Case series of psoriasis associated with tumor necrosis factor-α inhibitors in children with chronic recurrent multifocal osteomyelitis

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INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory bone disease of unknown etiology. It most commonly affects children and can lead to persistent bone pain and bone destruction.[1] Tumor necrosis factor-α inhibitors (TNFi) have been used to treat children with CRMO.[2] However, TNFi may induce or worsen psoriasis in CRMO.[3] Similar phenomena have been seen in inflammatory bowel disease (IBD),[4] rheumatoid arthritis,[5] and ankylosing spondylitis.[6] Psoriasis induced by TNFi in children with CRMO has not been well documented beyond one case report.[3] This case series aims to present 5 cases of patients with CRMO who had psoriasis after the initiation of TNFi.

Abbreviations used:

BSA:	body surface area
CRMO:	chronic recurrent multifocal osteomyelitis
HLA:	human leukocyte antigen
IBD:	inflammatory bowel disease
MRI:	magnetic resonance imaging
TNFi:	tumor necrosis factor-α inhibitor

CASE SUMMARIES

Clinical characteristics of CRMO and treatments of 5 patients are summarized in Table I. The characteristics of psoriasis and subsequent changes are presented in Table II.

Case 1

An almost 5-year-old girl presented initially with 3 months of worsening neck pain. Curettage of bone lesion in C2-C3 was performed. Pathology findings were consistent with CRMO. She was started on infliximab, methotrexate, and pamidronate. and 5 months after starting these medications well-demarcated erythematous papules and annular plaques studded with pustules developed on her neck, back, and extremities with significant scalp involvement and alopecia, consistent with psoriasis (Fig 1, *A*). Infliximab was discontinued, and she was treated with topical therapies, which led to improvement of her psoriasis. Etanercept and canakinumab were given sequentially as her CRMO worsened. However, she had no response to either, and infliximab was restarted. Because her psoriasis persisted, ustekinumab was added. This change led to improvement of psoriasis for approximately 1 year until ustekinumab was discontinued because of myalgias. Adalimumab and tocilizumab were trialed sequentially to replace infliximab but resulted in worsening of psoriasis (adalimumab) and worsening of CRMO (tocilizumab). Golimumab at 2 mg/kg every 4 weeks was initiated that induced complete resolution of CRMO on magnetic resonance imaging (MRI) and she only had very mild alopecia at her last clinical visit.

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Table I. Patient characteristics and medication use before psoriasis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age of CNO onset (yr)	5	7	11	12	7
Gender	Female	Female	Female	Female	Female
Race	White	White	White	White	White
Coexisting & FH of associated conditions	FH of IBD	FH of psoriasis and spondyloarthropathy	None	Crohn's disease	None
Bone lesions found on bone scan and MRI	C2, C3, C4, T8, sacrum, ischia, femur, tibia, fibula, cuneiform, talus, metatarsals, cuboid	C7, sacrum, femur, tibia, fibula, calcaneus	Ischia, ilia, pubis, sacrum, femur	Ischia, ilia, sacrum, acetabulum, femur	T6, T7, ischia, ilia, pubis, femur, tibia
Bone biopsy ruled out infection and malignancy	Yes	Yes	Yes	Yes	Yes
HLA-B27	Negative	Positive	Negative	Negative	Negative
TNFi usage	Infliximab 10-20 mg/kg IV every 3-4 weeks	Infliximab 10 mg/kg IV every 4 weeks	Adalimumab 40 mg SQ every other week	Infliximab 5 mg/kg IV every 8 weeks; adalimumab 40 mg SQ every other week	Infliximab 10 mg/kg IV every 4 weeks
Concurrent Medications	NSAID, corticosteroid, methotrexate, pamidronate	NSAID, corticosteroid, methotrexate, leflunomide, pamidronate	NSAID, corticosteroid, methotrexate, leflunomide, pamidronate	NSAID, corticosteroid, methotrexate, sulfasalazine, pamidronate	NSAID, methotrexate, pamidronate

CNO, Chronic nonbacterial osteomyelitis; *C*, cervical spine; *FH*, family history; *IBD*, inflammatory bowel disease; *IV*, intravenously; *NSAID*, nonsteroidal anti-inflammatory drug; *SQ*, subcutaneously; *T*, thoracic spine.

