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Myositis Induced by Isotretinoin: A Case Report and Literature Review

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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ABCDEF 1,4

Julián Alejandro Rivillas
Víctor Alfonso Santos Andrade
Andrés Alberto Hormaza-Jaramillo

1 Clinical Research Center, Lili Valley Foundation, Cali, Colombia
2 Clinical Neurology Service, Lili Valley Foundation, Cali, Colombia
3 Faculty of Health Sciences, Icesi University, Cali, Colombia
4 Rheumatology Service, Lili Valley Foundation, Cali, Colombia

Corresponding Author: Andrés Hormaza-Jaramillo, e-mail: andreshormazaj@hotmail.com
Conflict of interest: None declared

Patient: Male, 45-year-old
Final Diagnosis: Myositis induced by isotretinoin
Symptoms: Muscle pain in the upper limbs with marked functional limitation associated by coluria
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Unusual clinical course

Background: Retinoid-induced myositis is a rare condition encountered in clinical practice. Its occurrence implies a diagnostic challenge due to the multiple causes associated with myopathic syndromes. The most common clinical presentation is generalized affection. Focal myositis is even less frequent and easily misdiagnosed as muscular disease of other etiology.

Case Report: We describe a case of 45-year-old male with a history of nephrolithiasis and rosacea diagnosed by dermatology, who was management with isotretinoin 1 mg/kg per day in 2 doses with clinical improvement. Later, he presents muscle pain in the upper limbs with marked functional limitation associated by choluria, without muscular pains in other location; he had no history of using another medication. At his physical examination, vital signs were normal, with edema and pain in the bilateral bicipital region associated with limitation for flexion-extension of shoulders and elbows and high levels of creatine phosphokinase (CPK). He was transferred to the intensive care unit where he received fluid therapy because of the high risk of deterioration of renal function, very high CPK levels, and a history of obstructive uropathy. One year after this hospitalization, the cutaneous symptoms worsened and the patient voluntarily restarted isotretinoin and 5 months later he presented again with the same symptoms of the first episode.

Conclusions: Drug-induced myositis should be taken into consideration in the differential diagnosis of myopathic syndromes. Retinoids have the potential to cause varying degrees of myositis and their rapid identification could prevent major complications.

MeSH Keywords: Creatine Kinase • Dermatomyositis • Myalgia • Retinoids

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Background

Retinoids are a group of drugs derived from vitamin A widely used for the treatment of different recalcitrant dermatoses and neoplasms. Three generations of retinoids have been described. The first generation are formed by retinoids (retinol, retinal, tretinoin [retinoic acid], isotretinoin and alitretinoin), the second generation are the so-called mono-aromatics (etretinate and their metabolite acitretin) and third generation are the poly-aromatics (adapalene, bexarotene and tazarotene).

The mechanism of action that explains this group of drugs therapeutic effect and profile of adverse events include induction of apoptosis in cells of the neural crest (risk of teratogenicity), epidermal cells (cutaneous pharmacological effects), hepatocytes (release of transaminases and low density lipoproteins), myocytes (myalgias, myositis, and creatine phosphokinase [CPK] increase), as well as other cells [1]. Since the end of the 1980s, the adverse effects of retinoids on the musculoskeletal system have been known, and are clinically evident due to myalgias, cramps, hyperostosis, and arthralgias [2]. In the early 1990s, documented cases of myopathy and myositis associated with this therapy began to be reported [3–5]. We report the case of a patient with multifocal muscle involvement and serum CPK increase associated with the use of isotretinoin indicated by rosacea.

We carried out a search in PubMed, Scopus, and Embase with the terms “myositis”, “retinoid”, and “isotretinoin”, without temporal restriction or by language and those case reports and series of patient cases with retinoid-induced myopathy were selected for review.

