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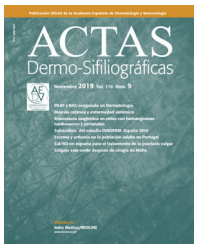

CASE AND RESEARCH LETTER

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 included exposure to drugs and poisons, infection, muscle enzyme deficencies, 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.[2] 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.[4,5] 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.[9] 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.[3]

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.[3] 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.

Author and Year	Age, y/Sex	Comorbidity	Other Medications	Isotretinoin Dose	Indication/Time on Isotretinoin	Rhabdomyolysis Trigger	Serum CK Level	Clinical Outcome
Paulsrud et al,[7] 2017	17/M	No	No	20 mg/d	Acne/2 mo	Physical exercise	18 800 IU/L	No sequelae
Madera et al,[11] 2016	18/M	No	No	40 mg/d 0.5 mg/kg/d	Acne/6 mo	Physical exercise	39 800 IU/L	No sequelae
Phillips et al,[12] 2015	33, F			1 mg/kg/d	Acne/3 wk	Physical exercise	66 000 IU/L	No sequelae
Inci et al,[13] 2015	19/M	No	No	60 mg/d	Acne/2 mo	Physical exercise (soccer)	18 500 IU/L	No sequelae
Kempeneers et al,[14] 2013	15/M	No	No	20 mg/d	Acne/2 mo	Physical exercise	22 763 IU/L	No sequelae
Hartung et al,[9] 2012	20/M	No	Diclofenac	40 mg/d	Acne/3.5 mo	Diclofenac? Physical exercise	82 100 IU/L	Death (ventricular fibrillation)
Gómez-Bernal et al,[8] 2011	16/M	No	No	0.4 mg/kg/d	Acne/11 mo	Physical exercise (weight lifting)	801 IU/L	No sequelae
Karaa et al,[15] 2009	18/M	No	Vitamins	Unspecified	Acne/several mo	Physical exercise (weight lifting)	232 000 IU/L	No sequelae
Guttman-Yassky et al,[16] 2003	23/M	No	No	0.5 mg/kg/d	Acne/10 d	Physical exercise	35 503 IU/L	No sequelae
Trauner et al,[17] 1999	49/M	No	No	1 mg/kg/d	Dissecting cellulitis/5 wk	Unknown	11 053 IU/L	No sequelae
Hodak et al,[18] 1986	16/M	No	No	0.5 mg/kg/d	Acne/4 wk	Unknown	918 IU/L	No sequelae
Present case	30/M	No	No	20 mg/wk	Seborrheic dermatitis/3 mo	Physical exercise (weight lifting)	128 084 IU/L	No sequelae

Abbreviations: CK, creatine kinase; F, female; M, male.

Isotretinoin is a safe drug that is well tolerated, but strict vigilance is needed when it is prescribed[3] 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.

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Ultrasound-Guided Fine-Needle Aspiration Biopsy and Core Needle Biopsy of Lymph Node and Subcutaneous Metastases From Lung Adenocarcinoma☆

PAAF y BAG ecoguiadas 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 armpit 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 anesthesia 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 malignant cells (Fig. 2). Histology of the CNB was diagnostic of adenocarcinoma metastasis (Fig. 3) and the

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