

## 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. Fistulous tract was also detected [Figures 1a and 2a].



Figure 1a: Forehead lesions at the time of presentation

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 osteitis 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



Figure 1b: Forehead lesions at 1 month postadalimumab therapy

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 spondyloarthritis is not supported by evidence and their efficacy is controversial.<sup>1</sup>

Based on previous reports of successful treatment of acne conglobata, sacroiliitis, seronegative spondyloarthritis, and SAPHO syndrome by tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) antagonists, we prescribed adalimumab (humira) 40 mg subcutaneously every other week with no loading dose on the basis of the dose used in spondyloarthritis treatment<sup>2,3</sup>. 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 [Figure 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.<sup>4</sup>

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 spondyloarthritis in patients using isotretinoin.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7,8</sup>

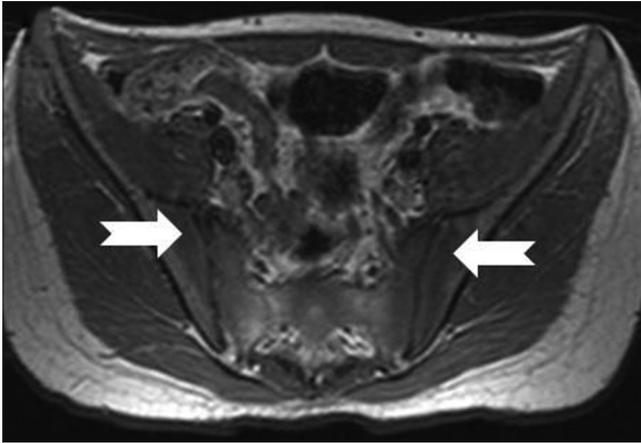
Upon failure of conventional therapies, we prescribed adalimumab. The off-label use of TNF- $\alpha$  antagonist was reported to successfully treat acne conglobata and sacroiliitis separately or as a component of SAPHO syndrome. Experiences with biological TNF- $\alpha$  blocking agents in SAPHO syndrome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



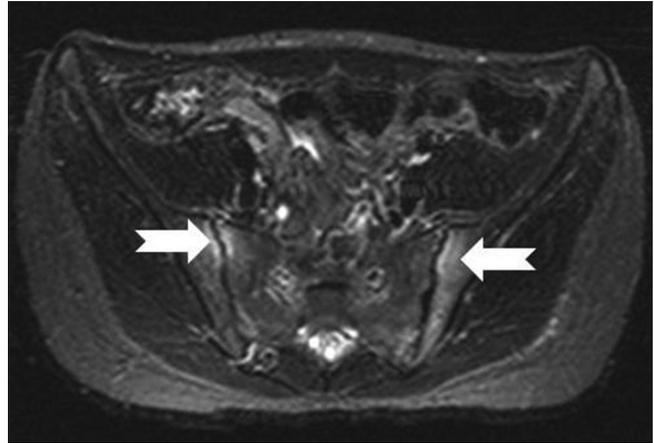
Figure 1c: Forehead lesions at 3 months postadalimumab therapy



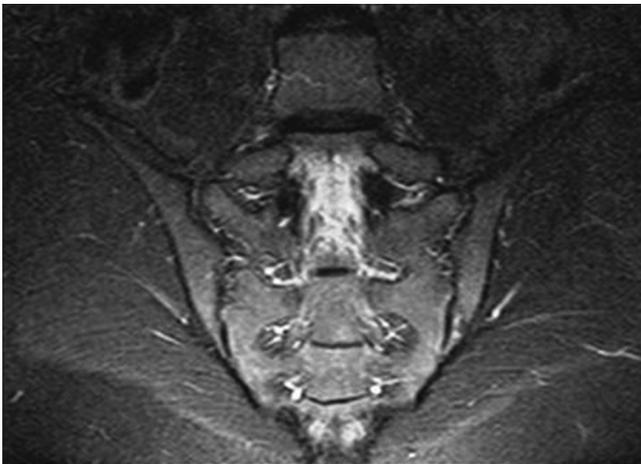
Figure 2a-c: (a) Left side of the face at the time of presentation (b) Left side of the face at 1 month postadalimumab therapy (c) Left side of the face at 3 months postadalimumab therapy



**Figure 3a:** Magnetic resonance imaging axial T1-weighted image showing early bilateral acute sacroiliitis (dark edema signal) of both sacral and iliac sides, No gross erosions or destructive changes



**Figure 3b:** Magnetic resonance imaging axial short T1 inversion recovery showing early bilateral acute sacroiliitis (bright edema signal) of both sacral and iliac sides



**Figure 3c:** Follow-up magnetic resonance imaging (coronal short T1 inversion recovery) after adalimumab revealing complete resolution of the previously reported bilateral sacroiliitis with no significant marrow signal alteration



**Figure 3d:** Follow-up magnetic resonance imaging (axial short T1 inversion recovery) after adalimumab revealing complete resolution of sacroiliitis with no significant marrow signal alteration.

drugs in spondyloarthropathy.<sup>9</sup> Infliximab and adalimumab each was reported to be successful in few cases.<sup>2,3</sup>

Thus, our case is the first case of isotretinoin-induced acne fulminans and acute seronegative sacroiliitis that was treated successfully with adalimumab.

An *in-vivo* research observed a marked increase of *TNF* gene transcripts in acne lesions. *TNF* is one of the main pro-inflammatory cytokines.<sup>10</sup> These cytokines are responsible for further follicular hyperkeratinization and inflammatory acne lesions.

Our case provides clinical evidence for the role of *TNF-α* in acne vulgaris pathogenesis. The significant disappearance of comedones after 2 months of therapy underscores the effect of *TNF-α* not only on inflammatory lesions but also on comedogenesis. This could be explained by the effect of *TNF-α* on follicular hyperkeratinization and induction of lipogenesis.<sup>11</sup>

However, in SAPHO syndrome, Massara *et al.*, denoted that anti-*TNF-α* therapy (infliximab) may induce persistent

amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations.<sup>9</sup> This observation may indicate different pathomechanisms of acne and pustulosis in SAPHO syndrome or different responses to the different types of anti *TNF-α* 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.

#### 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.

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**Conflicts of interest**

There are no conflicts of interest.

**Noha Mohammed Dawoud<sup>1,2</sup>,  
Basant Mohammed Elnady<sup>3,4</sup>,  
Tohamy Elkhoully<sup>5,6</sup>, Ayman Yosef<sup>7</sup>**

<sup>1</sup>Department of Dermatology, Andrology and STDs, Faculty of Medicine, Menoufia University, Shebin El Kom, Menoufia, Departments of <sup>3</sup>Physical Medicine and Rheumatology and

<sup>5</sup>Radiology, Benha University, Banha, <sup>7</sup>Department of Dermatology, Zagazig University, Zagazig, Egypt, Departments of <sup>2</sup>Dermatology, <sup>4</sup>Rheumatology and <sup>6</sup>Radiology, Alhada Armed Forces Hospital, Taif, Saudi Arabia

**Correspondence:** Dr. Noha Mohammed Dawoud,

Department of Dermatology, Andrology and S.T.Ds, Faculty of Medicine, Menoufia University, Shebin El kom 32817, Menoufia, Egypt.

E-mail: dr\_ndawoud@yahoo.com

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