# SAPHO Syndrome Associated With Hidradenitis Suppurativa Successfully Treated with Infliximab and Methotrexate

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***Abstract***

*SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare chronic inflammatory musculoskeletal disorder of unknown etiology observed in children and young adults, which involves both osteo-articular inflammation and skin abnormalities. We review the case of a 22-year-old male, who presented with a 5-year history of hidradenitis suppurativa (HS), acne vulgaris, joint stiffness, and pain. Previous ineffective treatments included isotretinoin and oral antibiotics. Marked improvement of all cutaneous features was noticed after the first dose of infliximab and methotrexate; continued treatment resulted in the complete remission of the arthritis and enthesopathy. This case report demonstrates the efficacy and safety of infliximab and methotrexate in refractory SAPHO syndrome.*

A 22-year-old male presented with a 5-year history of hidradenitis suppurativa (HS) and acne vulgaris. The patient also complained of joint and ligament stiffness and pain of unknown duration. There was no family history of arthritis or cutaneous disorders. Previously ineffective treatments included isotretinoin and oral antibiotics.

Examination of the skin revealed erythematous papules, pustules and nodules, purulent fistulae and extensive hypertrophic scars, located on the lateral and posterior neck, face, ear lobes, axillae, chest, and inguinal areas, bilaterally. A musculoskeletal examination showed reduced extension and rotation of the neck, extremely limited external rotation of the shoulders, thickening of the flexor tendons of the right hand, tenderness in the left third metacarpophalangeal (MCP) joint, and decreased mobility of the lumbar spine on lateral bending and lordosis. There was no dactylitis, and there were no ocular signs.

Laboratory evaluations were normal and included a complete blood count, comprehensive metabolic profile, and hepatic function tests. Hepatitis A, B, and C serologies and HLA-B27 were negative. Radiographic evaluation demonstrated pronounced spotty bone demineralization involving the third left finger and small bones of the left hand, and diffuse periarticular osteoporosis.

Based on the clinical and radiographic presentation, the SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome associated with severe HS was diagnosed. Oral methotrexate, 7.5 mg taken weekly, and folic acid, 1 mg taken daily, were initiated for the arthritis and enthesopathy; 875 mg of amoxicillin combined with 125 mg clavulanic acid was prescribed for the acneiform papules and pustules. After 4 weeks of therapy, the patient demonstrated no improvement of either the rheumatologic or cutaneous diseases. Amoxicillin-clavulanic acid was discontinued, and infliximab, 5 mg per kg given intravenously, was initiated, with doses at 0, 2, and 6 weeks, and afterward, every 6 weeks regularly. Concomitantly, oral methotrexate was increased to 10 mg weekly. After four infusions of infliximab, the patient noted nearly complete resolution of all inflammatory skin lesions and dramatic improvement of the joint symptoms. After the fifth infliximab infusion, however, there was a recurrence of both isolated pustules and mildly purulent nodules, involving the posterior nuchal area. These lesions resolved following the addition of doxycycline, 100 mg taken orally twice daily, for 1 month. No side effects were reported

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during the infliximab infusions. One year after presentation, the arthritis, enthesopathy, and HS are well-controlled on infliximab 5 mg per kg per infusion every 6 weeks, methotrexate taken orally 10 mg weekly, and doxycycline taken orally 150 mg once daily. Surgical revision of the most prominent scars (two separate procedures performed without discontinuation of the patient's medical therapy) involving the face, neck, and chest resulted in noticeable cosmetic improvement.

## Discussion

The acronym SAPHO describes the association of synovitis, acne, pustulosis, hyperostosis, and osteitis.[1-11] SAPHO is a rare chronic inflammatory musculoskeletal disorder of unknown etiology observed in children and young adults. Presentation involves both osteo-articular inflammation and skin abnormalities.[1-5] The cutaneous manifestations are present in 20% to 60%[2] of cases and may occur at anytime during the course of the disease. The most frequent disorder included is palmoplantar pustulosis,[4] followed by acne conglobata or acne fulminans, acneiform folliculitis, HS, psoriasis, Sweet syndrome, and pyoderma gangrenosum.[1-4] HS is more commonly found in the African-American subgroup of SAPHO patients, and it tends to be associated with high morbidity, poor response to medical therapy, and often requires surgical intervention.[3,4] Frequently, severe cases of HS are associated with bone erosions in the hands and feet.[3] Steinhoff and colleagues[3] reported seven cases of SAPHO associated with HS, with skin lesions located in the groin, axillae, perirectum, neck, and breasts. All patients required surgery for the management of the HS symptoms. Cases of SAPHO with associated HS may demonstrate ocular involvement (acute anterior uveitis,[4] bilateral keratitis[3]), persistent proteinuria,[4] and the presence of malignant tumors (iliac osteoblastic osteosarcoma).[5]

Insidious onset of intermittent pain and swelling in the bone and joints (bilateral and symmetrical) are characteristic features of the SAPHO syndrome. The most commonly affected bone sites are the metaphysis of the tubular bones, the flat bones, and the axial skeleton (spine, ribs, pelvis, sternum, and clavicle).[1] On histopathological examination, neutrophils and pseudo-abscesses are found in early bone lesions, while chronic lesions demonstrate the presence of lymphocytes with occasional plasma cells, histiocytes, and occasional noncaseating granulomas. As lesions progress, an infiltrate of mononuclear cells is present, along with enlarged and sclerotic trabeculae. The latter stage is characterized by increased marrow fibrosis.[2]

