

Can Isotretinoin Induce Sacroiliitis: Three Cases

İsotretinoin Sakroiliiti Tetikleyebilir Mi: Üç Vaka Nedeniyle

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Abstract

Our aim was to present three cases of retinoid-induced sacroiliitis demonstrated by magnetic resonance imaging and bone scintigraphy. Three patients with low back and hip pain, and lumbar stiffness after using isotretinoin for acne fulminans were described. Our cases were characterized by rapid resolution of pain and stiffness after isotretinoin treatment was discontinued. Although the association between isotretinoin therapy and sacroiliitis in arthritis patients was suggested in the literature it has not been clearly explained yet. Prospective studies are needed to reveal the causal relationship between isotretinoin and sacroiliitis. (*Romatizma 2008; 23: 157-9*)

Key words: isotretinoin, sacroiliitis, acne, side effects

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Özet

Bu çalışmada MR ve sintigrafi ile tespit edilen, retinoide bağlı 3 adet sakroiliit vakasını sunmayı amaçladık. Acne Fulminans için isotretinoin kullanımı sonrasında gelişen bel, kalça ağrısı ve bel hareketlerinde tutukluk nedeniyle araştırılan üç vakayı tanımlanmıştır. Vakalarımızda Isotretinoin kesildikten sonra ağrı ve tutukluk hızla geriledi. Isotretinoin ve sakroiliit arasındaki ilişki tartışmalı olup henüz tam olarak açıklanamamıştır. İso-tretinoin ve sakroiliit arasındaki neden sonuç ilişkisini ortaya koyabilmek için prospektif çalışmalara ihtiyaç vardır. (*Rheumatism 2008 23: 157-9*)

Anahtar Sözcükler: İzoretinoin, sakroileit, akne, yan etki

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Introduction

Isotretinoin, a vitamin A derivative, is approved for patients with severe acne not responding to standard therapy, including systemic antibiotic therapy. The drug may act through retinoic acid receptors to cause a variety of effects, including a reversal of androgenic effects on sebaceous glands. Acne fulminans is a clinical entity that is difficult to treat and the etiology of which is controversial. It mostly affects young adults. In addition to antibiotherapy, its treatment involves the use of isotretinoin, especially in persistent cases (1).

Three cases with persistent acne and acne fulminans were started on isotretinoin, and they were admitted to our clinic for lumbar pain which has developed in varying periods of time.

Case 1: An 18-year-old male patient was started on a 25 mg daily isotretinoin therapy for his acneic lesions, which appeared on the face, and upper trunk. After three

months, he began to suffer from pain in his lumbar region and hip while playing football, and therefore was taken under medical investigation. The pain was more intensely felt on the lower lumbar region and hip. Hip movements were painful, particularly during internal rotation, and 1/3 restricted. Sacroiliac stress tests were positive. Lumbar flexion was restricted and painful. Schober's test was measured as 3 cm. Erythrocyte sedimentation rate (ESR) was 87 mm/h, and C-reactive protein (CRP) was measured as 48.2 mg/l. ESR and CRP decreased followed by discontinuation of isotretinoin 33 mm/h and 9.3 mg/dl, respectively. Lumbar and hip pain relieved followed by started nonsteroidal anti-inflammatory drugs (NSAIDs). X-ray graphy and CT studies of the sacroiliac joint revealed no abnormality. In MRI examination of the sacroiliac joint, bone marrow edema was detected in the sacral and iliac wings of the right sacroiliac joint with coexisting intra articular fluid retention. (Figure 1). Scintigraphy showed increased uptake activities in the right sacroiliac joint. HLA B27 was negative.

Case 2: A 25-year-old female patient started to use isotretinoin two years ago for lesions on her face but she used it in an irregular interval. Afterwards, a severe lumbar pain and morning stiffness lasting 2 hours have developed within the last year. In the physical examination, the lumbar flexion was restricted and schober was 4 cm, the sacroiliac stress tests were positive. ESR and CRP were measured as 10 mm/h, and 5 mg/l, respectively. Other biochemical parameters were within their normal range. In the tomographic examination of the sacroiliac joint, increased sclerosis as well as irregularities (indicative of sacroiliitis) were noted on the articular aspects of each bone bilaterally, and more prominent at the proximal. Increased activity uptake was detected bilaterally on the sacroiliac joints at the late phase of the scintigraphy (Figure 2). HLA B27 was negative

Case 3: A 24-year-old male patient has used isotretinoin 15 mg daily for his acne vulgaris for a period of two years. He had been an amateur basketball player during and after using the medication. He was explored for the morning stiffness accompanied by lumbar pain which has started following the use of medication. He suffered lumbar pain and morning stiffness lasting more than 2 hours. In the examination, a minimal restriction in lumbar flexion was noted. The sacroiliac stress tests were bilaterally positive. Lumbar schober was measured as 6 cm. Other findings of the locomotor system were found to be normal. HLA-B 27 was positive. Other serologic and biochemistry tests were within their normal range, including acute phase reactants. The sacroiliac joint was normal on x-ray graphy and scintigraphic examination. In MRI examination, hyperintense signals were detected on T1-weighted and also on hypointense T2-weighted images, consistent with sacroiliitis.

None of the patients were positive for ANA, Anti-ds DNA, or ENA antibody.

