Gottron-Like Papules Induced by Sunitinib

Erupción simulando pápulas de Gottron inducida por sunitinib

To the Editor:

Sunitinib (Sutent; Pfizer, New York, USA) is a kinase pathway inhibitor that suppresses angiogenesis and cell proliferation. This antineoplastic agent is associated with several mild adverse events that include diarrhea, nausea, fatigue, and hypertension, as well as numerous skin lesions.[1-4] However, skin lesions resembling Gottron papules typical of dermatomyositis and that resolve after sunitinib is decreased or withdrawn have not previously been recognized.

We present the case of a 73-year-old man, diagnosed with metastatic kidney cancer, who had been receiving oral sunitinib monotherapy 375 mg/d for 4 years, with an acceptable level of disease control. The patient was referred to our department for assessment of a painful, asymptomatic, erythematous-violaceous, moderately indurated, confluent dermatosis that was present bilaterally and was most intense over the metacarpophalangeal joints and, to a lesser extent, the interphalangeal joints. This inflammatory process followed a linear distribution over the extensor tendons of the hands and feet (Figure 1, A and B). Strikingly, the palms of the hands and soles of the feet were completely unaffected.

Physical examination revealed no fever, joint pain, or any skin or systemic signs characteristic of dermatomyositis. Complete blood count included antinuclear antibodies, extractable nuclear antigens, anti-Jo1 antibodies, anti-Mi2 antibodies, creatine kinase, and aldolase; there were no significant abnormalities.

As a relationship with sunitinib treatment was suspected, a punch-biopsy was taken from one of the most infiltrated areas located in the skin overlying one of the interphalangeal joints. Histopathology confirmed microscopic changes similar to those commonly observed in patients treated with cytotoxic chemotherapeutic drugs, which include the presence of necrotic keratinocytes with loss of polarization, multiple mitoses in the basal and suprabasal epidermal layers, and a discrete intraepidermal and superficial perivascular lymphocytic infiltrate. In particular, in the lower third of the epidermis, there were numerous enlarged keratinocytes with an edematous eosinophilic cytoplasm, hyperchromatic nuclei, and prominent nucleoli, associated with spongiosis that gave rise to a pseudostratified pattern (Figure 2, A and B). Further histopathological findings of interest were changes in the eccrine ducts, compatible with eccrine squamous syringometaplasia (Figure 2, C and D). According to our experience, this phenomenon is a common finding in patients treated with kinase inhibitors.

Given the clinical and histological suspicion of toxicoderma caused by sunitinib, the decision was taken, in agreement with the oncologist, to withdraw the drug. The lesions immediately began to regress, leading to complete remission 3 months after withdrawal of the sunitinib.

Six months later, the drug was reintroduced due to recurrence of the neoplastic disease. Three months after its reintroduction, the skin lesions recurred and followed the same clinical pattern described above. The patient suffered considerable discomfort and was unable to engage in normal daily activities or even sleep; the total dosage of sunitinib was therefore reduced by 15%, leading to control of the symptoms.

Sunitinib is an oral kinase inhibitor that acts on various receptors, including vascular endothelial growth factor receptors 1 and 3, platelet-derived growth factor receptor α, colony-stimulating factor 1 receptor, and glial cell line-derived neurotrophic factor receptor. It also blocks the expression of various proteins, especially proteins KIT/CD117 and Flt-3.[4,5] Approved indications for this drug currently include gastrointestinal stromal tumors resistant to treatment with imatinib and metastatic kidney cancer.[4,5] Hand-foot skin reactions and stomatitis are the 2 most important adverse skin reactions to this anticancer drug and have been described in 36% of cases.[1-6] These hand-foot reactions are characterized by the appearance of erythematous-desquamative plaques that progressively develop a rough keratin layer on their surface in the form of a callus.[6] These lesions characteristically appear at pressure points on the palms and soles, and sometimes appear as lesions on the dorsal aspect of the fingers. In our patient, the palms and soles were completely unaffected.