Case Report

A 45-year-old male with a history of nephrolithiasis and rosacea diagnosed by dermatology received topical treatment without response. He started management with isotretinoin 1 mg/kg per day in 2 doses with clinical improvement. Three months after the patient began the medication and later an intensive exercise session, he consulted the emergency department because of 3 days of muscle pain in the upper limbs with marked functional limitation associated with choloria or dark urine, 2 days before admission. He did not present muscular pains in other location and did not have history of using another medication. At physical examination, vital signs were normal, with edema and pain in the bilateral bicipital region associated to limitation for flexion-extension of shoulders and elbows. The admission laboratories reported hemoglobin (Hb) 16.1 mg/dL, leukocytes 9040 cells/mL with normal differential, platelets 243 000 cells/mL, creatinine (Cr) 1.01 mg/dL, serum nitrogen 25 mg/dL, CPK 85 380 mg/dL, lactic dehydrogenase

(LDH) 2180 U/L, and aldolase 15.94 U/L. Similarly, laboratories were performed to rule out infectious or autoimmune etiology explaining the symptoms, which were negative. He was transferred to the intensive care unit (ICU) where he received fluid therapy because of the high risk of deterioration of renal function, very high CPK levels, and a history of obstructive uropathy. In this episode, magnetic resonance imaging (MRI) was not performed. During his stay in the ICU, there was no azotemia and his CPK level decreased to 5068 mg/dL with disappearance of myalgias. At discharge, alternate management for rosacea was recommended.

One year after this hospitalization, the cutaneous symptoms worsened and the patient voluntarily restarted isotretinoin, and 5 months later he presented with pain in the lower third of the right lower limb with slight limitation for walking. The physical examination revealed pain on the palpation of the posterior aspect of the right leg without other associated findings. The laboratory studies showed: Hb 14.5 mg/dL, leukocytes 5458 cells/mL, platelets 452 000 cells/mL, Cr 1.2 mg/dL (with 0.9 mg/dL prior) and CPK 152 mg/dL. MRI of the lower limbs was performed and showed changes in signal intensity in the muscular belly of the flexor digitorum longus, posterior tibialis, gastrocnemius, and to a lesser extent the extensor digitorum, compatible with multifocal myositis (see Figure 1). The medication with clinical improvement was suspended after 2 weeks of follow-up.

Discussion

We present here the case of a patient with recurrent myositis secondary to isotretinoin use with 2 episodes in different muscle groups with marked increase in CPK (first event) and alteration in MRI (second event) with complete recovery after agent suspension. Drug-induced myopathy is among the most common causes of muscle disease and includes alcohol, glucocorticoids, statins, cocaine, antimalarial drugs, antipsychotic drugs, colchicine, zidovudine, interferon, tumor necrosis factor- α inhibitors, and chemotherapeutic agents (e.g., gemcitabine) [6]. Other drugs with muscle involvement include vitamin A derivatives such our case and has a broad spectrum of manifestations [2].

First-generation retinoids, such as isotretinoin and all-trans retinoic acid (ATRA), are the most commonly used agents for the treatment of acne and acute promyelocytic leukemia (APL). Musculoskeletal adverse events are the most frequent, occurring from 16% to 51% of patients receiving this therapy [7,8]. These manifestations usually appear in the first month of treatment [9], usually associated with intense physical activity. The spectrum of clinical scenarios includes self-limited myalgias, asymptomatic and transient elevation of CPK to severe forms



Figure 1. Magnetic resonance imaging of lower limbs. (A) Coronal section in T1 fat saturation with increased signal intensity in extensor digitorum longus and tibialis posterior with fat cross-linking in the posteromedial region of the distal third of the leg and ankle (B). Axial section in T2 with fat saturation in the lower third of the right leg. Hyperintensity is observed in the flexor and extensor compartment of the leg.

of inflammatory myopathies like malignant rhabdomyolysis and necrotizing myositis that in some cases can be fatal [10].

The forms of myositis associated with ATRA in patients with APL present with fever, pleural and pericardial effusion, renal function compromise, increased acute phase reactants and

life-threatening complications, establishing the differentiation syndrome [11].

