Efficacy of Adalimumab on Severe Sapho Syndrome Likely Triggered by Isotretinoin

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Case Report

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Abstract

Background SAPHO (synovitis, acne, pustolosis, hyperostosis and osteitis) syndrome is a rare autoinflammatory chronic disorder, presenting with non-infectious inflammatory osteitis, sterile joint inflammation and skin manifestations including palmoplantar pustolosis and severe acne. It could be often misdiagnosed for its heterogeneous clinical presentation. Isotretinoin, which is commonly used for severe acne treatment, has been rarely described as possible trigger of osteo-articular manifestations, in particular sacroiliitis. Various biological treatment have been proposed in refractory patients.

Case presentation The case of an adolescent male, affected by acne fulminans and depression, who presented with sacroiliitis after a 10-week treatment with isotretinoin is presented and discussed. After SAPHO diagnosis, the boy started NSAIDs therapy but the onset of bilateral gluteal hidradenitis suppurativa required the switch to a tumour necrosis factor (TNF)-α antagonist (adalimumab). Despite specific therapy with sertraline, the patient continued to complain severe depression, this symptom has been widely reported in patient with SAPHO.

Conclusions Our case strengthens the hypothesis that isotretinoin could be a trigger of musculoskeletal involvement in SAPHO. The occurrence of hidradenitis suppurativa as additional clinical feature of SAPHO, already described in literature, supported the TNF-α blocker's commencement in our patient. Furthermore, the good outcome of our case confirms the efficacy of ADA treatment in obtaining persistent clinical remission of cutaneous and osteoarticular symptoms in SAPHO syndrome.

Background

Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) syndrome is an uncommon disease, characterized by chronic inflammatory osteoarticular and dermatological lesions. Its prevalence (< 1 in 10.000) is recognised as being underestimated [1]. The SAPHO syndrome is often misdiagnosed for its heterogeneous clinical presentation. Anterior chest wall and axial skeleton joints are the most commonly involved osteoarticular sites. Cutaneous manifestations include various acneiform and neutrophilic dermatoses: palmoplantar pustolosis is the most commonly reported lesion; moderate to severe acne, including acne conglobate, acne fulminans and hidradenitis suppurativa (HS) occurs approximately in 25% of patients[2]. Finally, patients may have the potential to develop depressive symptoms[3]

The pathogenesis of SAPHO syndrome is not completely defined, but likely includes a combination of genetic, infectious and immunological components leading to the activation of innate and cell-mediate immune system. Therefore, it is classified as an autoinflammatory disorder[4]. Isotretinoin, representing the first-choice treatment for severe acne in adolescents, has been reported as potential trigger of osteoarticular symptoms, although its pathogenesis remains unclear. Conversely, osteoarticular involvement triggered by isotretinoin has been very rarely described in SAPHO patients[5]. Since SAPHO syndrome is rare and no therapeutic trials are available, the therapy is aimed to modify the inflammatory process and control symptoms. Conventional first-line treatments include various drugs such as NSAIDs,

corticosteroids, DMARDs and bisphosphonates. Moreover, the use of anti-TNF agents has been proved to be a valid therapeutic regimen for unresponsive cases[6]. Recently, the use of adalimumab (ADA), a tumour necrosis factor (TNF)-α antagonist, has been proved to be a valid therapeutic regimen for SAPHO cases with HS and for the unresponsive ones[7]. We report a case of severe SAPHO syndrome, likely triggered by isotretinoin, successfully treated with ADA, with persisting depressive mood disorder.

Case Presentation

A Caucasian 15-year old male complained of severe acne and low back pain with inability to walk. His previous medical history was unremarkable except for the onset of acne vulgaris during his puberty. Three months before admission, he had showed a dramatic worsening of acne characterized by several cystic skin lesions with extensive ulcerating and inflammatory components, assuming a form of acne fulminans. Therefore, a course of systemic isotretinoin therapy was administered at the dose of 0.5 mg/kg/daily without any benefit. In addition, the boy developed depressive symptoms associated with insomnia and irritability. Thus, sertraline therapy was started.

