

Isotretinoin-induced Unilateral Sacroiliitis in a Patient with a Family History of Ankylosing Spondylitis and HLA B27 Positivity: A Case Report

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ABSTRACT

Isotretinoin (Iso) is used for the treatment of severe acne, and seronegative sacroiliitis is a rare side effect of this therapy. We present the case of a woman with unilateral sacroiliitis that began during Iso therapy. She had a family history of ankylosing spondylitis (AS) and human leukocyte antigen-B27 (HLA-B27) positivity. Magnetic resonance imaging (MRI) demonstrated acute inflammatory changes in the left sacroiliac joint. The Iso therapy was withdrawn, and after four more weeks, she was symptom-free. One year later, the inflammatory features of sacroiliitis were still preserved. We believe that Iso treatment may have induced or accelerated the emergence of sacroiliitis in patients with HLA-B27 positivity and family history of spondyloarthropathy. Patients should be questioned about their personal and family histories of spondyloarthropathy before being treated with Iso for acne, and alternative treatment modalities should be considered.

Keywords: HLA-B27, isotretinoin, sacroiliitis, spondyloarthropathy

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INTRODUCTION

Isotretinoin (Iso) is a vitamin A derivative that is increasingly being used to treat acne throughout the world. It has many side effects, such as neuromuscular and rheumatological disorders, and on rare occasions seronegative sacroiliitis has also been noted (1-6). A few cases of sacroiliitis with human leukocyte antigen-B27 (HLA-B27) positivity have been reported in the literature (2, 7), but to our knowledge, there have been no reports of sacroiliitis in a patient with a family history of spondyloarthropathy. In this case report, we present a patient with unilateral sacroiliitis that was precipitated by Iso therapy who also had a family history of ankylosing spondylitis (AS) and HLA-B27 positivity.

CASE REPORT

A 31-year-old female patient was referred to a physical medicine and rehabilitation outpatient clinic complaining of left buttock and lower back pain, especially at night. The patient was started on Iso therapy 20 mg daily, and this was gradually increased to 40 mg four months prior to her referral due to recalcitrant acne vulgaris. She was not taking any other medications. The complaints began with the onset of the Iso therapy and had become worse over the previous two months; however, the pain was relieved with movement and exercise. In addition, the patient had no history of arthritis, psoriasis, uveitis, inflammatory bowel disease, or any other systemic disease, but there was a history of AS on her father. A systemic physical examination of the patient was normal. However, a musculoskeletal evaluation revealed that the left sacroiliac joint was very painful, and sacroiliac stress tests were positive. The patient's modified Schober's test, chest expansion, and occiput-to-wall measurements were 7 cm, 4 cm, and 3 cm respectively, and she had normal but painful axial range of motion. Additionally, no neurological deficit was found. A laboratory investigation revealed an erythrocyte sedimentation rate (ESR) of 8 (normal range: 0-20 mm/hour) and a C-reactive

protein level of 0.65 (0-5 mg/l). Furthermore, her complete blood count was also in the normal range. However, the patient tested negative for the following: rheumatoid factor (RF), antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-cyclic citrullinated peptide antibodies (anti-CCP), hepatitis C, hepatitis B, human immune deficiency (HIV), brucellosis, and tuberculin purified protein derivative (PPD). Her urine culture was also all negative. In addition, the patient's complements (C3, C4) and immunoglobulin G and A (Ig G, Ig A) levels were within normal ranges. Besides these laboratory findings, the patient tested positive for HLA-B27. A lumbosacral and pelvic X-ray along with lumbar magnetic resonance imaging (MRI) showed no pathological findings, but an MRI of the sacroiliac joints demonstrated acute sacroiliitis and active inflammatory changes on the articular surfaces of the left side (Figure 1). The Iso therapy was withdrawn, and the patient began treatment with indomethacin 75 mg/day. Four weeks later, her pain was relieved, but in her follow-up period two months after the end of the Iso treatment, she was suffering from inflammatory back pain, and a recurrence of her buttock and lower back pain. The laboratory examinations and cultures were repeated, and all were normal. The patient was then prescribed sulfasalazine (500 mg tablet 2x2 daily) in combination with the indomethacin. After one year, the sacroiliac MRI was repeated, and the inflammatory features of the sacroiliitis were still preserved (Figure 2).