Focal myositis is one of the forms of muscular compromise associated with retinoids. This is defined by pseudo-tumoral inflammation of a muscle. The multifocal commitment given by the commitment of several muscle groups has also been described with the use of vitamin A analogues [12,13]. Differential diagnoses include denervation lesions secondary to radiculopathy, mechanical (trauma or intramuscular malformation), infectious diseases by virus (influenza, Coxsackie virus, cytomegalovirus), bacteria (Lyme disease, *Mycobacterium tuberculosis*), fungi (*Candida*, *Aspergillus*), or parasites (*Toxoplasma gondii*, *Trypanosoma cruzi*, *Sarcocystis*, *Taenia solium*, *Trichinella*); autoimmune diseases (systemic lupus erythematosus, Sjogren's syndrome), autoinflammatory (Behçet's disease), and other medications like statins or idiopathic causes [14]. In this reported case there was a clear temporal relationship between the onset of symptoms and the consumption of isotretinoin in both episodes (increase in CPK and multifocal myositis). Infectious, autoimmune and other causal medications were ruled out.

The laboratory studies should include CPK, which have been shown to be elevated in 37% to 41% of the reported case series [7,15]. The acute phase reactants might be normal. Electrodiagnostic studies are a tool to differentiate focal versus multifocal muscle involvement, as well to determinate peripheral nerve injury [14]. MRI is one of the key diagnostic tools. Hyperintensity in T2 and hypointensity in T1 are often identified in affected muscle with respect to normal muscles, accompanied by edema of surrounding tissues [16]. Muscle biopsy is performed in cases where there is doubt in the diagnosis.

The muscle compromise associated with retinoids usually has a benign course and yield with the administration of analgesics and suspension of medication. In some cases, myalgias may persist for several months [17].

The diagnosis of myositis associated with retinoids in our patient was justified for the following reasons: 1) temporal relationship in both episodes with the ingestion of the medication; 2) para-clinics ruled out infectious or metabolic causes; 3) findings on MRI during the second episode are compatible with multifocal myositis; and 4) improvement of the symptoms after the suspension of the therapy and the reappearance with the reintroduction of the same. The patient did not have weakness only pain and it was evident in the first episode for the diagnosis of rhabdomyolysis, on the other hand, in the second episode the symptoms were oriented to focal myositis, with no evidence of multifocal or nerve involvement. For this reason, in the case of our patient, no electrodiagnostic studies or muscle biopsy were performed. Finally, although the imaging findings of inflammation observed in focal myositis

Table 1. Cases of myopathy associated with retinoids reported in the literature (PubMed, Scopus, Embase).

