A case of autoinflammatory skin and bone disease flared by a change in osteoporosis management

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Key words: autoinflammatory syndromes; bisphosphonates; deficiency of interleukin-1 receptor antagonist; interleukin 1; osteoporosis; pyoderma gangrenosum, acne, and suppurative hidradenitis; pyogenic sterile arthritis, pyoderma gangrenosum, and acne; synovitis, acne, pustulosis, hyperostosis, and osteitis; teriparatide.

INTRODUCTION

Autoinflammatory syndromes are an incompletely understood spectrum of diseases that involve spontaneous inflammation caused by genetic variants of the innate immune system. Unlike autoimmune diseases, no high-titer autoantibodies are associated with the disease process. We report a case of autoinflammatory skin and bone disease that flared within 1 month of replacing alendronate with teriparatide therapy. Teriparatide, a recombinant form of parathyroid hormone (PTH), is used for the treatment of osteoporosis and may be prescribed for dermatology patients requiring long-term prednisone therapy. Bisphosphonates such as alendronate are used to treat osteoporosis and autoinflammatory disease; they possess anti-inflammatory properties and the ability to remodel bone. We hypothesize that replacing alendronate with teriparatide triggered this disease flare through stimulatory effects on inflammatory cytokines, specifically interleukin (IL)-1 and recommend caution when choosing a drug to treat osteoporosis in patients with autoinflammatory skin and bone disorders.

Abbreviations used:

IL:	interleukin
NR:	normal range
PAPA:	pyogenic sterile arthritis, pyoderma gangrenosum, and acne
PTH:	parathyroid hormone
SAPHO:	synovitis, acne, pustulosis, hyperostosis, and osteitis
WBC:	white blood cell

CASE REPORT

A man in his 60s with a 10-year history of pustulosis, pyoderma gangrenosum, dissecting cellulitis, and erosive arthropathy initially presented to our clinic with widespread exudative ulcerations, pustules, vegetative crusted plaques, and keloidal scarring primarily on the back, upper chest, face, head, and neck.

Pertinent laboratory test results included a normal white blood cell (WBC) count, normal calcium level, and a negative rheumatoid factor. Erythrocyte sedimentation rate was elevated at 52 mm/h (normal range [NR], 0–19 mm/h), and alkaline phosphatase level was elevated at 197 U/L (NR, 45–129 U/L). Wound culture grew 1+ methicillin-susceptible *Staphylococcus aureus*, sensitive to trimethoprim-sulfamethoxazole, which offered little improvement. Adalimumab was initiated, and after mild improvement, dapsone and later cyclosporine were added. His condition continued to worsen; thus, high-dose prednisone along with alendronate therapy for osteoporosis was initiated. After marked improvement of skin and joints, adalimumab and trimethoprim-sulfamethoxazole were continued, prednisone was tapered to 5 mg daily, and cyclosporine and dapsone were gradually discontinued. The patient's condition remained well controlled for more than 1 year.

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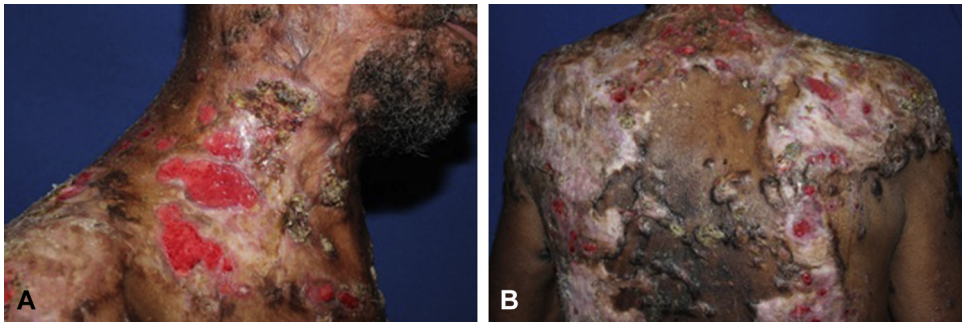

Fig 1. Flare of autoinflammatory syndrome. **A**, Thick adherent crusts and follicular destruction cover the scalp, sideburns, and beard area with numerous ulcerations on the upper chest. **B**, Extensive erythema and ulceration of the back improving with therapy. Keloidal scarring is noted.

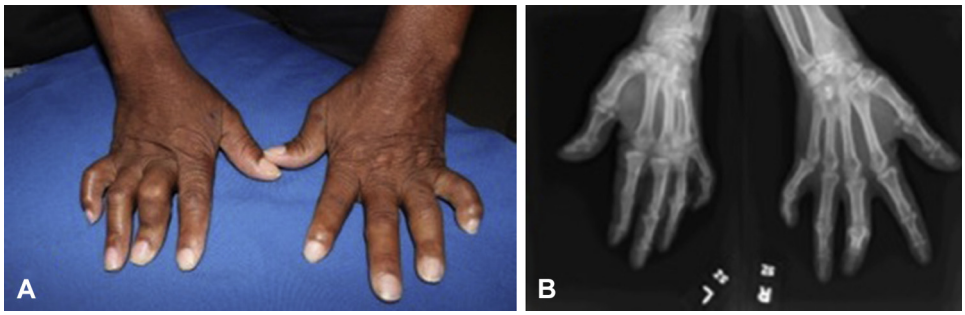

Fig 2. Erosive arthropathy. **A**, Bilateral finger swellings and deformities. **B**, Pencil-in-cup deformities noted on x-ray.