DISCUSSION

According to our literature review, eight cases of sacroiliitis exist in conjunction with Iso therapy, with the patients ranging in age from 17 to 28 (2-7). Moreover, only one of these patients was a female (2). Our patient was a 31-year-old female with different sociodemographic characteristics from these other cases. Furthermore, only two of the eight previously reported patients had HLA-B27 positivity and none of them had family history of

spondyloarthritis. The onset of inflammatory pain may occur at the same time that Iso treatment commences or at any time during the next three months. In our case, the pain started with the initiation of Iso therapy and progressed to the complaints of inflammatory characteristics over the next two months. However, it should be kept in mind that muscle pain is common with Iso treatment (8); therefore, the cause of the pain should be differentiated in these patients. Thorough clinical and sociodemographic features of the cases are shown in Table 1.

While acne fulminans and acne conglobata are classified as being clinically severe, with sacroiliitis sometimes developing independently of the Iso therapy, acne vulgaris does not induce sacroiliitis(8). Two patients with sacroiliitis associated with acne fulminans were reported before, after commencement of Iso therapy (2, 4). Our patient's primary diagnosis was acne vulgaris, therefore, sacroiliitis development was not expected.

The most common diagnostic method of sacroiliitis was MRI, and bilateral sacroiliac edema was found via imaging methods, such as MRI, computerised tomography, scintigraphy, in six cases (3, 5, 6, 7), in our research but two (2, 4). In this case, the clinical symptoms of unilateral sacroiliitis along with the unilateral MRI findings were remarkable.

A common trait found in the eight previously reported cases was that according to the radiological and clinical findings, improvement occurred after the cessation of Iso (4, 5, 3, 6, 7). However, the MRI findings of a case of sacroiliitis involving HLA-B27 positivity, fluctuated during a two-year follow-up period, and the patient experienced no relief from the pathological findings (7). Our case was also HLA-B27 positive and had a family history of AS. As often seen with Iso therapy, our patient's symptoms emerged after the initiation of this treatment, but she received rapid relief from the inflammatory pain soon after discontinuing the Iso and beginning the indomethacin therapy. However, inflammatory pain emerged again and sulfasalazine therapy was required two months later. One year later, the patient had an MRI to assess her condition, and the inflammatory findings of sacroiliitis were

still present. It might be possible that, patients with HLA B27 positivity may be more prone to develop sacroiliitis under Iso therapy or, sacroiliitis triggered by Iso might be mediated by HLA B27. Furthermore, family history of ankylosing spondylitis might also have been an important triggering risk factor for sacroiliitis in this case.

In recent years, many causes regarding the connection between Iso treatment and sacroiliitis have been suggested, but nothing definitive has ever been determined. It is also known that Iso therapy induces other autoimmune diseases, such as inflammatory bowel disease (9) and thyroiditis (10). In addition, it increases the oxidative toxicity in patients with acne vulgaris (11), and oxidative stress leads to DNA damage through the secretion of inflammatory cytokines (12). Additionally, retinoic acid induces matrix metalloproteinase-2 (MMP-2) enzyme activity (13), MMP enzymes are mediators of osteoarthritis and rheumatoid arthritis (14). Although it is believed that MMP-2 activity is related to oxidative stress, future studies should be conducted to confirm this (13).

CONCLUSION

In previous case reports, HLA-B27 has been reported as a mediator of sacroiliitis associated with Iso treatment, however family history of AS has never reported in patients with sacroiliitis on Iso treatment. Sacroiliitis may already arise in patients with HLA-B27 positivity and family history of spondyloarthropathy, at anytime in their lives. In the light of this case, it can be thought that, Iso treatment may have induced or accelerated the emergence of sacroiliitis in patients with HLA-B27 positivity and family history of spondyloarthropathy. In our opinion, patients who are scheduled to begin treatment with Iso, should be questioned about their personal and family histories, and if suspicious condition are present, HLA B27 should be checked and alternative treatment modalities should be primarily considered.