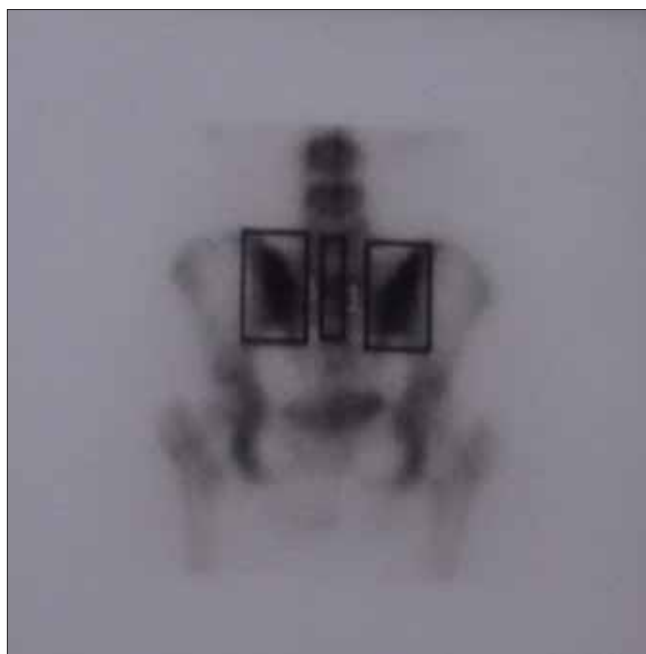


Figure 2. The late phase of the scintigraphy shows bilateral sacroiliitis.

Discussion

Isotretinoin is used in cases of acne fulminans and persistent acne either alone or in combination with a steroid, but there is no consensus on the use of Isotretinoin (2). In addition to its successful effects in the treatment of acne, it also has a series of side effects. Its most common musculoskeletal side effects are arthralgia, myalgia and vasculitis. Bone abnormalities mimicking seronegative spondyloarthropathy or DISH have been described in many cases. Side effects are seen in nearly 15% of the patients (2).

The association of isotretinoin therapy and sacroiliitis is not novel but much rare. In the literature, there exists information denoting that retinoids cause immune dysfunction, thereby leading to arthritis and vasculitis (3, 4). However, the mechanism by which isotretinoin leads to arthritis/sacroiliitis is poorly understood. The etiology of rheumatic disorders associated with retinoids is still obscure however it is presumed that immunomodulation by several mechanisms (such as an alteration of the cytokine balance) is probably ascribable to this interesting association (8). As a result of its detergent-like effects, isotretinoin induces some alterations in the lysosomal membrane structure of the cells, and this predisposes to a degeneration process in the synovial cells. Isotretinoin treatment may render cells vulnerable to mild traumas less than normal for producing an injury (5). There exists information indicating the potential role of mild-to-moderate traumas in arthritic conditions associated with isotretinoin use (6). Likewise, the complaint of our first case appeared during a football match, suggesting that the condition is related to cellular vulnerability. Similarly, that our third case had been using the drug when his complaints had appeared, and that he is



Figure 1. The MRI shows bone marrow edema in sacral and iliac wings of the right sacroiliac joint.

an amateur basketball player again supports the association between mild trauma and development of arthritis. Considering the drug's mechanism of effect as well as the cases presented in the literature, it becomes clear that the arthritis is nonspecific and aseptic. In a patient with sacroiliitis, the biopsy revealed that the synovial fluid was non-inflammatory in character (5). While two of our cases showed scintigraphic findings consistent with sacroiliitis, sacroiliitis was detectable in all our three cases with using MRI, yet no agent was able to be identified. An important feature of isotretinoin induced arthritis is that the pain resolves when the drug is discontinued and a treatment with NSAIDs are initiated. Bachmeyer et al. reported a patient with Isotretinoin induced bilateral sacroiliitis. An 18-year old man was treated for nodulocystic acne with oral Isotretinoin (50 mg/day) and one month later the patient complained of sudden onset back and hip pain. Sacroiliac stress tests were positive and CT scan showed widening and erosion of bilateral sacroiliac joint. Isotretinoin was withdrawn, and a non-steroidal anti-inflammatory drug was given resulting in a dramatic improvement (10). Camisa reports that the condition has resolved in two cases with arthritis, leaving no sequel (6). This information derived from the literature was also observed in two of our cases. In cases with sacroiliitis, particularly in those with acne fulminans, it is hard to decide whether the condition is actually triggered by isotretinoin or not. In a few cases, acne fulminans with sacroiliitis has been reported during isotretinoin treatment, suggesting the responsibility of Isotretinoin (9). Arthritis usually appears 2 to 10 weeks after onset Isotretinoin (11), but definite period was not described. First case is appropriate to this time. Second case had lumbar pain which started following the use of medication but it was not investigated. We could not explain different period of onset of symptom appearance and starting drug in third case.

It is well known that acne fulminans is a component of the SAPHO syndrome. It should be kept in mind that the sacroiliitis, which has developed in the first patient might be a part of this clinical entity. Besides, the fact that retinoids may lead to conditions such as costochondritis, hyperostosis, and tendinitis further complicates the current situation (7). However we believe that this case is an isotretinoin induced sacroiliitis because there were no signs and symptoms of SAPHO syndrome (except acne) before using isotretinoin. On the other hand, we did not have cer-

tain information about before onset Isotretinoin but, no one of all had not clinical or laboratory evidences, family history and some complaints related to sacroiliitis. Because of these, we assumed that these patients' locomotor systems were healthy before onset Isotretinoin.

We know that the relationship between isotretinoin and sacroiliitis is not clear in these patients. But some strong evidences reminded that this relationship was possible: (a) sacroiliitis resolved after discontinuation of isotretinoin and start NSAID pain complaints alleviated in all patients, (b) the first patient reported that the lumbar pain come back when the NSAID is stopped in first month. as we don't have information whether sacroiliitis improve or not without NSAID treatment, (c) we did not restart isotretinoid and the sacroiliitis or symptoms of sacroiliitis did not reoccur.

We speculate that isotretinoin can cause sacroiliitis and there are some evidences about relation of sacroiliitis and isotretinoin in literature.

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