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Bilateral Sacroiliitis Confirmed with Magnetic Resonance Imaging during Isotretinoin Treatment: Assessment of 11 Patients and a Review of the Literature

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ABSTRACT In recent years, several cases pointing at sacroiliitis due to isotretinoin treatment have been reported, but a causal association remains unproven. The aim of this study was to assess the characteristics of patients in whom bilateral sacroiliitis was detected while using isotretinoin treatment for acne and to review previous sacroiliitis cases treated with isotretinoin. In total, 11 patients who were diagnosed with sacroiliitis during isotretinoin treatment were identified, and patient characteristics were noted. Patients were classified according to magnetic resonance imaging (MRI) findings. The 11 patients (3 men and 8 women) ranged in age from 16 to 37 years (mean age 24.27 years). All the 11 (100.00%) patients presented with hip pain, which in 3 (27.27%) patients started in the first month, in 3 (27.27%) in the second, in 2 (18.18%) in the third, in 2 (18.18%) in the fourth, and in 1 (9%) in the fifth. HLA-B27 (human leucocyte antigen) was negative in all cases. MRI findings confirmed mild bilateral sacroiliitis in 5 (45.45%) patients, moderate in 3 (27.27%), and severe in 2 (18.18%). Although our study included a small number of cases, it indicates a strong association between isotretinoin and sacroiliitis.

KEY WORDS: arthritis, joint pain, adverse effect

INTRODUCTION

Isotretinoin, a synthetic analogue of vitamin A that has been prescribed to many acne patients worldwide, has some known and well-described severe adverse effects (1). However, the onset of bilateral sacroiliitis during isotretinoin use has only been reported in a few case reports; therefore, the risk has not been assessed (2-13). The aim of this study was to retrospectively examine the patients who were diagnosed with bilateral sacroiliitis while being treated with isotretinoin to clarify the association between isotretinoin and bilateral sacroiliitis.

PATIENTS AND METHODS

In this study, patients admitted to our Dermatology and Physical Therapy Clinic and Rehabilitation Clinic between January 2011 and January 2015 were evaluated. Eleven patients who developed bilateral sacroiliitis during systemic isotretinoin treatment for nodulocystic acne were analyzed retrospectively. For each patient, age, sex, dose of the isotretinoin treatment, time of initial arthralgia symptoms, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and human leucocyte antigen (HLA)-B27 results, and therapies used for sacroiliitis were recorded. MRI

findings with coronal, oblique, and axial T1, T2, and fat-saturation T2 sequences of the sacroiliac joints were assessed. Magnetic resonance imaging (MRI) scans were scored using the semi-quantitative Leeds Scoring System, in which bone marrow edema is graded from 1 to 3 (1=<25% of quadrant affected; 2=25-75% of quadrant affected; and 3=>75% of quadrant affected) according to the severity of the sacroiliitis. Patients were classified as having mild, moderate, or severe sacroiliitis using bone marrow edema grades of 1, 2, or 3, respectively.

RESULTS

In total, 11 patients with acne vulgaris who presented with bilateral sacroiliitis during isotretinoin treatment were included in this study (Table 1). None of the patients had acne fulminans or acne conglobata. The ages of the patients ranged from 16 to 37 years, with a mean age of 24.27 years. The number of men and women was 3 (27.27%) and 8 (72.72%), respectively. The initial dose of isotretinoin was 30 mg for the first month, and it was then increased to 40 mg/day for the following months for every patient. All 11 (100.00%) patients presented with bilateral hip joint pain and were classified as the inflammatory type. The hip pain started in the first month in 3 (27.27%) of the cases, in the second month in 3 (27.27%) cases, in the third in 2 (18.18%) cases, in the fourth in 2 (18.18%) cases, and in the fifth month in 1 (9.00%) case. All patients were negative for antinuclear antibodies, rheumatoid factor, and C3 and C4 tests. HLA-B27 was negative in all cases, and ESR and CRP levels were within normal limits. No patients had personal or family history of arthritis, and two of the patients reported back pain while one patient reported previous mild pain in the knees. MRI confirmed grade 1 bilateral sacroiliitis in 5 (45.45%) patients, grade 2 in 3 (27.27%) patients, and grade 3 in 2 (18.18%) patients (Figure 1). The severity of sacroiliitis was categorized as mild in 5 (45.45%) patients, moderate in 3 (27.27%) patients, and severe in 2 (18.18%) patients. Isotretinoin treatment was discontinued when the diagnosis of sacroiliitis was established. All patients were started on indomethacin at 150 mg/day. In 10 (90.90%) patients, laboratory results confirmed the symptoms had almost completely resolved within one month. Hip joint pain continued in one female patient (patient 10) with a personal history of recurring aphthous ulcers. Patient 10 developed painful genital ulcers on the labia minora, which resolved with scarring and superficial thrombophlebitis on the forearm within a month of the diagnosis of bilateral sacroiliitis. Pathergy test was negative, and the patient was diagnosed with Behcet's disease and was started on a treatment of colchicine at 150 mg/day and diclofenac sodium at 150 mg/day with gradual improvements over four months. Diclofenac sodium was discontinued in the fourth month after the symptoms of sacroiliitis completely resolved, and the patient continued colchicine therapy. Based on the