Study	Diagnosis	Sex	Age	Location	Medication	Time (days)	CPK	EMG	MRI	BX	Death
Sameem et al. (2016) [13]	Folliculitis decalvans	M	25	Pelvic	Isotretinoin	30	Elevated	Yes	No	No	No
Miranda et al. (1994) [5]	APL	M	33	Lower members	Tretinoin 45 mg/m ²	18	Elevated	No	No	Yes	No
Mangodt et al. (2018) [18]	Acne	M	15	Shoulders	Isotretinoin 20 mg (44 kg)	42	Not reported	No	No	No	No
Hartung et al. (2012) [10]	Acne conglobate	M	20	Generalized	Isotretinoin 40 mg/day	10	High	No	No	Yes	Yes
Alam et al. (2016) [19]	Acne vulgaris	M	31	Extraocular muscles	Isotretinoin 1 mg/kg per day	60	Not reported	No	Yes	No	No
Yu et al. (2009) [9]	LPA	F	51	Buttocks	ATRA 45 mg/m ²	18	Normal	Yes	Yes	No	No
Fiallo et al. (1996) [4]	Acne	F	19	Generalized	Isotretinoin 0.5 mg/kg	90	Normal	Yes	No	Yes	No
Fiallo et al. (1996) [4]	Nodulocytic acne	M	20	Generalized	Isotretinoin 0.5 mg/kg	15	Normal	Yes	No	No	No
Lister et al. (1996) [3]	Erythrodermic psoriasis	M	64	Generalized	Acitretin 50 mg per day	14	High	Yes	No	Yes	No
Ghelfi et al. (2017) [20]	LPA	M	43	Generalized	ATRA 45 mg/m ²	44	High	No	Yes	Yes	No
Pecker et al. (2014) [16]	LPA	M	15	Thigh	ATRA 45 mg/m ²	30	Elevated	No	Yes	No	No
Manglani et al. (2009) [21]	LPA	F	5	Calf	ATRA 45mg/m ²	10	High	No	Yes	No	No
Oliveira et al. (2008) [22]	LPA	F	29	Calf	ATRA 45 mg/m ²	21	Normal	No	Yes	No	No
Kanna et al. (2005) [23]	LPA	F	18	Thigh	ATRA 45 mg/m ²	5	Not reported	No	Yes	No	No
Martínez-Chamorro et al. (2002) [24]	LPA	F	28	Calf	ATRA 45 mg/m ²	6	Normal	Yes	Yes	No	No
Fabbiano et al. (2005) [25]	LPA	M	45	Lower limbs and myocardium	ATRA 45 mg/m ²	23	High	No	No	No	No
Van Der Vliet et al. (2000) [26]	APL	M	39	Legs and thighs	ATRA 45 mg/m	18	Normal	No	Yes	No	No
Van Der Vliet et al. (2000) [26]	LPA	F	35	Legs previous	ATRA 45 mg/m ²	20	Elevated	No	Yes	No	No
Chan et al. (2005) [27]	LPA	M	27	Calves	ATRA 45 mg/m ²	16	Elevated	No	Yes	No	No
Citak et al. (2006) [28]	LPA	F	11	Legs and arms	ATRA 45 mg/m ² per day	5	Normal	No	Yes	No	No
Corpuz et al. (2014) [29]	LPA	M	24	Thighs	ATRA 45 mg/m ²	3	High	No	No	No	No
Tae-Young et al. (2013) [30]	LPA	M	64	Calves	ATRA 45 mg/m ²	17	High	No	Yes	Yes	Yes

Table 1 continued. Cases of myopathy associated with retinoids reported in the literature (PubMed, Scopus, Embase).

Study	Diagnosis	Sex	Age	Location	Medication	Time (days)	CPK	EMG	MRI	BX	Death
Khan et al. (2012) [12]	Acne vulgaris	M	14	Buttocks and adductors of the thighs, quadriceps bilateral femoral	Isotretinoin	30 days	Normal	Yes	No	Yes	No
Mayorga-Bajo et al. (2016) [31]	LPA	M	47	Lower member	ATRA 45 mg/m ² per day	24	Normal	No	Yes	Yes	No
Sarifakioglu et al. (2011) [32]	Acne nodulocystic	M	15	Drumsticks	Isotretinoin 0.5 mg/kg per day	14 days	Normal	Yes	No	Yes	No

LPA – acute promyelocytic leukemia; Bx – muscle biopsy; MRI – magnetic resonance imaging; EMG – electromyography; CPK – creatine phosphokinase; M – Male; F – Female.

can mimic that of muscular dystrophy or inflammatory myopathy, the clinical evolution of our patient ruled out these diagnoses. The other hand, the patient did not present with weakness and remained a focal process.

We searched for reported cases of myositis related to retinoids. We found 23 articles with 25 patients (see Table 1). The majority of patients were male younger than 35 years of age, with symptom onset time within 30 days after initiating the medication and symptoms affecting the lower limbs.

Drug-induced myopathies require great attention because they cause great morbidity and in some cases are fatal. The timely suspension of medication prevents the progression of symptoms and related complications. This justifies the early identification of the clinical picture and its possible causative agents.

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Conclusions

Drug-induced myositis should be taken into consideration in the differential diagnosis of myopathic syndromes. Retinoids have the potential to cause varying degrees of myositis and their rapid identification could prevent major complications.

Conflicts of interest

None.

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