Thrombocytopenia Probably Induced by Acitretin

Trombocitopenia en probable relación con acitretina

To the Editor:

Retinoids are nonsteroidal hormonal compounds related to retinol. They were discovered more than 50 years ago and have various biologic effects. The oral retinoids currently used in dermatology have different indications and include isotretinoin, acitretin, bexarotene, and alitretinoin. We present the case of a patient who developed thrombocytopenia that was probably induced by acitretin.

The patient was a 78-year-old man with hypertriglyceridemia that had been controlled with fenofibrate for the previous 5 months. He consulted with lesions on the hands that had appeared with a burning sensation 8 months previously. Physical examination revealed delimited hyperkeratotic plaques on the palms and dorsum with nail pitting. He was diagnosed with psoriasis. The results of a complete blood count and biochemistry were normal, and treatment was started with acitretin (Acitretina IFC, 25 mg/d). The follow-up analysis performed 6 weeks later revealed a platelet count of 6000/μL (normal range, 177,000-450,000/μL). The patient was asymptomatic, with no bleeding, fever, or other manifestations. A complete blood workup (clotting, biochemistry [kidney profile, liver profile with lactate dehydrogenase], antinuclear antibodies, anti-DNA antibodies, lupus anticoagulant, antiphospholipid antibodies, complement, electrophoresis, immunoglobulins, thyroid hormones, vitamin B₁₂, folic acid, and serology [hepatitis B and C, human immunodeficiency virus]) was performed to rule out possible causes of thrombocytopenia. The results were normal. Abdominal ultrasound revealed fatty liver disease with no splenomegaly. Specialists from the hematology department decided to suspend acitretin as a potential cause, since it had been started only a short time previously. Fenofibrate was maintained, and intravenous immunoglobulin was started (0.4 g/kg in 3 doses), as was methylprednisolone (1 mg/kg/d, tapering dose). The platelet count returned to normal 4 weeks later (226,000/μL). The skin lesions were treated with topical corticosteroids. The complete blood count remained unaltered 6 months later.

Acitretin is a second-generation monooacetic retinoid. It is an active metabolite of its precursor, etretinate, and has been marketed since 1997. Acitretin is indicated for severe psoriasis, pustular psoriasis, congenital ichthyosis and ichthyosiform disorders, cutaneous and mucous lichen planus, and severe disorders with dyskeratosis and/or hyperkeratosis. It has an antiproliferative effect on psoriatic plaques, reducing thickness, erythema, and desquamation. It also has an anti-inflammatory effect. Given that its pharmacokinetics, effectiveness, and adverse reactions vary from person to person, the dose must be selected on an individual basis, with every attempt made to reach a minimum efficacious dose. Like all retinoids, it is teratogenic, and most adverse effects are dose-dependent and reversible. The most frequent are mucocutaneous effects and lipid and hepatic abnormalities. The Summary of Product Characteristics of Neotigason and that of Acitretina IFC do not mention hematologic abnormalities, and a review of the literature reveals few cases. In fact, no cases of thrombocytopenia induced by acitretin have been reported, although 3 cases caused by etretinate (10-50 mg/d) have been described in psoriasis patients between 15 days and 2 months after initiation of treatment; the platelet count fell to 2000 in one of the cases and took more than 2 years to return to normal. In the remaining cases, values took weeks to return to normal. The Summary of Product Characteristics of isotretinoin reports anemia, thrombocytopenia, thrombocytosis, and neutropenia as common adverse effects. The literature contains 5 case reports of thrombocytopenia that appeared between a few days and up to 6 months after initiation of isotretinoin. Diagnosis of the cases of retinoid-induced thrombocytopenia was based on symptoms once other causes had been ruled out. Other reported hematologic abnormalities include acitretin-induced agranulocytosis (1 case), neutropenia (2 cases), and isotretinoin-induced agranulocytosis (2 cases). Furthermore, there has also been a report of a case of paroxysmal nocturnal hemoglobinuria and another of anemia caused by vitamin B₁₂ and folic acid deficiency induced by isotretinoin. In the case of bexarotene and alitretinoin, the Summary of Product Characteristics reports hematologic abnormalities. Leukopenia, mainly neutropenia, is common with bexarotene, although platelet abnormalities are unusual; thrombocytosis is common with alitretinoin.

The mechanisms underlying drug-induced thrombocytopenia fall into 2 categories: suppression of platelet

Table 1 Criteria for the Diagnosis of Drug-Induced Thrombocytopenia.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initiation of the suspect drug before onset of thrombocytopenia and normalization of the platelet count after withdrawal</td>
</tr>
<tr>
<td>2</td>
<td>The suspect drug is the only one administered before onset of thrombocytopenia or other drugs are continued or reintroduced after withdrawal of the suspect drug, with no changes in the platelet count</td>
</tr>
<tr>
<td>3</td>
<td>Other causes of thrombocytopenia are ruled out</td>
</tr>
<tr>
<td>4</td>
<td>Reintroduction of the suspect drug induces recurrence of thrombocytopenia or thrombocytopenia is detected in laboratory tests</td>
</tr>
</tbody>
</table>