Table 1. Characteristics of the bilateral sacroiliitis patients of our study during isotretinoin therapy

Patient number	Sex/ Age	Isotretinoin Dose	Time of initial symptom	ESR (0-20 mm/h)/CRP (0-5mg/L)	HLA-B27	MRI score/ Sacroiliitis severity	Therapy	Previous history
1	22/F	20-40 mg/day	4 months	19/0.04	-	1/ Mild	Indomethacin	-
2	16/M	20 mg/day	1 month	4/0.01	-	2/ Moderate	Indomethacin	-
3	25/F	20-40 mg/day	3 months	17/1.3	-	2/ Moderate	Indomethacin	Knee pain
4	32/F	20-40 mg/day	3 months	6/1.23	-	1/ Mild	Indomethacin	Back pain
5	24/F	20-40 mg/day	2 months	19/0.30	-	1/ Mild	Indomethacin	-
6	19/F	20 mg/day	1 month	16/0.72	-	1/ Mild	Indomethacin	-
7	17/M	20-40 mg/day	4 months	11/0.52	-	2/ Moderate	Indomethacin	Back pain
8	21/F	20-40 mg/day	2 months	27/0.48	-	3/ Severe	Indomethacin	-
9	37/F	20-40 mg/day	2 months	16/0.10	-	3/ Severe	Indomethacin	-
10	36/F	20-40 mg/day	5 months	9/1.10	-	2/ Moderate	Indomethacin, diclofenac sodium, colchicine	-
11	18/M	20 mg/day	1 month	13/0.30	-	1/ Mild	Indomethacin	-

*F: female; M: male; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HLA: human leucocyte antigen

Table 2. Review of cases with isotretinoin-induced sacroiliitis

	Sex/ Age	Isotretinoin Dose	Time of initial symptom	ESR/CRP	HLA-B27	Radiologic findings	Therapy
Bachmeyer *et al.*	M/17	10-50 mg/day	5 months	45/36.00	-	X-ray-CT: Widening and erosion of sacroiliac joints, scintigraphy: Increased uptake in sacroiliac joints	Piroxycam, prednisolone
Barbareschi *et al.*	M/17	30 mg/day	days	↑/↑	-	X-ray-CT: Widening and erosion of left sacroiliac joint,	NSAID, sulfasalazine, prednisolone
Geller *et al.*	M/18	40 mg/day	1 month	-	-	Scintigraphy: Light bilateral sacroiliitis	NSAID
Elias *et al.*	M/17	0.5 mg/kg/day	6 weeks	58/-	-	X ray: Asymmetric bilateral sacroiliitis, calcaniitis	Prednisolone, indomethacin
Zonelato *et al.*	M/14	0.5 mg/kg/day	12 days	30/93.40	-	Scintigraphy: Bilateral sacroiliitis multiple osteoarticular bone activity	Prednisolone, acetaminophen
Dincer *et al.*	M/18	25 mg/day	3 months	87/48.20	-	Scintigraphy: Increased uptake of right sacroiliac joint, MRI: Bone marrow edema	NSAID
	F/25	-	2 years	10/5	-	Scintigraphy: Increased uptake on sacroiliac joints, CT: Increased sclerosis	-
	M/24	15 mg/day	2 years	N/N	+	MRI: Sacroiliitis	-
Eksioglu *et al.*	M/20	30-50 mg/day	3 months	50/19.00	+	MRI: Diffuse sub-articular edema	Naproxen
Yılmazer *et al.*	F/20	30-40mg /day	3 months	52/2.75	+	MRI: Bone marrow edema,	Diclophenac, prednisolone
Yılmaz Tasdelen *et al.*	M/23	20-40 mg/day	8 weeks after 6 months of isotretinoin	1/9.45	-	MRI: left active inflammatory sacroiliitis	Naproxen, sulfasalazine, prednisolone
Yasar Bilge *et al.*	F/31	-	3 months	11/0.13	-	MRI: Bone marrow edema	Indomethacin
	M/16	-	11 months	8/0.05	-	MRI: Sclerosis	Indomethacin
	M/22	-	24 months	23/1.10	-	MRI: Sacroiliitis	Indomethacin
	F/19	-	3 months	2/0.80	-	MRI: Bone marrow edema	Indomethacin
	F/22	-	9 months	12/0.40	-	MRI: Bone marrow edema	Indomethacin
Levinson *et al.*	E/17	20-40 mg/day	3 months	69/24.00	-	MRI: Moderate to severe sacroiliitis with joint effusions and florid bone marrow edema in the sacroiliac joints	Naproxen
Rozin *et al.*	E/28	30 mg/day	20 days	35/1.3	-	Scintigraphy: Increased uptake on sacroiliac joints, MRI: Diffuse sub-articular edema	ACTH depo injection, ethodolac

