Adalimumab as a successful treatment for acne fulminans and bilateral acute sacroiliitis with hip synovitis complicating isotretinoin therapy

Sir,

We report a case of an adolescent male patient who was treated by isotretinoin for moderate acne vulgaris with sudden development of acne fulminans and incapacitating acute sacroiliitis with bilateral hip arthritis presenting new challenges for therapy.

A 16-year-old male patient presented to the emergency unit of Al-Hada armed forces hospital, Taif, KSA complaining of severe progressive back pain of sudden onset with inability to ambulate. Over the last 6 months, he had received oral isotretinoin for the treatment of moderate acne vulgaris starting at 0.6 mg/kg (30 mg/d) with gradually increasing dosage till 1.5 mg/kg (80 mg/d) in the last month with no response and even worsening of lesions.

Examination revealed low-grade fever of 37.8°C and ulcerated crusted erythematous lesions with scattered pustules, nodules, and open comedones all over the face. Fistuolous tract was also detected [Figures 1a and 2a].

Rheumatologic consultation reported limitation of back movement in all planes and no joint arthritis or enthesopathy. The patient was admitted for 3 days; all routine investigations were normal, except for leucocytosis. HLA B27 antigen was negative.

Magnetic resonance imaging (MRI) showed evidence of bilateral sacroiliitis and hip synovitis with minimal effusion [Figure 3a and b]. Lumber and sacral spines were free from spondylodiscitis with no radiologic evidence of periostitis or hyperostosis.

Patient was diagnosed with acne fulminans and bilateral acute sacroiliitis along with hip synovitis complicating isotretinoin therapy. SAPHO syndrome was excluded because facial lesions were mainly ulcerated with few nodulocystic lesions, no radiologic evidence of hyperostosis or ostitis together with presence of systemic symptoms and inducing factor (isotretinoin). Oral isotretinoin was stopped. Prednisolone (0.6 mg/kg/d) and amoxicillin clavulanate 1 g/12 h with topical potassium permanganate 1/8000, fusidic acid cream, and benzoyl peroxide 2.5% gel were prescribed for 1 week, which resulted in mild improvement of facial lesions. Regarding
musculoskeletal symptoms, two alternative full therapeutic doses of non steroidal anti inflammatory drugs were prescribed for 4 weeks without improvement. The use of systemic steroids in the management of axial spondyloarthropathy is not supported by evidence and their efficacy is controversial.1

Based on previous reports of successful treatment of acne conglobata, sacroiliitis, seronegative spondyloarthropathy, and SAPHO syndrome by tumor necrosis factor-α (TNF-α) antagonists, we prescribed adalimumab (humira) 40 mg subcutaneously every other week with no loading dose on the basis of the dose used in spondyloarthropathy treatment2,3. Patient’s ability to move was restored after 1 week of the first injection and continued improving with subsequent injections. Acne lesions showed gradual improvement during the first month of therapy [Figures 1b and 2b], and interestingly comedones disappeared almost completely after 3 months of therapy [Figures 1c and 2c]. The patient was maintained on adalimumab (humira) for 12 months without any adverse effects, which was later stopped with follow-up period of 3 months, with no relapse and complete resolution of the lesion on MRI [Figures 3c and d].

In the present case, we considered therapy with isotretinoin to be the triggering factor of acne fulminans. This could be explained by the exaggerated hypersensitivity reactions of type III and IV after massive contact with Propionibacterium acnes antigens favored by the fragility of the pilosebaceous epithelium induced by the drug.4

Involvement of the sacroiliac joints occurs in 21% of acne fulminans cases. Prevalence of sacroiliitis is not accurately identified in patients using isotretinoin; however, a prospective study in 2015 reported 23.1% prevalence of spondyloarthropathy in patients using isotretinoin.5 In our case, acute sacroiliitis could be an adverse effect of isotretinoin which was prescribed in high dosage without concomitant systemic corticosteroid or as a sequelae of acne fulminans that developed as a complication to isotretinoin.

It was suggested that isotretinoin could induce solubilization of the liposomal membrane and consequently cytopathic destruction of the synovium, causing arthritis.6 Ekisioglu and others suggested that the positivity of antigen HLA-B27 renders the patient susceptible to sacroiliitis; however, other cases described in the literature and our reported case do not prove this statement.7,8

Upon failure of conventional therapies, we prescribed adalimumab. The off-label use of TNF-α antagonist was reported to successfully treat acne conglobata and sacroiliitis separately or as a component of SAPHO syndrome. Experiences with biological TNF-α blocking agents in SAPHO syndrome are few and follows the use of these

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**Figure 1c:** Forehead lesions at 3 months postadalimumab therapy

**Figure 2a-c:** (a) Left side of the face at the time of presentation (b) Left side of the face at 1 month postadalimumab therapy (c) Left side of the face at 3 months postadalimumab therapy
Infliximab and adalimumab each was reported to be successful in few cases.\textsuperscript{2,3} Thus, our case is the first case of isotretinoin-induced acne fulminans and acute seronegative sacroiliitis that was treated successfully with adalimumab.

An \textit{in-vivo} research observed a marked increase of TNF gene transcripts in acne lesions. TNF is one of the main pro-inflammatory cytokines.\textsuperscript{10} These cytokines are responsible for further follicular hyperkeratinization and inflammatory acne lesions.

Our case provides clinical evidence for the role of TNF-\(\alpha\) in acne vulgaris pathogenesis. The significant disappearance of comedones after 2 months of therapy underscores the effect of TNF-\(\alpha\) not only on inflammatory lesions but also on comedogenesis. This could be explained by the effect of TNF-\(\alpha\) on follicular hyperkeratinization and induction of lipogenesis.\textsuperscript{11}

However, in SAPHO syndrome, Massara \textit{et al.}, denoted that anti-TNF-\(\alpha\) therapy (infliximab) may induce persistent amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations.\textsuperscript{9} This observation may indicate different pathomechanisms of acne and pustulosis in SAPHO syndrome or different responses to the different types of anti TNF-\(\alpha\) therapy.

In conclusion, although acute sacroiliitis and large joint synovitis are rare complications of isotretinoin therapy, they may be so severe, incapacitating, and resistant to conventional therapy. Adalimumab could be used as a successful treatment for acute sacroiliitis and acne fulminans complicating isotretinoin therapy. Moreover, it could be a promising treatment for acne vulgaris resistant to isotretinoin therapy.

\textbf{Declaration of patient consent}

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for her images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his entity, but anonymity cannot be guaranteed.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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How to cite this article: Dawoud NM, Elnady BM, Elkhouly T, Yosef A. Adalimumab as a successful treatment for acne fulminans and bilateral acute sacroiliitis with hip synovitis complicating isotretinoin therapy. Indian J Dermatol Venereol Leprol 2018;84:104-7.

Received: September, 2016. Accepted: July, 2017.