Severe Rhabdomyolysis Associated With Low-Dose Isotretinoin Therapy

Rabdomiolisis grave asociada al tratamiento con bajas dosis de isotretinoína

To the Editor:

Isotretinoin revolutionized the treatment of acne\(^1\) and has been used successfully in many other skin diseases.\(^2\) Its adverse effects, which are fewer at low doses of the drug, have been well described.\(^3\) Frequent side effects are muscle pain and elevated serum creatine kinase (CK) concentrations.\(^4,5\) However, few publications on an association of this drug and rhabdomyolysis have appeared. We report the case of a patient who developed severe rhabdomyolysis while on a low-dose regimen of isotretinoin.

A 30-year-old man with no remarkable medical history, who was a fourth-year resident physician in dermatology, self-prescribed oral isotretinoin at a dose of 20 mg/wk to treat seborrheic dermatitis refractory to topical agents. He did not undergo any laboratory testing prior to starting treatment was not taking any other medications or using street drugs. Three months later he developed myalgia and passed dark-colored urine after a 45-minute session of intense anaerobic exercise. He was afebrile and had no other symptoms. He went to the emergency department, where tests showed a highly elevated serum CK concentration (128 084 IU/L [reference, 0–195 IU/L]) and elevated liver enzymes (aspartate aminotransferase, 860 U/L [reference, 0–35]; and alanine aminotransaminase, 223 U/L [reference, 0–45 U/L]). Renal function, plasma electrolytes, and full blood count results were normal. He was admitted, isotretinoin suspended, and intravenous fluids infused to force diuresis and urine alkalinization. The CK concentration gradually fell and symptoms gradually improved. Renal function never deteriorated, and he was discharged after 8 days. On follow-up he remained asymptomatic; serum CK levels, blood counts, and thyroid function test results also remained normal. He was advised not to resume taking isotretinoin.

Six months later he restarted regular aerobic and anaerobic exercise with no future incidents.

Rhabdomyolysis is the breakdown and necrosis of striated muscle tissue, usually after the muscle has been severely damaged.\(^6\) Other causes include exposure to drugs and poisons, infection, muscle enzyme deficiencies, metabolic myopathies, endocrine disorders, electrolyte disturbances, and central hyperthermia.\(^6\) Clinical features include muscle pain and weakness, dark-colored urine, and CK levels 5-fold higher than reference values.\(^6\) Complications, among them renal insufficiency, electrolyte imbalances and disseminated intravascular coagulation, can be life-threatening.\(^6\) Treatment involves life-support measures and intense hydration to prevent kidney failure.\(^6\)

Isotretinoin has been used successfully to treat acne and is indicated for many skin diseases, including hidradenitis suppurativa, seborrheic dermatitis, rosacea, folliculitis decalvans, and viral warts, among others.\(^7\) Myalgia is a common adverse effect that appears in more than 25% of patients on high-dose regimens (0.7–1.0 mg/kg/d), but only rarely must treatment be suspended if it develops.\(^3\) Asymptomatic serum CK elevation during isotretinoin therapy, which has been well documented, is considered a benign self-limited event. Only rarely does the concentration increase 5-fold. CK monitoring during therapy is not recommended and changes do not justify interrupting treatment.\(^3,5\) However, some authors have reported an association between CK elevation and rhabdomyolysis, particularly after intense physical exercise (Table 1),\(^7,8\) and 1 case of fatal rhabdomyolysis related to isotretinoin has been reported.\(^1\) It seems reasonable to periodically check CK concentrations in patients on this drug if they practice sports and to warn them to avoid intense exercise. Patients on statins and antipsychotic medications, which are associated with rhabdomyolysis, should also be followed and warned. Moreover, the physician should inquire about muscle and joint pain, urine color, and muscle weakness during medical visits.\(^7\)

Low-dose isotretinoin therapy has proven effective\(^10\) and is associated with a lower rate of side effects, including myalgia, than therapy at higher doses.\(^1\) Even so, a case of rhabdomyolysis was described in an adolescent treated with 20 mg/d.\(^7\)

We identified no other toxins, medications, drugs, or endocrine disorders that could explain our patient’s symptoms. He has remained asymptomatic since suspending isotretinoin and has been able to resume physical exercise. We therefore think that this drug and intense exercise were responsible for the episode of acute muscle damage.

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Table 1  Summary of Case Reports of Rhabdomyolysis Secondary to Isotretinoin Therapy.