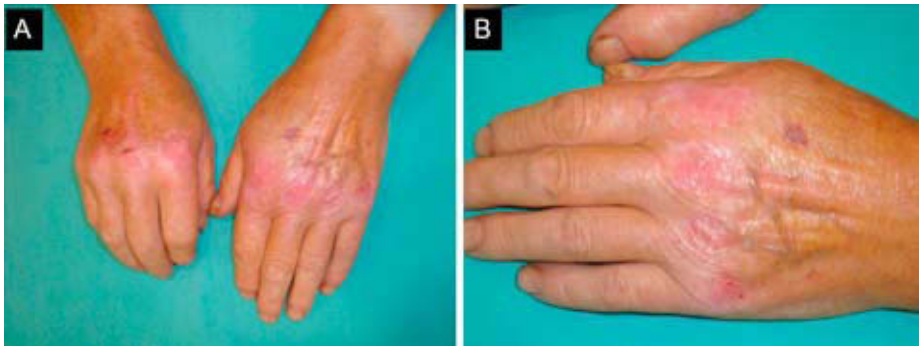

Figure 1 A and B, Nonpruritic, confluent violaceous erythema affecting the skin, present bilaterally, mainly over the metacarpophalangeal joints.

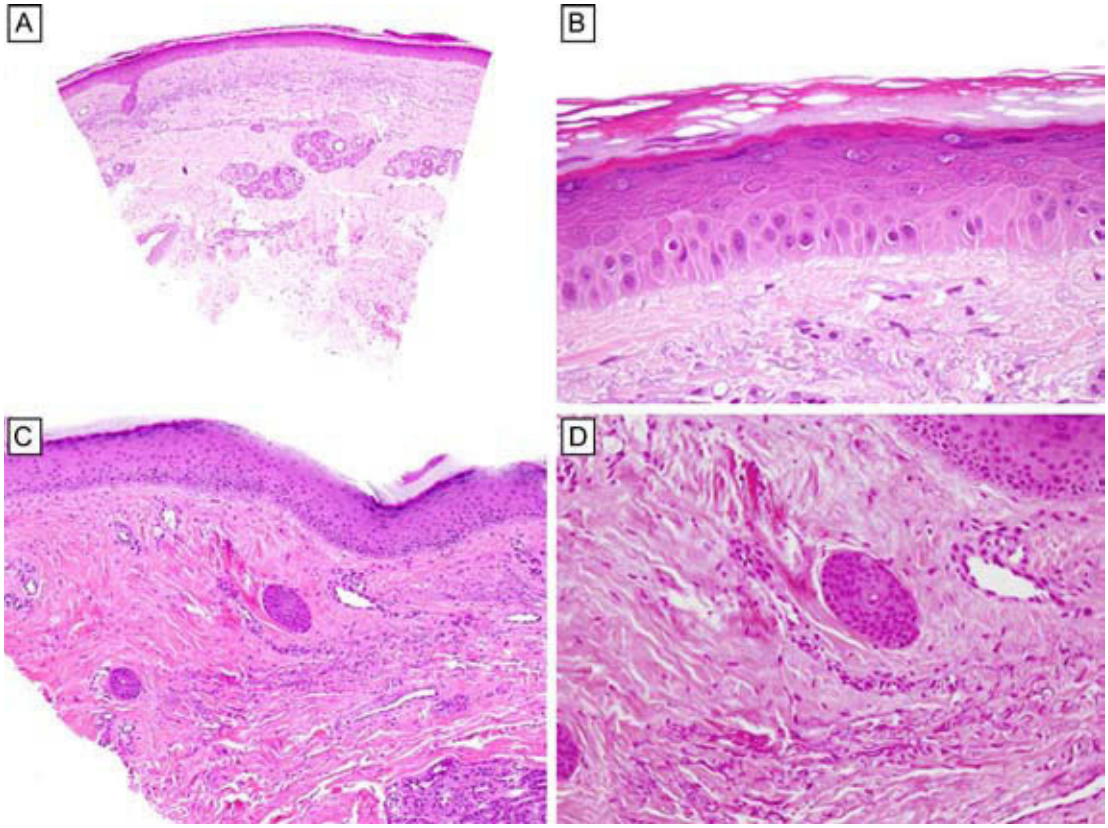

Figure 2 A, Presence of keratinocytes with loss of polarization, multiple mitoses in the basal and suprabasal epidermal layers, and an intraepidermal and superficial perivascular lymphocytic infiltrate (hematoxylin-eosin, original magnification, ×25). B, Multiple keratinocytes with edematous eosinophilic cytoplasm, hyperchromatic nuclei, and prominent nucleoli, arranged in a pseudostratified pattern in the lower third of the epidermis (hematoxylin-eosin, original magnification, ×100). C and D, Changes in the eccrine ducts compatible with eccrine squamous syringometaplasia (hematoxylin-eosin; C: original magnification, ×25; D, original magnification, ×100).