Inflammatory arthritis may be part of the SAPHO syndrome.[12] Previous studies comparing patients with psoriatic arthritis and SAPHO describe clinical similarities; however, they fail to demonstrate a common immunogenetic background. SAPHO syndrome shows no clear association with either HLA-B27[13] or HLA-Cw6,[13] but does exhibit correlation with HLA-B39[12] and HLA-B61.[12] In addition, higher frequencies of MDM2 SNP309G and p53 SNP 72 C alleles are observed in SAPHO patients when compared with psoriasis and psoriatic arthritis patients.[14] Both of these alleles have been linked to an insufficient p53 response, due to an imbalance between MDM2 and p53 regulation, favoring less effective apoptosis involving the infiltrating inflammatory cells.[14]

The pathologic role of microorganisms is debatable in the SAPHO syndrome. Previous reports indicate the presence of *Propionibacterium acnes* and coagulase-negative staphylococci in the bone lesions and rarely coagulase-positive staphylococci.[1] The SAPHO syndrome could represent a form of "reactive osteitis" to these bacterial triggering agents.[1]

Familial cases of SAPHO syndrome have been described[15,16]; however, genetic analyses fail to demonstrate variations in the coding regions or splice sites of genes known to cause auto-inflammatory bone disorders (e.g., Majeed syndrome, murine CRMO and cherubism), other skin inflammatory disorders (e.g., PAPA syndrome: pyogenic arthritis, pyoderma gangrenosum, and acne), and mutations in NADPH oxidase (NCF4 gene).[15] Ferguson and coworkers[15] demonstrated reduced oxidative burst in the neutrophils from subjects of a family with SAPHO syndrome-like phenotype when compared to the normal population. The findings were suggestive of an intrinsic defect in neutrophilic function.

In a series of 29 patients, SAPHO syndrome demonstrated elevated IL-8 and IL-18 plasma levels. Also, IL-8 and TNF-α production by purified neutrophils was higher than in the healthy controls, with normal levels of oxidative burst and IL-18 production. But the induction of neutrophil IL-8 and TNF-α production by *P. acnes* was impaired in the SAPHO group. Interestingly, neutrophil IL-8 and TNF-α production decreased after 28 days of etanercept treatment. The study failed to detect autoantibodies in SAPHO patients. The conclusion was that the SAPHO syndrome might be the result of an abnormal immunological response due to the presence of *P. acnes*, increasing both the humoral and cellular inflammatory responses; these results were reinforced by the observation that etanercept was able to modulate PMN activation.[6]

Therapeutic options for SAPHO are currently limited and often based on anecdotal reports. The first-line therapeutic agents are nonsteroidal antiinflammatory drugs (NSAIDS) and analgesic medications, which often provide limited benefit. Second-line agents include methotrexate, sulfasalazine, cyclosporine, and leflunomide.[9] Calcitonin, bisphosphonates, and corticosteroids are effective in some cases. Calcitonin acts by decreasing bone turnover, while biphosphonates inhibit bone resorption and suppress IL-1β, IL-6, and TNF-α secretion. Antibiotics, more specifically macrolides, may be beneficial for SAPHO patients, not only due to the bactericidal properties but also due to the antiinflammatory and immunomodulatory effects.[9]

There is growing evidence that TNF-α inhibitors are effective for SAPHO patients. Intense expression and production of TNF-α have been observed in bone biopsy specimens of two patients by in situ hybridization and immunohistochemistry.[17] The patients were successfully treated with infliximab and etanercept therapy, and response was maintained over a period of 9 months.[17] Additional evidence of favorable clinical outcomes with anti-TNF-α therapy for SAPHO syndrome patients was described by Moll and associates.[7] Seventeen patients, all with osteoarticular features and 78% with skin involvement, were treated with infliximab therapy. Twelve patients (66%) responded immediately after the first infusion of infliximab and four (22%) responded after the second infusion. Skin features, especially acneiform lesions, demonstrated improvement (70%) during the first 3 months of therapy, with sustained response.[7] TNF-α inhibitors were also used by Abdelghani and colleagues[18] in six cases, and clinical response was observed in 66.6%.

## Conclusion

Case reports and series demonstrate the efficacy of TNF-α inhibitors for the treatment of the SAPHO syndrome.[7,17,18] Our patient presented features of the SAPHO syndrome with concomitant HS and had failed the traditional therapeutic options for acne vulgaris and HS. However, marked improvement of all cutaneous features was noticed after the first infliximab infusion, and continued treatment resulted in the complete remission of the both the arthritis and enthesopathy. The treatment was well tolerated, durable, and without adverse events. In conclusion, in this patient, infliximab markedly improved all cutaneous and rheumatologic manifestations of the SAPHO syndrome associated with HS and should be considered for refractory cases.

### *Disclosure Statement*

Aieska De Souza, M.D., has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony. Gary E. Solomon, M.D., has been a Consultant or Speaker Bureau participant with Abbott, Amgen, BMS, Centocor, Roche, UCB, and Wyeth-Pfizer. Bruce E. Strober, M.D., is an advisor, consultant, and/or investigator for and received honoraria from Amgen, Abbott, Centocor, Celgene, Pfizer, Leo Pharma, and Novartis.

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