Table II. Characterization of psoriasis and the outcome of intervention in 5 patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Onset of psoriasis	5 mo after infliximab	2 mo after infliximab	4 mo after adalimumab	4 mo after infliximab 4 mo after adalimumab	3 mo after infliximab
Psoriasis morphology					
Annular, hyperkeratotic papules	Yes	Yes	Yes	Yes	Yes
Pustules	Yes	No	No	No	Yes
Palmar and/or plantar	No	No	Yes	Yes	No
Alopecia	Yes	Yes	Yes	Yes	Yes
BSA affected (%)	75	2-3	10	10	10
Outcome	90% improvement in BSA 2 mo after discontinuation of Infliximab with addition of topical corticosteroids	Resolved 8 mo after infliximab discontinued and with topical corticosteroids	Alopecia resolved 5 mo after adalimumab discontinued. Persistent plantar psoriasis <1% of BSA controlled with topical corticosteroids	Psoriasis and alopecia improved significantly 3 mo after infliximab discontinued. Mild psoriasis on adalimumab controlled with topical corticosteroids	Resolved 2 mo after infliximab discontinued in addition to systemic corticosteroids

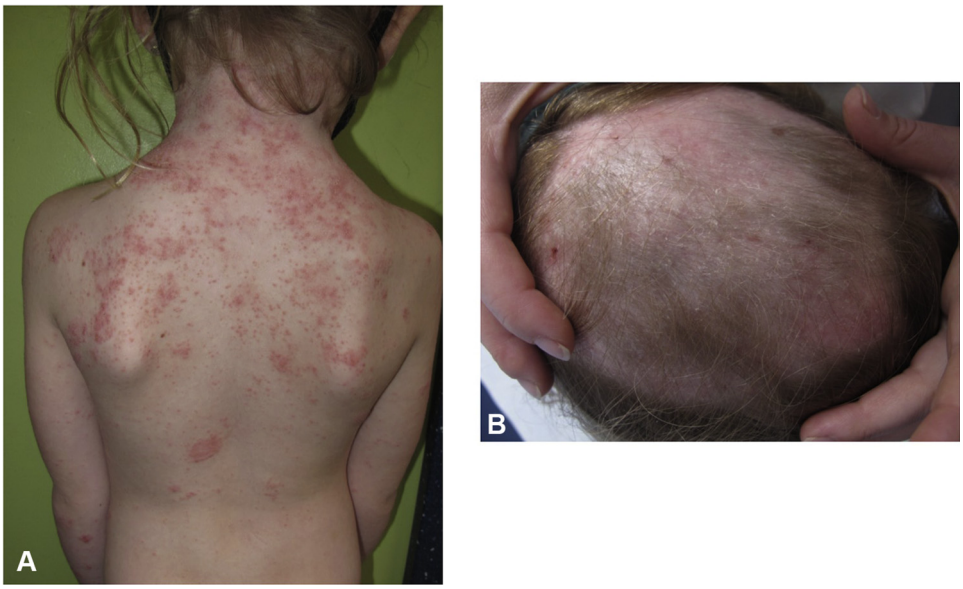

Fig 1. Psoriasis and alopecia after initiation of TNFi. **A**, Diffuse erythematous pustules on the upper back of patient 1. **B**, Severe alopecia with mild papules on scalp of patient 4.

Case 2

A 12-year-old girl had CRMO diagnosed after a 2-year workup for neck pain. Initial disease was limited to C7; it then progressed to the other areas (see Table I). She was initially treated with naproxen and leflunomide. Infliximab was added when her MRI showed disease progression. Her CRMO improved significantly. However, 2 months after starting infliximab, scattered erythematous papules and annular scaly plaques and scalp alopecia developed. Midpotency topical corticosteroids were started. Due to continued breakthrough CRMO pain, her dose of infliximab was increased, which led to worsening of her psoriasis. Consequently, her infliximab was discontinued. Pamidronate and methotrexate were initiated. Her psoriasis began to improve after infliximab was discontinued and was noted to be completely resolved 5 months after discontinuation of infliximab.

Case 3

An 11-year-old girl had CRMO diagnosed based on MRI and bone biopsy after a few months of right hip pain. She was treated with piroxicam. Repeat MRI showed numerous pelvic lesions that resulted in initiation of adalimumab. Her CRMO improved, but 4 months later, erythematous annular papules and plaques with hyperkeratotic scale developed on the upper and lower extremities, including the plantar surfaces of the feet (Fig 2, *A*). She was started on mid- and high-potency topical corticosteroid therapies with little response. Methotrexate was added to treat her psoriasis, but she continued to have worsening rash with progression of scalp involvement and alopecia. So adalimumab was discontinued and pamidronate infusions were initiated for her CRMO. Her psoriasis improved quickly after discontinuation of adalimumab, with almost complete resolution after 2 months and hair regrowth within 5 months.

