OLGU SUNUMU CASE REPORT

DOI: 10.5336/caserep.2018-61492

Spondyloarthritic Changes During Acitretin Treatment

Barış GÜNDOĞDU[a],
Ayşe Serap KARADAĞ[b]

[a]Department of Rheumatology,
İstanbul Okan University
Faculty of Medicine,
[b]Clinic of Dermatology,
İstanbul Medeniyet University
Göztepe Training and Research Hospital,
İstanbul, TURKEY

Received: 20.05.2018
Received in revised form: 12.08.2018
Accepted: 27.08.2018
Available online: 05.03.2019

Correspondence:
Barış GÜNDOĞDU
İstanbul Okan University
Faculty of Medicine,
Department of Rheumatology,
İstanbul, TURKEY
barisgund@hotmail.com

ABSTRACT Keratosis follicularis, also called as Darier disease, is a rare disease characterized by keratotic papules in sebum-rich skin areas. Oral or topical retinoids, topical or systemic glucocorticoids frequently utilised in the treatment of keratosis follicularis. Aberrant musculoskeletal signs are not normally expected in keratosis follicularis, however, they may rarely arise from oral retinoids like acitretin. In this case, inflammatory type back pain, morning stifness and limitation of spinal mobility were developed after acitretin therapy. The patient's blood tests revealed acute inflammation and sacroiliac MRI showed right-sided sacroiliitis in the patient. The pathophysiological mechanisms of such complications related to the use of systemic retinoids are currently unclear. We report the development unilateral sacroiliitis after the use of acitretin in a 57-year-old woman with keratosis follicularis who previously not diagnosed as spondyloarthritis.

Keywords: Acitretin; darier disease; spondylitis, ankylosing

Keratosis follicularis, also known as Darier disease, is an uncommon autosomal dominant disease characterized by fatty hyperkeratotic papules in the seborrheic areas of the skin, mucous membrane changes, and nail abnormalities.[1]

Spondyloarthritis (SpA) contains a group of rheumatic diseases such as ankylosing spondylitis (AS), psoriatic arthritis, undifferentiated SpA, and a genetic link with Human Leukocyte Antigen B27 (HLA-B27). The distinctive musculoskeletal symptoms are divided into axial (sacroiliitis, spondylitis) or peripheral (arthritis, enthesitis, dactylitis) disease. AS, the typical form of the axial SpA, is defined by the postinflammatory structural detriment of the sacroiliac joints on classic radiography. Most of patients, nevertheless, have same axial symptoms and signs of active sacroiliitis on magnetic resonance imaging (MRI) in the lack of such radiographic alterations, producing a risk of delayed or overlooked diagnosis. Hence, in 2009, the Assessment of SpondyloArthritis International Society (ASAS) proposed recent classification criteria for axial SpA, comprising patients both with (AS) and without radiographic sacroiliitis-the latter type by that means formally described as non-radiographic axial SpA (nr-axSpA).[2]

CASE REPORT

A 57 year-old female patient was firstly admitted to rheumatology clinic with the complaints of inflammatory type low back pain, morning stiffness, and limitation of spinal mobility. The patient's anamnesis included keratosis follicularis, diabetes mellitus, hyperlipidemia, and hypertension. Skin biopsy had been performed at the age of 15 and keratosis follicularis was diagnosed in this case. She did not describe psoriasis, inflammatory bowel disease, genitourinary and gastrointestinal infections in her medical history. There was no known SpA and autoimmune dermatologic diseases in the patient's family history. The keratosis follicularis recurred 6 months ago after a long quiescent period and the patient was evaluated by an experienced dermatologist. On dermatological examination, red to brown keratotic papules with a greasy texture on the submammary skin, and crusted lesions over the abdomen were seen (Figure 1). Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis (SAPHO) syndrome was excluded because the specific clinical findings of rare SpA subtype were not detected in the patient. It was considered no need for the skin re-biopsy, and systemic retinoid treatment in addition to previous topical therapy was prescribed promptly due to extent of the disease. The patient used acitretin at a dose of 25 mg daily for 3 months in the maintenance treatment of Darier's disease after the initial dose of 10 mg daily for 6 weeks. On physical examination, bilateral hip joint range of motion and lumbar spinal movements in sagital and frontal planes were slightly limited. Sacroiliac joint provocation test (Patrick's test) was positive on the right side. Cheilitis, palmoplantar desquamation and xerosis related to the use of acitretin were also noticed (Figure 2). The patient's initial investigations revealed mild normochromic-normocytic anemia and high acute phase response. On the other hand, renal and liver function tests were within normal limits. Additionally HLA-B27, tuberculin skin test, and Rose Bengal test were negative (Table 1). Plain pelvic radiography showed only grade I sacroiliitis on the right side, however, normal findings on lumbosacral spine imaging

