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CASE REPORT

A Case With Bilateral Sacroiliitis and Polyneuropathy Development Due to Isotretinoin Use

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Isotretinoin is a vitamin A derivative used in acne treatment when standard treatment including systemic antibiotics fails. Isotretinoin exerts its effects via retinoic acid receptors. However, it often causes mucocutaneous, musculoskeletal, neurological, and ocular adverse effects. Most common musculoskeletal adverse effects include arthralgia and miyalgia. Rarely, seronegative sacroiliitis can be seen. Neurological adverse effects are generally related to central nervous system. In patients using isotretinoin, sensorial fibers are involved earlier than motor fibers in peripheral nervous system. This involvement is more prominent in sensorial nerves and myelin fibers at distal. In this article, we report a 25-year-old male case who developed demyelinating polyneuropathy and sacroiliitis after six months of isotretinoin use.

Keywords: Isotretinoin; polyneuropathy; sacroiliitis.

Isotretinoin is a vitamin A derivative used in acne treatment when standard treatment with systemic antibiotics fails. It exerts its effects via retinoic acid receptors.[1] Isotretinoin-related musculoskeletal adverse effects include arthralgia, myalgia, and vasculitis. Adverse effects may be observed in 15% of the patients.[2] Furthermore, diffuse idiopathic skeletal hyperostosis and osseous abnormalities mimicking seronegative spondyloarthropathy has been reported. Recently, a case of sacroiliitis and polyneuropathy was reported.[3] Herein, we report a case of demyelinating polyneuropathy and sacroiliitis after six months of isotretinoin use.

CASE REPORT

A 25-year-old man presented with back pain, bilateral hip pain, and paresthesia in hands. Hip pain started approximately three months ago, and was accompanied by longstanding morning stiffness. Patient reported that he experienced pain particularly at night and when he woke up in the morning, and his pain did not radiate to legs. He had also paresthesia in both arms for two months, involving his fingers, in particular. His history was non-specific except for the use of isotretinoin (20 mg/day initial dose used during the first three months, then increased to 40 mg/day for the following months) six months ago due to acne fulminans.

Physical examination revealed limited and painful lumbar movements in all directions. Modified Schober's test was measured as 19 cm, while fingertip to floor distance was measured as 5 cm. There was full range of motion in hip joint, however, hip movements were painful. Chest expansion, sacroiliac provocation tests (mennel, gaenslen), and neurological examination findings were normal. Tinnel's sign and Phalen's

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maneuver were negative. Thus, the underlying origin of the back pain was considered to be inflammatory, and laboratory tests were performed. Laboratory analysis demonstrated normal biochemical values and complete blood count. Acute phase reactants including C-reactive protein and erythrocyte sedimentation rate were 3 mg/L (normal range: 0-3 mg/L) and 1 mm/h (0-15 mm/h), respectively. Urinalysis was normal. Serum vitamin B 12 and folic acid levels, thyroid function tests, and parathyroid hormone levels were within normal range. Hepatitis panel, including hepatitis B surface antigens, hepatitis B surface antibodies, hepatitis C virus antibodies, and human immunodeficiency virus antibodies, was negative. Serological evaluations including anti-cyclic citrullinated peptide and anti-nuclear antibody tests were negative. In addition, rheumatoid factor test was also negative. Spinal magnetic resonance imaging (MRI) was considered to be normal. However, sacroiliac MRI showed bilateral bone marrow edema and subchondral sclerosis (Figure 1 and Figure 2). Nerve conduction studies and electromyography revealed sensorimotor demyelinating polyneuropathy (Table 1 and Table 2).

DISCUSSION

Isotretinoin is a retinoid used in the treatment of severe and persistent acne either alone or in combination with steroid. It often causes mucocutaneous, musculoskeletal, neurological, and ocular adverse effects. Most common musculoskeletal adverse effects include arthralgia and myalgia. Rarely, seronegative sacroiliitis can be seen. Adverse events may be explained by immunomodulatory mechanisms and effects of retinoids on neural tissue development and differentiation, tumoral tissue growing, loss of synaptic transmission, and function. Neurological adverse effects are generally related to central nervous system. These include headache, insomnia, hearing loss, epileptic seizure, and pseudotumor cerebri.[4,5] In patients using isotretinoin, sensorial fibers are involved earlier than motor fibers in peripheral nervous system. This involvement is more prominent in sensorial nerves and myelin fibers at distal of extremities.[3,6] Deficiency of vitamin B12, diabetes mellitus type I and type II, colchicine, and alcohol use may cause sensorimotor polyneuropathy in distal extremities.[7] The history of the present case was non-specific in terms of these factors.