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Age, y/Sex</th>
<th>Comorbidity</th>
<th>Other Medications</th>
<th>Isotretinoin Dose</th>
<th>Indication/Time on Isotretinoin</th>
<th>Rhabdomyolysis Trigger</th>
<th>Serum CK Level</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paulsrud et al, 7 2017</td>
<td>17/M</td>
<td>No</td>
<td>No</td>
<td>20 mg/d</td>
<td>Acne/2 mo</td>
<td>Physical exercise</td>
<td>18 800 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Madera et al, 11 2016</td>
<td>18/M</td>
<td>No</td>
<td>No</td>
<td>40 mg/d 0.5 mg/kg/d 1 mg/kg/d</td>
<td>Acne/6 mo</td>
<td>Physical exercise</td>
<td>39 800 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Phillips et al, 12 2015</td>
<td>33, F</td>
<td>No</td>
<td>No</td>
<td>60 mg/d</td>
<td>Acne/2 mo</td>
<td>Physical exercise (soccer)</td>
<td>66 000 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Inci et al, 13 2015</td>
<td>19/M</td>
<td>No</td>
<td>No</td>
<td>20 mg/d</td>
<td>Acne/2 mo</td>
<td>Physical exercise</td>
<td>39 800 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Kempeneers et al, 14 2013</td>
<td>15/M</td>
<td>No</td>
<td>No</td>
<td>20 mg/d</td>
<td>Acne/2 mo</td>
<td>Physical exercise</td>
<td>22 763 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Hartung et al, 9 2012</td>
<td>20/M</td>
<td>No</td>
<td>Diclofenac</td>
<td>40 mg/d</td>
<td>Acne/3.5 mo</td>
<td>Diclofenac? Physical exercise</td>
<td>82 100 IU/L</td>
<td>Death (ventricular fibrillation)</td>
</tr>
<tr>
<td>Gómez-Bernal et al, 8 2011</td>
<td>16/M</td>
<td>No</td>
<td>No</td>
<td>0.4 mg/kg/d</td>
<td>Acne/11 mo</td>
<td>Physical exercise (weight lifting)</td>
<td>801 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Karaa et al, 15 2009</td>
<td>18/M</td>
<td>No</td>
<td>Vitamins</td>
<td>Unspecified</td>
<td>Acne/several mo</td>
<td>Physical exercise (weight lifting)</td>
<td>232 000 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Guttmann-Yassky et al, 16 2003</td>
<td>23/M</td>
<td>No</td>
<td>No</td>
<td>0.5 mg/kg/d</td>
<td>Acne/10 d</td>
<td>Physical exercise</td>
<td>35 503 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Trauner et al, 17 1999</td>
<td>49/M</td>
<td>No</td>
<td>No</td>
<td>1 mg/kg/d</td>
<td>Dissecting cellulitis/5 wk</td>
<td>Unknown</td>
<td>11 053 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Hodak et al, 18 1986</td>
<td>16/M</td>
<td>No</td>
<td>No</td>
<td>0.5 mg/kg/d</td>
<td>Acne/4 wk</td>
<td>Unknown</td>
<td>918 IU/L</td>
<td>No sequelae</td>
</tr>
<tr>
<td>Present case</td>
<td>30/M</td>
<td>No</td>
<td>No</td>
<td>20 mg/wk</td>
<td>Seborrheic dermatitis/3 mo</td>
<td>Physical exercise (weight lifting)</td>
<td>128 084 IU/L</td>
<td>No sequelae</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase; F, female; M, male.
Ultrasound-Guided Fine-Needle Aspiration Biopsy and Core Needle Biopsy of Lymph Node and Subcutaneous Metastases From Lung Adenocarcinoma

PAAF y BAG ecografiadas en metástasis ganglionar y subcutánea de adenocarcinoma de pulmón

To the Editor:
A 55-year-old female smoker was seen for 3 subcutaneous nodules that had appeared during the preceding month.

The patient had a history of colon cancer (6 years earlier) but was cancer-free at the time of the consultation. Physical examination revealed 3 firm nodules of 1 cm in diameter located beneath healthy-looking skin on the upper chest, rib cage, and arm pit on the right side of the body (Fig. 1). Doppler ultrasound revealed 3 ovoid hypoechoic lesions in the subcutaneous tissue that lacked posterior reinforcement, exhibited internal vascularization, and were compatible with 2 subcutaneous metastases and 1 lymph node metastasis. After providing written informed consent, the patient underwent fine-needle aspiration (FNA) of the axillary adenopathy with a 21-G needle and core-needle biopsy (CNB) of the lesion on the upper chest with an 18-G needle. The procedures were performed under local anaesthesia with ultrasound guidance in the operating room of the dermatology service on the same day as the consultation, with no complications. FNA cytology was positive for malignantly cells (Fig. 2). Histology of the CNB was diagnostic of adenocarcinoma metastasis (Fig. 3) and the

References

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Isotretinoin is a safe drug that is well tolerated, but strict vigilance is needed when it is prescribed even at low doses. Although testing prior to starting therapy would not have prevented the development of rhabdomyolysis in our patient, it could lower the risk of complications such as hepatitis and severe dyslipidemia. We think that patients on this drug should be warned to refrain from intense exercise and that physicians should watch for symptoms suggestive of rhabdomyolysis so that treatment can be started promptly.

Conflicts of Interest
The authors declare that they have no conflicts of interest.