Other adverse skin reactions associated with this drug include, in descending order of frequency, facial swelling, yellowish skin discoloration, hair color changes, splinter hemorrhages, erythematous rash on the trunk, alopecia, facial acneiform rash, and dysesthesia of the scalp.[1-4]

We describe a case of a chronic rash with a clinical pattern similar to Gottron papules; this is considered to be a finding characteristic of dermatomyositis. The absence of systemic symptoms, other skin lesions, and blood abnormalities, together with the histological findings described above, suggest the role of sunitinib as the etiologic agent of the skin reactions. This dermatomyositis-like pattern has been previously described in patients undergoing treatment with hydroxyurea over extended periods of time.[7]

It is important to recognize the different adverse skin reactions associated with this drug, due to the increase in its long-term use in the management of oncological diseases.

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A. Martorell-Calatayud,[a,*] O. Sanmartín,[a] V. Traves-Zapata,[b] C. Guillén[a]

[a]*Servicio de Dermatología, Fundación Instituto Valenciano de Oncología, Valencia, Spain*
[b]*Servicio de Anatomía Patológica, Fundación Instituto Valenciano de Oncología, Valencia, Spain*

*Corresponding author.
Email address: antmarto@hotmail.com
(A. Martorell-Calatayud).

Reproducibility of the Diagnosis of Onychomycosis by Dermatologists in a Clinical Setting

Reproducibilidad del diagnóstico dermatológico de onicomicosis en el ámbito clínico

To the Editor:

We recently published a brief report describing observer agreement in the dermatologic context of toenail disorders.[1] The report described good agreement for most signs of onychomycosis except for transverse striae, trachyonychia, and changes in color of the nail plate. Earlier studies suggested that the clinical diagnosis of onychomycosis by dermatologists can show a surprising level of agreement, whereas more specific signs of onychomycosis are less reproducible, suggesting that there are clinical criteria other than those conventionally used in reaching the dermatologic diagnosis of onychomycosis.[2] Further to our preceding study, we decided to investigate the reproducibility of a clinical diagnosis of onychomycosis in the dermatologic outpatient setting.

To do so, we carried out a new prospective cross-sectional study in 3 dermatology departments, following approval from the ethics committee of each hospital. In the study, examination of the nails of consecutive patients older than 30 years of age seen in the dermatology outpatient clinics at these hospitals was added to the protocol for routine dermatologic examination. The study recruited patients who presented nail abnormalities in which onychomycosis was included in the differential diagnosis (together with onycholysis, subungueal hyperkeratosis, change in color or dystrophy of the nail plate, all larger than 5 mm). All patients (N=76) gave their consent to participate in the study. Each patient was separately examined by 2 dermatologists who answered the question "Is onychomycosis the most likely diagnosis?" Stata 10.1 (StataCorp, College Station, Texas, USA) was then used to calculate the κ statistic (a measure of interobserver agreement to exclude what would be expected by chance). The study was conducted by 8 dermatologists, grouped in interchangeable pairs, each of which contributed between 6 and 36 diagnostic assessments.

The dermatologist pairs obtained a total probability of agreement of 71%, compared to 51% expected by chance. The κ statistic was 0.41, which indicates moderate agreement as defined by Landis-Koch.[3] The κ values vary according to the prevalence of the clinical findings (in our study, the prevalence would correspond to the one observed in a general dermatology outpatient clinic, allowing it to be generalized to similar clinical settings).

Our results suggest that the dermatologic diagnosis of onychomycosis is readily reproducible between observers and, therefore, may be considered a valuable component in the clinical diagnosis of the condition. Nevertheless, its validity should be investigated in future studies.

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M. Cabanillas,[a,*] I. García-Doval,[b] B. Monteagudo,[a] O. Suárez-Amor,[a] F. Allegue,[c] L. Pérez-Pérez,[c] M. Ginarte,[d] J. Labandeira,[d] A. Zulaica[c]

[a]*Servicio de Dermatología, Complejo Hospitalario Arquitecto Marcide-Novoa Santos, SERGAS, Ferrol, La Coruña, Spain*
[b]*Servicio de Dermatología, Complexo Hospitalario de Pontevedra (CHOP), SERGAS, Pontevedra, Spain*
[c]*Servicio de Dermatología, Complexo Hospitalario Universitario de Vigo (CHUVI), SERGAS, Vigo, Pontevedra, Spain*
[d]*Servicio de Dermatología, Complexo Hospitalario Universitario de Santiago (CHUS) SERGAS, Facultad de Medicina, Santiago de Compostela, La Coruña, Spain*

*Corresponding author.
E-mail address: Miguel.Cabanillas.Gonzalez@sergas.es
(M. Cabanillas).