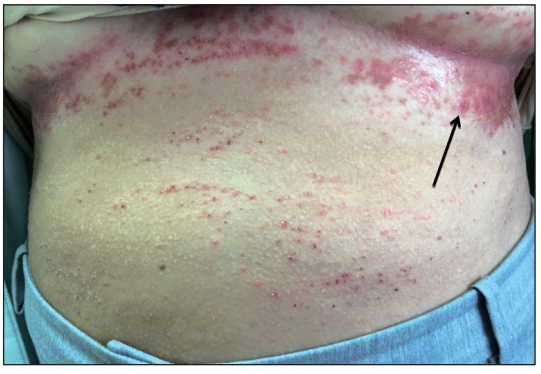

FIGURE 1: Findings of typical keratosis follicularis on the submammary area (black arrow).

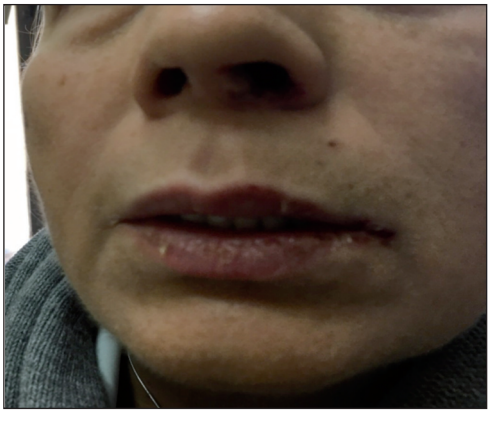

FIGURE 2: Oral mucosal changes due to acitretin treatment.

were seen. Enthesitis was also detected in both heels on lateral calcaneus x-ray. Sacroiliac MRI showed acute right-sided sacroiliitis with minimal chronic findings (Figure 3, Figure 4). Therefore, nr-axSpA was diagnosed according to ASAS classification criteria for axial SpA, and sulfasalazine started at 500 mg twice daily for 1 month in addition to naproxen. Eventually, the clinical signs of the patient improved after 1 month of follow-up (Table 1).

DISCUSSION

Keratosis follicularis consists of characteristic keratotic papules in the seborrheic skin areas like nasolabial folds, back, chest, ears, forehead, and scalp. Many patients have slight flexural involvement with scattered papules in the axillae, groin, or, submammary skin as in this case. Besides, mucosal lesions in the oral cavity are detected in a small

TABLE 1: Laboratory tests.

Parameters	Pre-treatment	Post-treatment	Reference values
WBC (x103/µL)	9.5	7.43	4.5-11
Neutrophils (x103/µL)	5.77	3.95	1.56-6.13
Hb (g/dl)	**10.5**	**10.5**	13.1-17.2
RBC (M/uL)	**3.76**	**3.67**	3.8-5.48
Hct (%)	**32**	**31.3**	36.2-38.6
PLT (x103/µL)	390	210	150-400
ESR (mm/h)	**88**	**32**	<20
CRP (mg/dl)	**1.7**	0.2	0-5
Total Protein (g/dL)	7.2	7.1	6.4-8.2
Albumin (g/dL)	4.5	4.2	3.4-5
Creatinine (mg/dl)	0.8	0.8	0.6-1.0
ALT (U/L)	13	14	15-50
Urinalysis	Normal	Normal	---
Anti-HCV	Negative (0.11)	---	0-0.99
HBsAg	Negative (0.18)	---	0-0.99
Anti-HBs	**Positive (20.72)**	---	0-9.99
HLA-B27(Flow cytometry)	Negative	---	---
Rose Bengal Test	Negative	---	Negative if titer <1/8 Positive if titer ≥ 1/8

ALT: Alanine Aminotransferase; **CRP:** C-Reactive protein; **ESR:** Erythrocyte sedimentation rate, **Hb:** Haemoglobin; **HBsAg:** Hepatitis B surface antigen; **anti-HBs:** Hepatitis B surface antibody, **anti-HCV:** Hepatitis C virus antibody; **Hct:** Hematocrit; **HLA-B27:** Human Leukocyte Antigen B27; **Plt:** Platelets; **WBC:** White blood cells.