Ten weeks after starting isotretinoin, the patient experienced increasing low-back pain with progressive inability to walk and restriction of daily activities. At admission to the emergency department he was afebrile, suffering and unable to walk. Physical examination revealed a decreased axial range of movement, sacroiliac pain and severe nodulocystic acne with abscesses on his face, neck and thorax. Laboratory investigations revealed systemic inflammation (CPR 7.15 mg/dl [normal range < 0.5 mg/dl], ESR 84 mm/h [normal range < 30 mm/h], WBC 14,950/mmc, 70% neutrophils). All rheumatologic parameters including complement and autoantibodies were within normal range. The patient tested negative for HLA-B27 typing. Culture of the pustular lesions was positive for *Staphylococcus aureus.* Antibiotic therapy with clindamycin was introduced and isotretinoin was interrupted. Pelvis and hip X-ray was unremarkable. Magnetic resonance imaging (MRI) showed moderate bone marrow edema and osteitis of transverse process of fifth lumbar vertebra (Figure 1a) and symmetrical sacroiliitis (Figure 1 b). The association of acne *fulminans* and osteitis suggested the diagnosis of SAPHO syndrome. Whole body MRI revealing anterior chest wall and axial involvement, including sacroiliac joint and spine, confirmed this hypothesis. Consequently, intravenous antibiotics were interrupted and, NSAIDS and oral rifampicin were started, in order to control the inflammatory status and the cutaneous lesions, respectively. The depressive disorder was persisting, despite the specific treatment, along with the other complaints. Nevertheless, during the following weeks osteoarticular involvement and cutaneous manifestations worsened and gluteal bilateral HS appeared. Therefore, ADA was subcutaneously administered at the dosage of 40 mg/dose every 2 weeks. After 3–4 weeks of treatment a progressive improvement both of cutaneous lesions and osteoarticular symptoms was reported and ADA administration interval (at the same dose of 40 mg) was extended at 4 weeks. After six months of favourable ADA treatment, the boy experimented a relapse of his osteoarticular symptoms. Therefore, ADA was administered again every two weeks obtaining a long-lasting remission. An MRI performed 12 months later, has shown no evidence of abnormal vertebral bone marrow signal (Figure 1A), sterno-

clavear effusions and sacroiliitis synovitis (Figure 1B). After 24-months treatment with ADA, the disease maintains complete remission of both cutaneous and osteoarticular symptoms. In the figure 2 are shown cutaneous lesions on the face, on the back and on the sternal region before ADA treatment (Figure 2 a-b-c) compared to the cutaneous findings of the same regions after such therapy (Figure 2 A-B-C). On the contrary, the depressive mood disorder persists and negatively affects the quality of patient life.

Discussion And Conclusions

SAPHO syndrome is an uncommon auto inflammatory disease characterized by osteoarticular and cutaneous manifestations. Although its pathogenesis remains unclear, SAPHO syndrome could be the consequence of the complex interactions between polygenic and exogenous factors triggering the disease burden[2].

In our case acne fulminans had preceded the onset of sacroiliitis. The patient experienced osteoarticular symptoms 10 weeks after being on isotretinoin. This drug has been already found to be associated with acute spondyloarthritis, in adults and in adolescents[8]. It has been shown that isotretinoin alters the formation of cytokines, such as tumour necrosis factor (TNF) and interleukin 1 (IL1). In addition, isotretinoin has detergent-like properties and could alter cell membrane structures, promoting the degenerative process of joints. Finally, retinol and acid retinoic has been shown to induce metalloproteinases activity, which increase degradation of membranes[5].

Isotretinoin was documented as a possible provoking factor for articular symptoms in SAPHO only in a few cases[6910] Likewise, we herein present a case where SAPHO was possibly precipitated with isotretinoin. Indeed, the temporal sequence between isotretinoin introduction and musculoskeletal disease suggests an inducing role of this drug in the pathogenesis of sacroiliitis.

Therefore, the previous use of isotretinoin should be investigated by paediatricians approaching adolescents affected by acne and osteoarticular symptoms, especially if the axial skeleton is involved. Further studies are needed to better clarify isotretinoin role in patients with SAPHO syndrome.

In our case the patient did not favourably respond to the NSAIDs therapy. Considering the severe osteoarticular involvement, acne fulminans and the occurrence of HS we decided to start biologic therapy as second line treatment. A rapid clinical improvement with ADA administration every 2 weeks was observed and confirmed by radiological 12-month follow-up. In addition, stable clinical remission of both cutaneous and osteoarticular symptoms was confirmed up to 24 months.

Available literature has reported that TNF-antagonists have been successfully used for the treatment of acne fulminans. Moreover, most cases of refractory SAPHO syndrome were treated with anti-TNF agents, such as infliximab and adalimumab. Furthermore, ADA is considered the first-choice biologic agent in moderate/severe HS after failure of conventional treatments with antibiotics[11]. In our patient, ADA

determined a rapid response of cutaneous and musculoskeletal involvement with maintenance of clinical disease remission during the treatment period.

Finally, our patient who had complained depression since the worsening of acne, still maintained his severe psychiatric disorder in the following years, despite the sertraline therapy and the dermatological and rheumatological stable remission. The association between many immuno-mediated inflammatory diseases and depressive mood disorders is already reported. However, there is no related literature concerning psychiatric symptoms in SAPHO patients, out of a recent study by Lu *et al,* revealing a high prevalence (46%) of depression in SAPHO patients.

The association between isotretinoin and sacroiliitis has been already described but its pathogenetic mechanism remains undefined; in contrast, the role of isotretinoin as trigger of musculoskeletal involvement in SAPHO has been rarely reported.