Presence of clinical or electrophysiological peripheral neuropathy after systemic use of retinoid was reported within 10 days in earliest case, and after four years in latest case.[8,9] Peripheral neuropathy recovers after withdrawal of drug. This recovery may occur within two weeks to 2.5 years.[8,10] There is conflicting data in the literature regarding peripheral neuropathy related to isotretinoin use.[6,11,12] In a study by Canpolat et al.,[12] no neuropathy was detected by electrophysiological evaluations in 15 patients

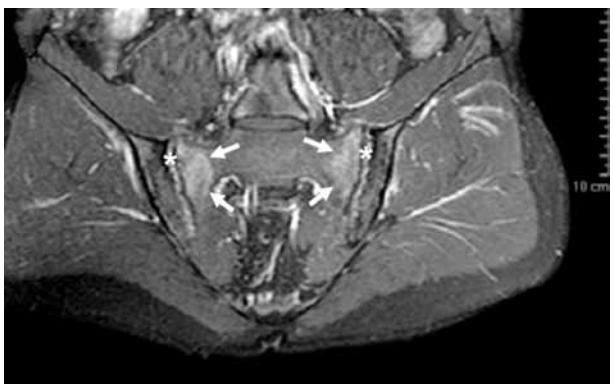

Figure 1. Magnetic resonance imaging findings during drug use. Contrast T_1-weighted fat-suppressed sequences at the oblique coronal plane reveal increased uptake of contrast material at both sacroiliac joints (asterisks), and increased uptake of contrast material at sacrum (arrows) due to bilaterally subarticular bone marrow edema.

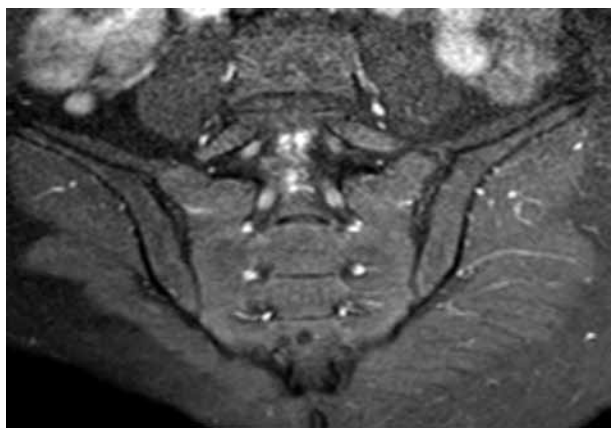

Figure 2. Magnetic resonance imaging findings after discontinuation of drug. Contrast T_1-weighted sequences at the oblique coronal plane reveal normal findings.

Table 1. Nerve conduction studies performed during drug use

Nerve	Recording site	SDL (ms)	SV (m/s)	SAP (μV)	MDL (ms)	MV (m/s)	CMAP (Mv)	F (ms)
Right median	APB/2.P	3.5	39	27	3.3	57.2	8.5	–
Right ulnar	ADM/5.P	3.2	41.4	40	4.3	60.2	10.6	–
Left median	APB/2.P	3.2	44	50	3.8	54	6.2	27.5
Left ulnar	ADM/5.P	3.1	37.7	28	4.3	50.4	9.3	–
Right radial	APB/1.P	3.2	37	17	4.7	48	8.2	–
Left tibial	AH	–	–	–	5.2	48	7.8	51.1
Left peroneal	EDB	–	–	–	5.3	54	2.3	
Left sural	Foot lateral	Absent	Absent	Absent	–	–	–	–

APB: Abductor pollicis brevis; ADM: Abductor digiti minimi; AH: Abductor hallucis; EDB: Extensor digitorum brevis; SDL: Sensory distal latency; SV: Sensory velocity; SAP: Sensory action potential; MDL: Motor distal latency MV: Motor velocity; CMAP: Compound muscle action potential.

treated with systemic isotretinoin (0.5 mg/kg/day) at the end of six months. However, authors detected a significantly decreased sensory conduction velocity and action potential amplitude in median, ulnar, and sural nerves. In another study, sensorial neuropathy was detected in 18 patients treated with systemic isotretinoin (1 mg/kg/day) at the rates of 44% and 83% in electrophysiological evaluations at three and six months, respectively.[6] However, Chroni et al.[11] failed to detect clinical or electrophysiological neuropathy in 18 patients treated with systemic isotretinoin (1 mg/kg/day) at one and three months. These differences can be related to duration or dose of isotretinoin use. Currently, the exact mechanism of isotretinoin leading to peripheral neuropathy is unclear. In a study, it has been demonstrated that retinoid affects nerve tissue development in vivo and in vitro.[13] Abnormal peripheral nerve conduction may be due to alteration of lipid composition of nerve membrane by retinoid.[14]