*M: male; F: female; NSAID: non-steroid anti-inflammatory drugs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein;

chronology of events and the improvement of the sacroiliitis after the discontinuation of isotretinoin in all our patients, sacroiliitis is associated with isotretinoin treatment.

DISCUSSION

For severe acne, arthralgia was noted in 16% of patients during treatment with systemic isotretinoin (14). Acne fulminans is a rare condition characterized by the abrupt onset of nodular acneic and ulcerative lesions, which may be accompanied by fever, arthralgias, myalgias, and osteolytic lesions (15). The SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome is considered a member of the spondyloarthropathy family, which may present with unilateral or bilateral sacroiliitis (16). Acne conglobata may also be associated with the musculoskeletal symptoms of arthralgia and arthritis (17). Five of the reported patients with sacroiliitis during isotretinoin treatment were classified as acne fulminans, however it is not clear whether isotretinoin caused sacroiliitis or if sacroiliitis is a systemic symptom of an acne fulminans flare (2-6). In our study, no patients were diagnosed with sacroiliitis due to acne fulminans, acne conglobata, or SAPHO syndrome because sacroiliitis appeared after isotretinoin treatment without any increases of systemic symptoms related to these diseases and it resolved after withdrawal of the drug. Isotretinoin is suggested to be responsible for the systemic symptoms of patients with acne fulminans due to the increased fragility of the pilosebaceous epithelium and the massive contact with *Propionibacterium acnes* antigens, leading to exaggerated hypersensitivity reaction types III and IV (18). Altered neutrophil function in the predisposed patients with hyper-reactivity to inflammatory mediators and decreased phagocytosis of *propionibacterium acne* is also another theory regarding the induction of acne fulminans (18).

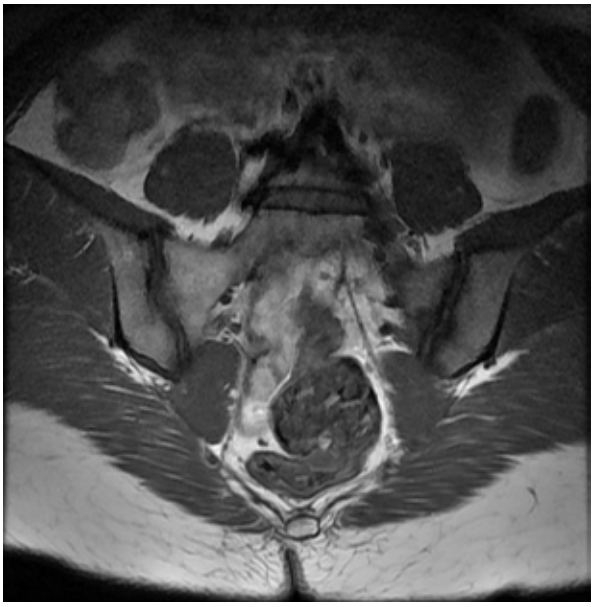

Figure 1. Oblique coronal plane fat saturation T1-weighted MRI image of the sacroiliac joints demonstrating bilateral bone marrow edema.