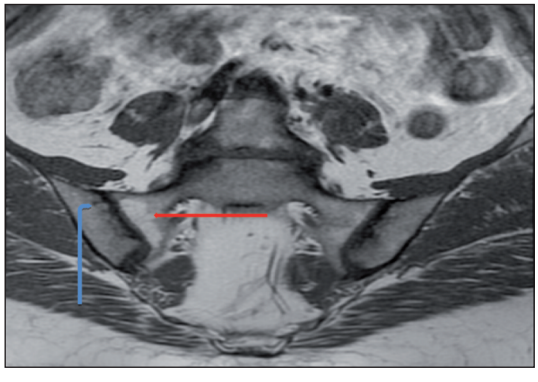

FIGURE 3: Semi-coronal T1-weighted sequence of MRI shows fatty degeneration (straight red arrow) on the sacral side of right SI joint with small erosions On its iliac side (blue oblique arrow).

number of patients. These abnormal and pathognomonic mucosal changes occur as white papules with a central depression but there were no such findings in our case. Additionally, the involvement of hands in keratosis follicularis is prevalent clinical feature in contrast to this case. The lesions on palms contain punctate keratosis, palmar pits, and hemorrhagic macules.

The abnormal dermatological findings are typically not seen for axial SpA. In this context, between 10% and 25% of the patients with classic AS have concomitant psoriatic lesions when considering several previously reported case series in the literature. The involvement of axial skeleton occurs

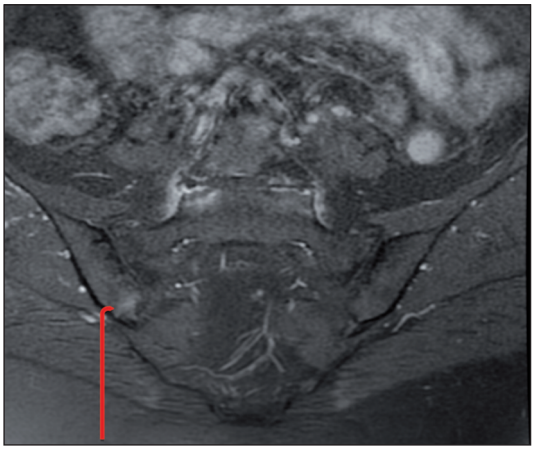

FIGURE 4: Short tau inversion recovery (STIR) sequence of MRI reveals bone marrow edema on the inferior aspect of the right sacroiliac joint (red oblique arrow).

in 5% of the patients with psoriasis. Patients with concomitant psoriasis tend to elicit more peripheral arthritis.[3] Conversely, the typical findings of psoriasis in our patient have not been detected until now.

The etiology of SpA has not been fully elucidated but it is thought that the complex interaction of genetic (for example, HLA-B27, other non-major histocompatibility complex genes), and environmental factors like abnormal intestinal microbiota, biomechanical stress induce the activation of autoimmunity as against keratosis follicularis.[4]

Apart from topical treatments and basic measures, oral retinoids (eg, acitretin, isotretinoin, alitretinoin, etretinate) have been the most effective treatment for keratosis follicularis via obtaining some decrease of symptoms in 90% of patients. These systemic medications reduce hyperkeratosis, smoothen papules, and reduce odor. Retinol (Vitamin A) is known to be major compound for normal epithelial growth and differentiation, although the mode of this effect is not openly elucidated. Both retinol and retinoic acid are capable of reversing hyperkeratotic and metaplastic dermal changes. However, this influence is just obtained at dosages associated with considerable local or systemic toxicity ordinarily, and prolonged utilisation of oral retinoids is restricted by their substantial adverse effects, including mucosal dryness, photosensitivity, hyperlipidemia, hepatotoxicity, and skeletal hyperostosis.

Acitretin which used in the treatment of our patient is a synthetic aromatic derivative of retinoic acid. This drug is particularly indicated for psoriasis. Moreover, it has been used as monotherapy or in multi-drug treatment regimens for a range of another robust-to-treat dermatoses, comprising hyperkeratotic and inflammatory clinical conditions such as keratosis follicularis, palmoplantar pustulosis, lichen planus, Sjogren-Larsson syndrome and non-melanoma skin cancers.[5] Nevertheless, arthralgia, myalgia, arthritis, skeletal hyperostosis and extraosseous calcification may emerge during maintenance treatment or over time.[6,7] Bone pain, arthralgia and myalgia are common but new hyperostotic lesions and extraskeletal calcification may occur very rare. As distinct from this, nr-axSpA occurred in this case without other significant rheumatological manifestations. Unlike acitretin, case series and observational studies have been reported that another oral retinoic acid derivative (isotretinoin) causes the findings of axSpA.[8] However, the patients included in these studies were diagnosed with acne vulgaris or fulminans not Darier's disease. Furthermore, the mechanisms entailing atypical musculoskeletal findings such as sacroiliitis that develop after the use of systemic retinoids are not clearly explained. On the other hand, their immunomodulatory effect that leads to abnormal modifications in cytokine balance may be a possible cause of side effects.[9] Additionally, systemic retinoids induce some alterations in the lysosomal membrane of the cells due to its detergent-like features which mediating a cytopathic obliteration of the synovial cells and making the bone structure vulnerable to mechanical irritation. Thus, these drugs may cause spondyloarthritic changes similar to the emergence of acute peripheral arthritis during systemic treatment for acne vulgaris.