Conflict of Interest

REFERENCES

1. Chroni E, Monastirli A, Tsambaos D. Neuromuscular adverse effects associated with systemic retinoid dermatotherapy. *Drug Saf* 2010; **33**: 25–34.
2. Dinçer Ü, Çakar E, Kıralp MZ, Demirdal ÜS, Ülker RN. Can isotretinoin induce sacroiliitis: three cases. *Rheumatism* 2008; **23**: 157–9.
3. Bachmeyer C, Charoud A, Turc Y, Callot V, Blum L, Aractingi S. Isotretinoin-induced bilateral sacroiliitis. *Dermatol* 2003; **206**: 285–6.
4. Barbareschi M, Paresce E, Chiaratti A, Ferla Lodigiani A, Clerici G, Greppi F. Unilateral sacroiliitis associated with systemic isotretinoin treatment. *Int J Dermatol* 2010; **49**: 331–3.
5. Rozin AP, Kagna O, Shiller Y. Sacroiliitis and severe disability due to isotretinoin therapy. *Rheumatol Int* 2010; **30**: 985–6.
6. Levinson M, Gibson A, Stephenson G. Sacroiliitis secondary to isotretinoin. *Australas J Dermatol* 2012; **53**: 298–300.
7. Eksioğlu E, Öztekin F, Unlu E, Cakci A, Keyik B, Karadavut IK. Sacroiliitis and polyneuropathy during isotretinoin treatment. *Clin Exp Dermatol* 2008; **33**: 122–4.
8. Knitzer RH, Needleman BW. Musculoskeletal syndromes associated with acne. *Semin. Arthritis Rheum* 1991; **20**: 247–55.
9. Crockett SD, Porter CQ, Martin CF, Sandler RS, Kappelman MD. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. *Am J Gastroenterol* 2010; **105**: 1986–93.
10. Gursoy H, Cakmak I, Yildirim N, Basmak H. Presumed isotretinoin-induced, concomitant autoimmune thyroid disease and ocular myasthenia gravis: a case report. *Case Rep Dermatol* 2012; **4**: 256–60.

11. Erturan İ, Naziroğlu M, Akkaya VB. Isotretinoin treatment induces oxidative toxicity in blood of patients with acne vulgaris: a clinical pilot study. *Cell Biochem Funct* 2012; **30**: 552.
12. Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What's new. *J Eur Acad Dermatol Venereol* 2003; **17**: 663–9.
13. Dalmolin RJ, Zanotto-Filho A, De Oliveira RB, Duarte RF, Pasquali MA, Moreira JC. Retinol and retinoic acid increase MMP-2 activity by different pathways in cultured Sertoli cells. *Free Radic Res* 2007; **41**: 1338–47.
14. Burrage PS, Mix KS, Brinckerhoff CE. Matrix metalloproteinases: role in arthritis. *Front Biosci* 2006; **11**: 529–43.

Table 1: The summary of the Iso induced cases

	Sex	Age yr	Type of Acne	Iso dose	Onset time	HLA -B27	Family Hx	SI	Tx	Pain Prognose	Control Imaging
Bachmeyer (2003)	M	18	AF	50mg	1 mo	(-)	(-)	Bilat	NSAID	Resolved	none
Eksioglu (2007)	M	20	AV	40mg	2 mo	(+)	(-)	Bilat	NSAID	Resolved	MRI findings(+)
Dinçer (2007)	M	18	AV	5mg	3 mo	(-)	(-)	Unilat	NSAID	Resolved	none
	F	25	AV	NM	NM	(-)	(-)	Bilat	NSAID	Resolved	none
	M	24	AV	15mg	NM	(+)	(-)	Bilat	NSAID	Resolved	none
Barbareschi (2010)	M	17	AF	30mg	Few days	(-)	(-)	Unilat	NSAID-SLZ Prednison	Resolved	none
Rozin (2010)	M	28	AV	30mg	20 days	(-)	(-)	Bilat	NSAID Synacten	Resolved	none
Levinson (2011)	M	17	AV	40mg	1 mo	(-)	(-)	Bilat	NSAID	Resolved	MRI Normal
Our case	F	31	AV	40mg	2 mo	(+)	(+)	Unilat	NSAID-SLZ	Fluctuation	MRI findings(+)