On follow-up bone densitometry, baseline osteopenia of the proximal femur and early osteoporosis of the lumbar spine and femoral neck remained unchanged. Based on these findings and endocrinology consultation, alendronate was replaced with teriparatide. Within 1 month of starting teriparatide, the patient's joint complaints abruptly flared, and widespread ulcerations and crusted plaques recurred on the scalp, neck, and trunk (Fig 1).

Complaints of eye, knee, and hand pain ensued. Conjunctival redness, knee swelling, and bilateral finger swelling (Fig 2) were noted on physical examination. Although the patient remained afebrile, his WBC count increased to 24,500 (NR, 4.5−11) with 87% neutrophils (NR, 40%−75%). Calcium level increased to 10.8 mg/dL (NR, 8.7−10.4 mg/dL), and alkaline phosphatase level remained elevated at 209 U/L. No previous WBCs, including those drawn during high-dose prednisone therapy, had been this elevated, and all previous calcium levels had been in the normal range. Wound cultures grew rare *Proteus*, rare β-hemolytic group G *Streptococcus*, and 1+ methicillin-susceptible *S aureus*, again sensitive to trimethoprim-sulfamethoxazole.

Teriparatide was promptly discontinued, alendronate restarted, and prednisone increased. Adalimumab and trimethoprim-sulfamethoxazole regimens were continued. After minimal improvement and based on its success in treating other autoinflammatory conditions, anakinra, 100 mg subcutaneous daily, was substituted for the adalimumab. After 30 days of anakinra therapy, the patient's skin lesions showed marked improvement with no new ulcerations or pustules. Despite insurance denial of further anakinra and adalimumab, the patient's condition steadily improved allowing for tapering of prednisone. At 9-month follow-up his disease was well controlled on prednisone, 5 mg daily.

DISCUSSION

Autoinflammatory disorders involving skin and joints are a spectrum of disease. They include the following syndromes: pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA); synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO); aseptic multifocal osteomyelitis, periostitis, and pustulosis, seen in deficiency of interleukin-1 receptor antagonist (DIRA); and pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH).[1-3] Our patient's widespread pustulosis, pyoderma gangrenosum, dissecting cellulitis, erosive arthropathy, and response to anti-inflammatory agents indicate his

condition exists on the spectrum of these related syndromes.

Overproduction of IL-1β was found to occur in PAPA syndrome and is a major therapeutic target of the disorder.[1] Anakinra, an IL-1 receptor antagonist, has proven successful in controlling flares of PAPA and deficiency of interleukin-1 receptor antagonist and improving symptoms in pyoderma gangrenosum, acne, and suppurative hidradenitis and SAPHO,[1-3] implying a major etiologic role of IL-1β in these disorders. Nitrogenous bisphosphonates have been effective in treating bone involvement in the autoinflammatory syndromes of SAPHO, chronic recurrent multifocal osteomyelitis, and diffuse sclerosing osteomyelitis of the mandible.[4-6] Patients treated with bisphosphonates for these diseases have shown improvements ranging from decreased pain levels to reduction of lesions on bone imaging.[4-6] The beneficial effects of bisphosphonates may be attributed to bone remodeling and anti-inflammatory properties, specifically lowering secretions of IL-1β, IL-6, and tumor necrosis factor-α.[4]

Teriparatide, an anabolic agent, is a recombinant form of PTH given intermittently to increase number and activity of osteoblasts, ultimately improving bone mass and skeletal architecture.[7] In contrast to bisphosphonates, which lower inflammatory cytokine production, studies have found that PTH increases IL-1 and IL-6 production and acts synergistically with IL-1 to promote bone resorption.[8,9] We postulate that the initiation of teriparatide concurrent with discontinuation of alendronate flared our patient's autoinflammatory disease possibly owing to net stimulatory effects on cytokine production, specifically IL-1. The patient's hypercalcemia concurrent with this flare provides evidence of a teriparatide effect, as transiently elevated calcium levels are commonly reported during treatment.[10] Anakinra, an IL-1 receptor antagonist, was successful in improving and inducing remission of our patient's disorder, supporting a key role of IL-1 in our patient's condition.

Although infection might precipitate flares of autoinflammatory syndromes, no new significant pathogens grew on skin culture during our patient's flare. He remained afebrile on chronic trimethoprim-sulfamethoxazole therapy.

Here we report a change in osteoporosis management contemporaneously linked to an acute flare of an autoinflammatory disorder. Teriparatide is known to promote and work synergistically with IL-1; thus, it is reasonable to believe its use combined with the removal of alendronate's anti-inflammatory properties may have led to an increased inflammatory state; we thus recommend caution when choosing a drug to treat osteoporosis in patients with autoinflammatory skin and bone disorders.

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