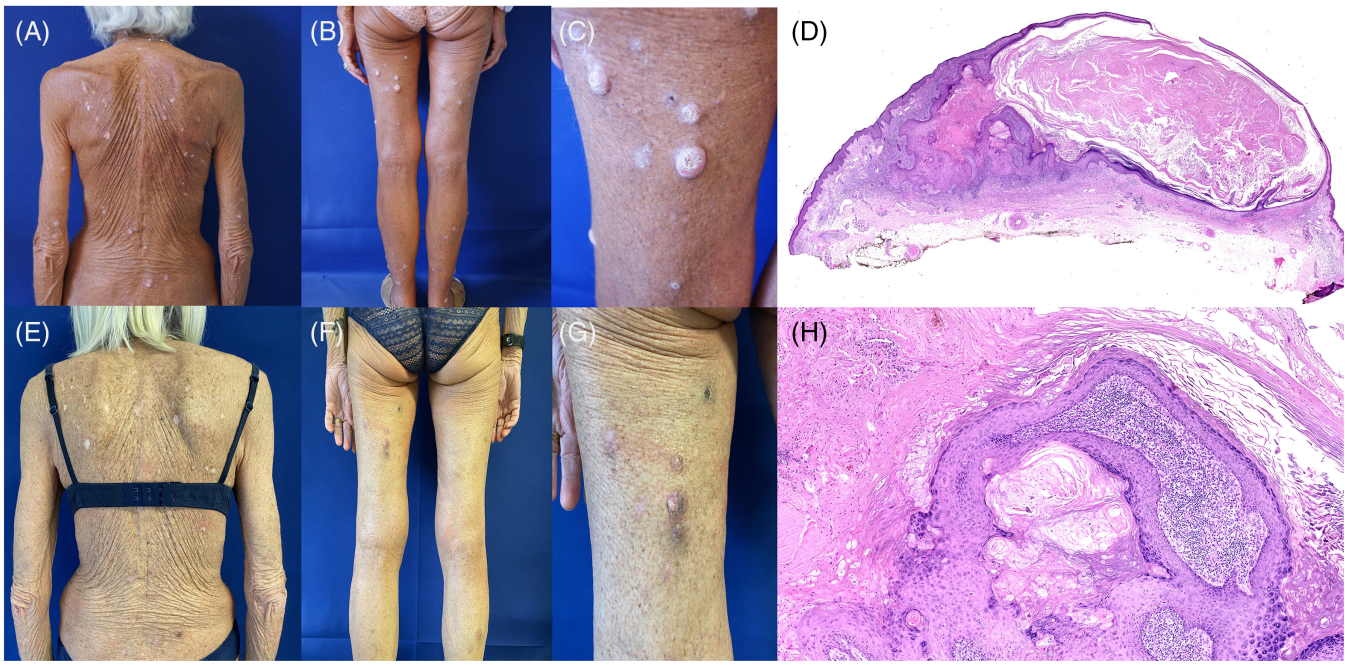

FIGURE 1 Several follicular papules and erythematous nodules with keratotic centers on trunk (A) and lower limbs (B). Detail of some crateriform nodules of the lower limb (C). Histopathological examination revealed ortho-and parakeratotic cells within central crater and of atypical keratinocytes in the infundibulum of the follicles (D,H). Disappearance of pruritus and of the majority of lesions after 4 months of administration of subcutaneous methotrexate at the dosage of 15 mg/week (E–H)

At dermatological evaluation there were numerous follicular papules and several erythematous nodules with keratotic centers on the upper limbs, lower limbs, and trunk; eight crateriform tumors were also detected (Figure 1A–C). The physical examination did not show any mucosal involvement or lymphadenopathy. Blood exams were within the normal range and human immunodeficiency virus was not detected.

Histopathological examination of the specimen obtained from one crateriform lesion revealed ortho-and parakeratotic cells within central crater and, in the other side proliferation, of atypical keratinocytes in the infundibulum of the follicles (Figure 1D,H).

A conclusive diagnosis of GEKA was made.

It was recommended to the patient to avoid sun exposure and to use sunscreens with high sun protection factor (SPF 50/50+). The largest skin lesions were surgically removed and oral acitretin was started (0.5 mg/kg/day), without any substantial improvement after 5 months of treatment. Therefore, a treatment with subcutaneous methotrexate (MTX) 15 mg/week was undertaken, resulting in the disappearance of pruritus and the majority of lesions after 4 months (Figure 1D–F). The dosage was then tapered (10 mg/week); no new lesions appeared during the treatment and following a 1 year of follow-up.

The choice of MTX in our patient was also guided by the recent diagnosis of rheumatoid arthritis, this therapy has in fact allowed to control both diseases with a single drug.

Nofal et al.[7] proposed the following consistent diagnostic criteria for GEKA: generalized eruption of disseminated well-demarcated papules with progressive course, onset in adulthood, lack of family history, typical histopathology, and severe and persistent itch. Variable criteria include a masked face, mucosal lesions, crateriform nodules, and ectropion.

These criteria allow to differentiate this form from other variants, such as the Ferguson–Smith-type (familial, non-pruritic, multiple self-healing KA arising on sun-exposed areas) and the Witten–Zak type (multiple familial KA).

In general, eruptive KA are considered a rare and serious disorders because the eruption is diffuse, persistent and recurrent; pruritus is constant, the treatment is often disappointing and the disease remains a continuing therapeutic challenge.[8,9]

MTX is reported by other authors as a second-line therapy in GEKA, with contradictory results.[6,10,11]

Although there are few cases of GEKA treated in with MTX, several cases of therapeutic success of intralesional MTX in patients with KAs, including eruptive ones, are found in the literature.[12–14]

The effectiveness of MTX in keratinocytic tumors is likely related to its antiproliferative and anti-tumoral activity: the competitive inhibition of the folic acid reductase enzyme, which is essential to supply methyl donor groups for DNA, enables the conversion of dihydrofolic to tetrahydrofolic acid, blocking the production of thymidylic acid, a pyrimidine metabolite. Without thymidylic acid, DNA synthesis is impossible and cell division is therefore arrested.[12]

In our case, subcutaneous administration was preferred over intralesional administration of MTX for two main reasons: (1) higher patient compliance, given the number of lesions to be treated, (2) potential benefit in treating rheumatoid arthritis of MTX being administered subcutaneously.

Our patient had an excellent response to moderate doses of MTX, and the disease control was maintained even at lower doses, with the important benefit of simultaneously controlling the progression of rheumatoid arthritis.

However, a careful counseling about the sun protection was crucial, given the patient's history of sun exposition and chronic photodamage.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Filippi Federica[1,2]
Miriam Anna Carpanese[1,2]
Lidia Sacchelli[1,2]
Camilla Loi[1,2]
Marco Adriano Chessa[1,2]
Federico Bardazzi[1,2]

[1]*Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy*
[2]*Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*

Correspondence
Filippi Federica Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Massarenti, 1 40138 Bologna, Italy.
Email: federicafilippi8@gmail.com

ORCID

Filippi Federica https://orcid.org/0000-0001-8173-4257
Lidia Sacchelli https://orcid.org/0000-0003-4388-4523
Camilla Loi https://orcid.org/0000-0001-6700-9534

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