M: Male, F: Female, AF: Acne Fulminans, AV: Acne Vulgaris, mo: Month, nm: Not Mentioned, MRI: Magnetic Resonance Imaging, CT: Computerized Tomography, NSAID: Nonsteroid Anti Inflammatory Drug, SLZ: Sulfasalazine, Unilat: Unilateral, Bilat: Bilateral

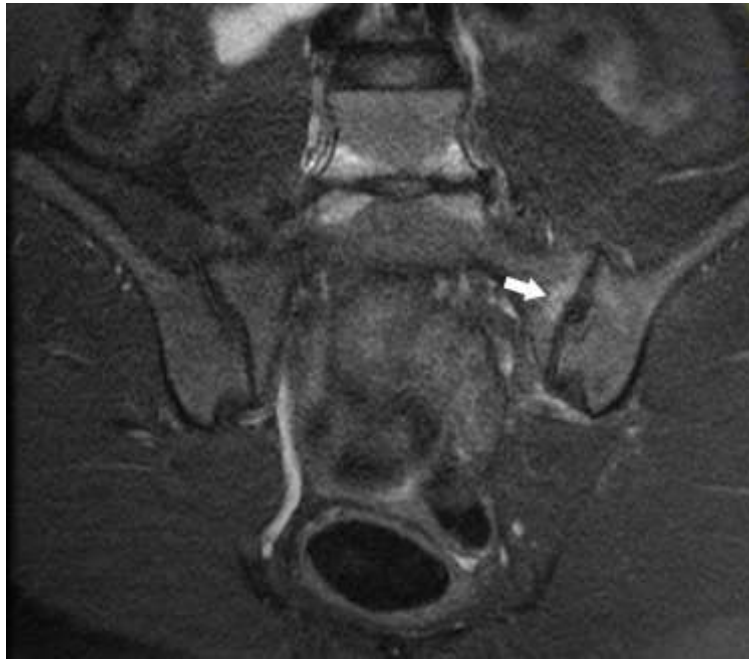


Fig 1: Coronal fat-suppressed T2-weighted MR image shows the increased signal intensity (arrow) in left sacroiliac joint

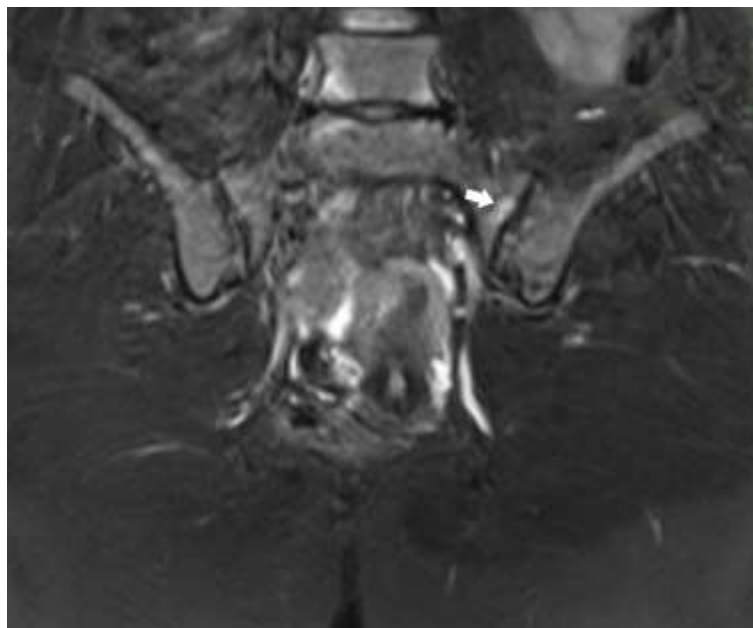


Fig 2. 1 Year later, coronal fat-suppressed T2-weighted MR image shows the increased signal intensity (arrow) in left sacroiliac joint