Level of Evidence

Definitive: Criteria 1, 2, 3, and 4
Probable: Criteria 1, 2, and 3
Possible: Criterion 1
Improbable: Absence of criterion 1

Source: Chong et al.
production in bone marrow and increased destruction or clearance of platelets in peripheral blood. The first is accompa-
nied by pancytopenia, which is usually caused by chemotherapy, and is dose-dependent. The second mechanism is divided
into 3 subtypes: the nonimmune subtype, in which the drug
has a toxic effect on platelets; the immune subtype, which is
carried by drug-specific antibodies that bind to the platelets
and is responsible for most cases of drug-induced thrombo-
cytopenia; and the autoimmune subtype, in which antibodi-
es are not drug-dependent. The most frequently involved
drugs are quinine and trimethoprim-sulfamethoxazole, although
vancomycin, anti-inflammatory drugs, anticonvulsive
agents, diuretics, and tuberculous drugs also play a role.
The incidence of drug-induced thrombocytopenia is
around 0.6-1.6 cases/100 000 person-years, although this
figure may be underestimated. The condition should be
suspected mainly in polymedicated hospitalized adults
with severe acute thrombocytopenia (generally <10 000/μL).
Drug-induced thrombocytopenia usually appears 1 to 2
weeks after initiation of therapy, and recurrences are
observed early after reinduction. Patients usually present
petechiae, purpura, hematomas, mucosal bleeding, and a
risk of internal bleeding (including brain hemorrhage).
The condition can also be fatal. Diagnosis is based on clinical
findings, depending on the temporal relationship between
initiation of drug therapy and onset of thrombocytopenia
and after ruling out other causes (infection [mainly viral],
vaccination, pregnancy, lymphoproliferative diseases,
autoimmune diseases, and idiopathic thrombocytopenic
purpura) (Table 1). The ideal approach would be to demon-
strate the presence of specific antiplatelet antibodies;
however, the relevant tests are not usually available and are
not performed as part of daily clinical practice. The platelet
count recovers 1 to 2 weeks after the culprit drug has been
withdrawn; in severe cases, corticosteroids, immunoglobu-
linis, and even platelet transfusions are necessary. In patients
with drug-induced thrombocytopenia, corticosteroids can be
withdrawn quickly after the platelet count recovers; in
idiopathic thrombocytopenic purpura, however, the course of
treatment is longer. In the case we report, thrombocy-
topenia resolved quickly after withdrawal of acitretin and
treatment with corticosteroids and immunoglobulins. Given
the clear temporal relationship and clinical course after
withdrawal of acitretin, we decided not to readminister
the potential culprit drug to confirm the diagnosis.

References
1. Acitretina. Ficha técnica o resumen de las características
del producto [accessed November 19, 2014]. Available in:
2. Carretero G, Ribera M, Belinchón I, Carrascosa JM, Puig L,
3. Seishima M, Oda M, Yamanaka S. Thrombocytopenia possi-
5. Liang R. Thrombocytopenia associated with etretinate therapy.
S, Curto-Iglesias JR. [Transient thrombocytopenia proba-
bly induced by isotretinoin] Spanish. Actas Dermosifiliogr.
7. Chave TA, Mortimer NJ, Hutchinson PE. Agranulocytosis and
8. Commens C. Cyclical neutropenia and retinoid therapy with
9. Özdemir MA, Kose M, Karakkucu M, Ferahtas A, Patiroglu T,
Koklu E. Isotretinoin-induced agranulocytosis. Pediatr Dermo-
10. Chong BH, Choi PY, Khachigian L, Perdomo J. Drug-induced
11. M. García-Arpa,* M. López-Nieto,
J.L. Santiago Sánchez-Mateos, M. P. Sánchez-Caminero
Servicio de Dermatología, Hospital General Universitario
de Ciudad Real, Ciudad Real, Spain
*Corresponding author.
E-mail address: mgarcia73@yahoo.es (M. García-Arpa).

Cerebral Involvement as the First Extracutaneous
Manifestation of Mycosis
Fungoides

*Mycosis fungoide con afectación cerebral como primera manifestación extracutánea

To the Editor:

Mycosis fungoides is the most common cutaneous lymphoma.
The probability of systemic involvement depends on disease
extension and is very low during the early stages, when the
clinical course is usually indolent. However, the risk of extra-
cutaneous disease 20 years after diagnosis is 10% in patients
with generalized plaques and 35.5% in patients with tumor-
ous lesions. The most common finding is enlarged regional
lymph nodes, although any organ can be affected, especially
the lungs, spleen, liver, and gastrointestinal tract. Central
nervous system (CNS) involvement is very uncommon, even
more so in the absence of extracutaneous disease.

The patient was a 47-year-old woman with erythematous-
desquamative lesions that first appeared 6 years previously
and were diagnosed as stage 1b mycosis fungoides after
4 inconclusive biopsies. During a 4-year follow-up period
she received treatment with potent topical corticosteroids,
psoralen-UV-A, interferon, and oral bexarotene. During the
last year, the patient developed tumors lesions (Fig. 1A),
with 14% Sézary cells (<1 000/μL) in peripheral blood and
unremarkable findings on a computed tomography (CT) scan