Isotretinoin-induced acute severe myopathy involving pelvic girdle muscles: A case report

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Abstract:
Oral isotretinoin has been in widespread use for more than three decades. It causes numerous side effects; skin and mucous membrane being commonly involved. Musculoskeletal adverse effects are also known to occur, but pelvic girdle myopathy is rarely reported. We report myopathy involving pelvic girdle muscles in a young male who received oral isotretinoin for folliculitis decalvans.

Key words:
Drug-induced myopathy, folliculitis decalvans, isotretinoin

Isotretinoin is an orally active synthetic retinoid that has revolutionized the treatment of acne. The drug might be tried in folliculitis decalvans which is difficult to treat rare, chronic, inflammatory condition of scalp leading to scarring alopecia.[1] Isotretinoin causes various side effects, but most of them are predictable and well described. Musculoskeletal adverse effects such as myalgia, arthralgia, arthritis, and muscle damage are known to occur; however, these are usually mild,[2] and involvement of pelvic girdle muscles is rarely reported. In this paper, we describe a patient who developed severe acute myopathy of lower limb and pelvic girdle muscles while being on isotretinoin for folliculitis decalvans.

Case Report

A 25-year-old male dentist presented with recurrent episodes of intensely pruritic follicular pustules on the scalp from last 3 years. The lesions would start from the vertex and then extend peripherally; each episode was followed by scarring. There was no history of any systemic complaint. General physical examination and systemic examination were noncontributory. Musculoskeletal examination was normal. Mucocutaneous and nails were not affected. Skin biopsy from the lesions showed neutrophilic infiltrate at the follicular infundibulum with a pathological diagnosis of folliculitis decalvans. After sending baseline hemogram, liver chemistry, and complete lipid profile, the patient was started on isotretinoin 20 mg capsules (patient’s weight was 78 kg) daily to be taken with food. In view of a slow response, this dose had been doubled by another dermatologist to 40 mg daily. In addition, the patient was prescribed topical antibacterial washes. The patient responded well to the revised dose of isotretinoin, but 1 month into treatment the patient had to travel a long distance. On reaching his destination, he experienced severe body cramps and a generalized feeling of ill-health. He was flown back home and brought to the hospital. On reception in the hospital, the patient was listless, ill-looking, and febrile. Systemic examination showed the patient had tachycardia. Musculoskeletal examination revealed normal joints; however, there was a weakness of lower limb and girdle muscles. Grover’s sign for proximal myopathy was positive. Deep tendon reflexes were normal. There was generalized skin tenderness, but no erythema or peeling except for palmar erythema. Lip cheilitis was seen. Mucosae were normal. No lymphadenopathy was seen. Investigations revealed leukopenia and thrombocytopenia. A raised level of creatinine phosphokinase (CPK) of 317 IU/L and lactate dehydrogenase was seen. Electromyogram (EMG) and muscle ultrasound were consistent with myopathy. Retroviral serology and hepatitis B and C serology were negative. Antinuclear antibody and anti-U1RNP were also negative. Muscle biopsy was not done. A provisional diagnosis of acute myopathy was done. Muscle biopsy was not done. A provisional diagnosis of acute myopathy was done.
of isotretinoin-induced myopathy was made. Isotretinoin was discontinued. The patient responded to bed rest and supportive treatment comprising analgesics in the course of a few weeks. Rechallenge with isotretinoin was avoided for ethical reasons.

**Discussion**

Drug-induced myopathies or toxic myopathies demand awareness and attention: they might cause significant morbidity; hundreds of drugs have myotoxic potential; early recognition and prompt response aid full recovery; patients on myotoxic drugs need follow-up for neuromuscular adverse effects and CPK levels; prudent selection of dosage might mitigate the risk of myotoxicity; many myotoxic events result from drug–drug interactions. Last but not the least, pharmacogenomics has an immense role in this regard which needs to be elucidated. Identification of the patients at risk and careful choice of medications in this population call for an insight.

Drug-induced myopathies can manifest as muscle weakness, increased CPK levels, myalgia, myoglobinuria, and EMG and histologic changes. Clinical picture can range from mild muscle pain and cramps to severe weakness with rhabdomyolysis, renal failure, and death. Statins, steroids, antiviral therapy, colchicine, and chloroquine are names of some drugs incriminated for myotoxicity. Mechanism of drug-induced myotoxicity is multifactorial: brunt may be on muscle organelles, for example, mitochondria, lysosomes, and myofibrillar proteins; muscle antigens can get altered leading to inflammation or immunologic reaction; nutritional and electrolyte imbalances may occur resulting in muscle dysfunction. Muscle constitutes 45% of total body mass and it is well perfused and display dynamic metabolic machinery. Skeletal muscles are responsible for 80% of total glucose uptake and >30% of resting metabolic rate. These inherent properties make muscles vulnerable to toxic effects of circulating drugs.

Arthralgia and myalgia have been reported in 2–5% of patients receiving oral isotretinoin >0.5 mg/kg/day. Malaise, fever, and increase in CPK may be associated in some patients. CPK may be raised in a variable percentage of patients receiving isotretinoin; it may or may not be associated with muscular signs and symptoms and is more common in patients indulging in vigorous physical exercise.

Isotretinoin is a prodrug; it gets isomerized to all-trans-retinoic acid in the body. Substantial evidence favors the role of forkhead box class O (FoxO) transcription factors in therapeutic, adverse, teratogenic, and chemopreventive effects of the drug. Isotretinoin causes hyperactivation of FoxO1 which mediates upregulation of atrogin 1 and muscle-specific ring finger protein 1, the two ubiquitin ligases involved in skeletal muscle atrophy. Thus, isotretinoin causes FoxO-induced catabolic events in muscle cells that may manifest as muscular signs and symptoms as well as release of CPK.

Differential diagnosis of muscle disorders can be broad. In our patient, drug-induced myopathy was diagnosed keeping in view following criteria: first, temporal relationship between drug intake and appearance of muscle signs and symptoms; drug-induced myopathy appears weeks or months after use of the offending drug. In our patient, free period of several weeks existed between the commencement of treatment with isotretinoin and appearance of features of myopathy. Second, our patient had never experienced muscular symptoms in the past. Third, absence of any other apparent cause of myopathy. Fourth, the EMG depicted myopathic type action potential with normal nerve conduction study [Figure 1]. Fifth, complete resolution of signs and symptoms following discontinuation of isotretinoin. Besides, the young age of the patient and concomitant physical exertion during the treatment could be the contributory factors. The ADR was reported by Sher-i-Kashmir Institute of Medical Sciences, Srinagar via Indian Pharmacopoeia Commission-National Coordinating Center, Pharmacovigilance Programme of India on VigiFlow (Case Safety Report ID: 2016-26687). A causality category of “probable/Likely” using World Health Organization-Uppsala Monitoring Centre Causality Assessment Scale was assigned to this adverse event.

It is important that the clinicians are aware of toxic effects of isotretinoin on muscles and that pelvic muscle involvement is possible as well though not supported by enough literature. Early recognition and prompt action can avert permanent damage to muscles.

![Electromyogram of the affected muscles showing myopathic type action potential](image-url)
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Conflicts of Interest
There are no conflicts of interest.

References