In our case, clinical findings of neuropathy exacerbated after increasing the isotretinoin dose from 20 mg/day to 40 mg/day. Electrophysiological evaluation at sixth month revealed demyelinating polyneuropathy, being more prominent in sensorial fibers. Electrophysiological findings were normalized two months after withdrawal from treatment. These results are in agreement with other studies which detected neuropathy.[3,6]

Acne fulminans is a component of SAPHO syndrome (acronym for Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis). In SAPHO syndrome, constitutional symptoms, abnormal laboratory findings and musculoskeletal symptoms are observed as well as necrotizing acne. Sacroiliitis was detected in 21% of the patients having acne fulminans in association with arthritis. In addition, development of sacroiliitis after systemic isotretinoin treatment was also reported in patients with SAPHO syndrome.[15,16] Dinçer et al.[17] reported

Table 2. Nerve conduction studies performed after discontinuation of drug

Nerve	Recording site	SDL (ms)	SV (m/s)	SAP (μV)	MDL (ms)	MV (m/s)	CMAP (Mv)	F (ms)
Right median	APB/2.P	2.6	53	30	2.8	58.5	9.3	–
Right ulnar	ADM/5.P	2.4	50	47	2.8	53	7	–
Left median	APB/2.P	2.8	53.6	60	3.1	61	7.8	20.2
Left Ulnar	ADM/5.P	2.4	54.9	41.2	3.1	50	7.5	–
Right radial	APB/1.P	2.7	47	19	3.5	54	8.4	–
Left tibial	AH	–	–	–	–	–	–	–
Left peroneal	EDB	–	–	–	3.8	48	3.4	–
Left sural	Foot lateral	2.9	54.4	10.1	–	–	–	–

APB: Abductor pollicis brevis; ADM: Abductor digiti minimi; AH: Abductor hallucis; EDB: Extensor digitorum brevis; SDL: Sensory distal latency; SV: Sensory velocity; SAP: Sensory action potential; MDL: Motor distal latency MV: Motor velocity; CMAP: Compound muscle action potential.

sacroiliitis development in three patients aged 18-25 years who used 15-25 mg/day isotretinoin for a time period ranging from three months to two years. Unilateral sacroiliitis developed in patients who used isotretinoin for three months while bilateral sacroiliitis developed in patients who used isotretinoin for two years. Human leukocyte antigen B27 (HLA-B27) positivity was detected in one of three cases. Ekşioğlu et al.[3] also reported bilateral sacroiliitis and demyelinating polyneuropathy in a patient 20 years old, who used isotretinoin for three months (30 mg/day during first two months and 40 mg/day during last month). HLA-B27 positivity was detected in this case. Our patient was 25 years old and used isotretinoin for six months (20 mg/day during first three months and 40 mg/day during last three months). Sacroiliitis developed bilaterally in our case. Sacroiliitis in our case was linked to isotretinoin use, as the patient had no musculoskeletal complaint prior to isotretinoin use. Furthermore, hip pain, back pain and active sacroiliitis findings on MRI emerged three months after prescription of isotretinoin. Complaints and active sacroiliitis findings on MRI disappeared two months after withdrawal from drug.

Arthritis generally appears two or 10 weeks after treatment.[18] Arthritis may be related to immunomodulatory effects and damage at lysosomal membrane of synovial cells caused by retinoid.[19] Ekşioğlu et al.[3] detected HLA-B27 positivity in their case, suggesting that genetic structure may trigger the development of sacroiliitis. In our case, HLA-B27 was negative. However, HLA-B44 positivity, which is found in Behçet's disease, was detected, although diagnostic criteria for Behçet's disease (oral ulcers, genital ulcers, ocular lesions, skin lesions and positive pathergy test) weren't fulfilled in our case.[20] We also think that genetic model can play a role in our case, as suggested by Ekşioğlu et al.[3] Further studies are needed to elucidate etiopathogenesis in such cases.

In conclusion, sacroiliitis should be kept in mind among musculoskeletal adverse effects, and peripheral neuropathy as a nervous system adverse effect associated with isotretinoin use.

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