When articles and case reports have published up to now are evaluated in the literature, AS and keratosis follicularis may coexist very rarely in the same patient.[10] In another case report, it was emphasized that a combination of two diseases could be a new subset of spondyloarthritis.[11] In recent years, only one case affected by keratosis follicularis with psoriatic-like lesions of the scalp has been reported.[12] Achilles tendinitis, unilateral sacroiliitis, synovitis in wrist and metacarpophalangeal joints of the right hand were also diagnosed in that patient, and HLA-B27 test was positive unlike our case.

As a result, we believe that the coexistence of keratosis follicularis and axSpA is not the clinical property of a subset of SpA as opposed to a previously published papers. Moreover, because of their different etiopathogenetic pathways, both diseases might be detected coincidentally. As previously emphasized, immune dysfunction occurs in patients using acitretin. So, this agent which is used effectively other than isotretinoin in keratosis follicularis may lead to sacroiliitis with a considerably

possibility. Further prospective observations can reveal the existence of this association more strongly. Lastly, based on our current knowledge, these two different clinical diseases have been highlighted for the first time.

Informed Consent

Informed consent was obtained from the patient.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Barış Gündoğdu;* ***Design:*** *Barış Gündoğdu;* ***Control/Supervision:*** *Ayşe Serap Karadağ;* ***Data Collection and/or Processing:*** *Barış Gündoğdu;* ***Analysis and/or Interpretation:*** *Barış Gündoğdu;* ***Literature Review:*** *Ayşe Serap Karadağ;* ***Writing the Article:*** *Barış Gündoğdu;* ***Critical Review:*** *Ayşe Serap Karadağ.*

REFERENCES

1. Takagi A, Kamijo M, Ikeda S. Darier disease. J Dermatol. 2016;43(3):275-9. [Crossref] [PubMed]
2. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009; 68(7):777-83. [Crossref] [PubMed]
3. Goupille P. Psoriatic arthritis. Joint Bone Spine. 2005;72(6):466-70. [Crossref] [PubMed]
4. Gaston JSH. Recent advances in understanding spondyloarthritis. F1000Res. 2017;6:304. [Crossref] [PubMed] [PMC]
5. Dunn LK, Gaar LR, Yentzer BA, O'Neill JL, Feldman SR. Acitretin in dermatology: a review. J Drugs Dermatol. 2011;10(7):772-82. [PubMed]
6. Mørk NJ, Austad J, Kolbenstvedt A. Bamboo spine mimicking Bekhterev's disease caused by long-term acitretin treatment. Acta Derm Venereol. 2006;86(5):452-3. [Crossref] [PubMed]
7. Vincent V, Zabraniecki L, Loustau O, Godfrin B, Latour FB, Railhac JJ, et al. Acitretin-induced enthesitis in a patient with psoriatic arthritis. Joint Bone Spine. 2005;72(4):326-9. [Crossref] [PubMed]
8. Baykal Selçuk L, Aksu Arıca D, Baykal Şahin H, Yaylı S, Bahadır S. The prevalence of sacroiliitis in patients with acne vulgaris using isotretinoin. Cutan Ocul Toxicol. 2017;36(2): 176-9. [Crossref] [PubMed]
9. Shapiro PE, Edelson RL. Effect of retinoids on immune system. In: Saurat JH, ed. Retinoids: New Trends in Resarch Therapy. Geneva: Retinoid Symposium; 1985. p.225-35.
10. Ben Taarit C, Turki S, Fazaa B, Kammoun M, Ben Maiz H. [Darier disease and ankylosing spondylitis: a new case]. Rev Med Interne. 1997;18(10):821-2. [Crossref]
11. Saraux A, Bourgeais F, Fauquert P, Le Goff P. [Ankylosing spondylitis and Darier's disease. A new spondyloarthropathy?]. Rev Rhum Mal Osteoartic. 1990;57(2):164-5. [PubMed]
12. Cosso C, Rongioletti F, Zampogna G, Camellino D, Cutolo M, Cimmino MA. Seronegative spondyloarthritis and Darier's disease: more than a casual association? Reumatismo. 2013;65(2):86-9. [Crossref] [PubMed]