Arthritis that is mild in severity and disappears without sequelae has been reported in a few cases involving mono or oligo arthritis of the hip, knee, ankle, shoulder, elbow, wrist, and finger joints (17-22). An adult onset Still's disease triggered by isotretinoin treatment of acne conglobata has been noted as well (23). Immune dysfunction occurs in patients using isotretinoin, with possible mechanisms and pathways leading to arthritis and vasculitis (18). Because of its detergent-like properties, isotretinoin induces some alterations in the lysosomal membrane structure of the cells, facilitating a cytopathic destruction of the synovial cells and making the structure sensitive to mechanical irritation (18). Matsuoka *et al*. measured the isotretinoin concentration (131 ng/mL) obtained from the synovial fluid of a patient's knee, confirming the drug caused the arthritis (18). Gene polymorphisms of retinoic acid receptor alpha genes in the frequencies of CTG, TTG, and TTT haplotypes are suggested to be associated with arthralgia of patients using isotretinoin, which makes some people prone to rheumatologic side-effects (24). Dincer *et al*. reported two cases – a football and a basketball player – with sacroiliitis during isotretinoin treatment, indicating the relation between mild trauma and arthritis (7). None of our patients were interested in sports.

In our literature search, 18 patients (13 men, 5 women) with isotretinoin-induced sacroiliitis were observed to up to now (Table 2) (2-13). In our study, sacroiliitis was observed mostly in women. Among these, 3 cases had unilateral and 10 cases had bilateral sacroiliitis, though the laterality of 5 cases was not mentioned in the related report (2-13). Ages ranged between 14 and 31 years, and the mean age was 20.44 years. The time of initial symptoms of sacroiliitis after administration of isotretinoin differed between a few days and 2 years (2-13). HLA- B27 was found to be positive in 3 cases (7-9). Eksioglu *et al*. noted the patients with HLA-B27 positivity could be susceptible to developing sacroiliitis during isotretinoin treatment (8). We did not observe the HLA-B27 positivity in any patients. X-ray, computed tomography scan, bone scintigraphy, and MRI were used for the detection of sacroiliitis (2-13). An MRI of the sacroiliac joints has become a valuable tool for the early diagnosis of sacroiliitis in patients with inconclusive radiographic findings (25). Positive MRI findings have

been reported to have the same significance as a positive test for HLA-B27 (25). Hermann *et al*. showed the MRI may reveal both active and structural signs of sacroiliitis, while conventional radiography and computed tomography only demonstrate structural or chronic changes (25). The improvement in the sacroiliitis of our patients is visible through the resolution of symptoms. In fact, confirmation with radiological imaging after resolution of the symptoms is suggested by authors (11). In the present study, the clinical findings of Behcet's disease appeared in one patient during isotretinoin treatment. Sacroiliitis has been observed in 6% of patients with Behcet's disease (26). Whether the drug triggered sacroiliitis or if sacroiliitis is an articular manifestation of Behcet's disease remains unclear in this case. In most cases (10/18) in the literature, the clinical symptoms were self-limited and resolved after isotretinoin was discontinued and non-steroid anti-inflammatory drugs (NSAID) were administered (4,7,8,11). All our patients except one with Behcet's disease improved within a month after isotretinoin had been discontinued. Bachmeyer *et al*. returned patients to isotretinoin therapy a few weeks after withdrawal at a dose of 0.1 mg/kg/day, but a relapse of pain occurred 48 h later. However, they continued treatment in combination with prednisolone and then increased the isotretinoin dose to 0.5 mg/kg/day (2). Zanelato *et al*. also restarted isotretinoin with prednisolone after 30 days of withdrawal (6). Yılmazer *et al*., Elias *et al*., and Bachmeyer *et al*. treated patients with prednisolone (15 mg/day, 30 mg/day, 30 mg/day, respectively) in addition to diclofenac sodium for 6 weeks (9). Tasdelen *et al*. and Barbareschi *et al*. used sulfasalazine added to prednisolone and anti-inflammatory drugs for remission (3,10).

CONCLUSIONS

Not enough cases have yet been reported to determine whether there is a true association between isotretinoin and sacroiliitis, but dermatologists should be aware of the rheumatologic symptoms of the patients. Recent data from the literature confirm the discontinuation of the drug and administration of anti-inflammatory drugs result in an almost complete resolution of the symptoms. The role and mechanism of isotretinoin as a causative factor in sacroiliitis must be investigated further.

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