In severe cases of SAPHO syndrome, ADA therapy proved to be efficacious determining persistent clinical remission of cutaneous and osteoarticular symptoms.

SAPHO patients may have the potential to develop depressive symptoms, but this mood disorder seems to be independent from the course of the disease.

List Of Abbreviations

NSAIDs: nonsteroidal anti-inflammatory drugs

HS: hidradenitis suppurativa

ADA: adalimumab

DMARDs: disease modifying antirheumatic drugs

CRP: C-Reactive protein

ESR: erythrocyte sedimentation rate

WBC: white blood cells

MRI: magnetic resonance imaging

TNF: tumour necrosis factor

IL: interleukin

Declarations

Ethics approval and consent to participate: This study has been approved by the institutional reviewed board of the Meyer Children Hospital

Consent for publication: Written informed consent for publication of their clinical details and/or clinical images was obtained from the parent of the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and material: not applicable

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Authors contributions: All authors read and approved the final manuscript. ML collected all clinical data and reviewed the medical chart of the patient. CF and TG contributed to analyze the case. ST supervised the project and help in writing the manuscript.

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Figures

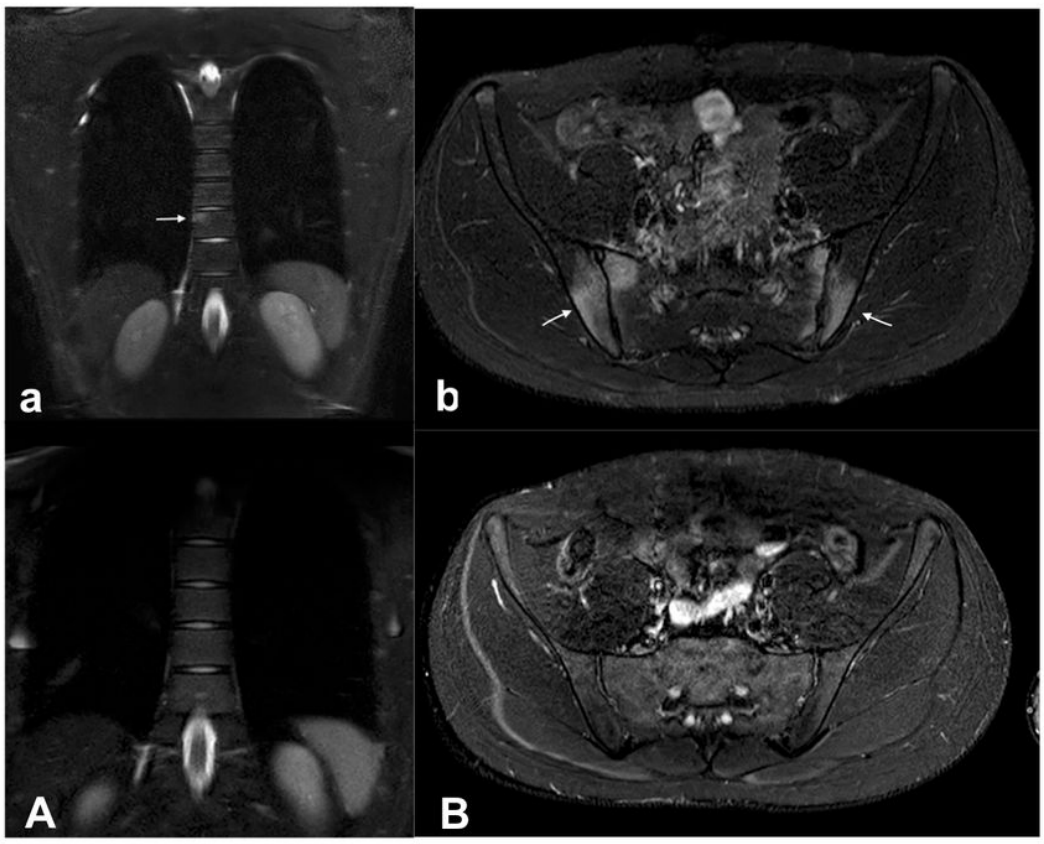

Figure 1

MRI STIR images of lumbar osteitis and sacroiliac involvement before (upside) and after ADA treatment (downside).

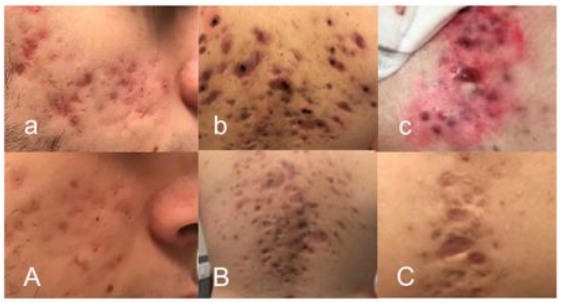

Figure 2

Cutaneous lesions on the face, back and sternal region before (upside) and after (downside) ADA treatment.