Case 4

An 11-year-old girl had Crohn's disease diagnosed initially and was treated with infliximab and methotrexate. Approximately 4 months after initiation of infliximab, hyperkeratotic erythematous plaques developed in the scalp with significant alopecia (Fig 1, *B*) and well-demarcated erythematous plaques on the palms (Fig 2, *B*). Topical corticosteroids were initiated, but her psoriasis did not significantly improve until infliximab was discontinued. Two months later, she had worsening of CRMO and did not respond to meloxicam and sulfasalazine. She was transitioned to pamidronate infusions but continued to have persistent pelvic inflammation; therefore, adalimumab was added. Although her pain improved, she noticed a recurrence of a similar rash on her scalp and palms. She was restarted on mid- to high-potency topical corticosteroids and tar-based shampoos, and her adalimumab dose was spaced from every 2 weeks to every 3 weeks. Her psoriasis improved, with complete hair regrowth and resolution of scalp rash. She continued to have persistence of her palmar rash, but it was managed with topical corticosteroids.

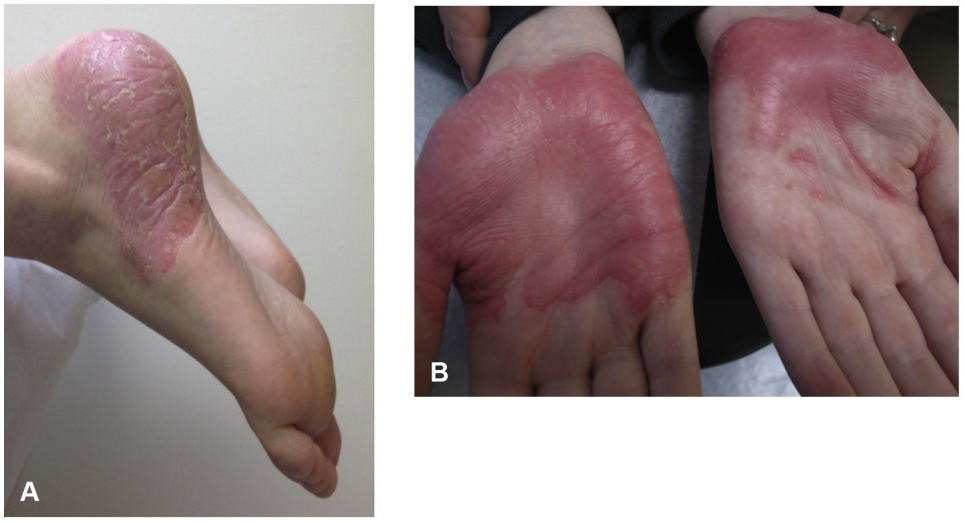

Fig 2. Palmoplantar psoriasis after initiation of TNFi. **A**, showed plantar psoriasis in patient 3. **B**, Diffuse erythema secondary to psoriasis in patient 4.

Case 5

An 8-year-old girl had CRMO diagnosed when she presented with bilateral leg pain that was associated with abnormal gait and ankle swelling. An MRI found lesions concerning for CRMO. She was started on pamidronate, methotrexate, and infliximab. Within 3 months of starting infliximab, well-demarcated erythematous papules, plaques, and few annular plaques developed, some that were studded with pustules, located on her legs, genitalia, face, and scalp with alopecia. Initially, her rash was diagnosed as bacterial folliculitis and treated with cephalexin with no improvement. She was evaluated by the dermatology department and diagnosed with psoriasis. Mid- to high-potency topical corticosteroids and tar-based shampoos were initiated, and her infliximab was stopped while continuing pamidronate for her CRMO. Her psoriasis improved over the course of the next month, with only a few plaques remaining on her scalp and extremities that were controlled with topical treatments.

DISCUSSION

We report 5 cases of CRMO that developed psoriasis after the initiation of monoclonal TNFi therapy with infliximab or adalimumab. The psoriasis resolved after discontinuing the offending agent in 3 cases, switching to a different TNF inhibitor in 1 case, and adding ustekinumab in 1 case in addition to use of topical corticosteroids. In 3 of the cases, continuing or adding methotrexate did not improve psoriasis.

Mocci et al[7] reported that psoriasis as a reaction has been described in almost every condition treated with TNFi therapy as well as the resolution of psoriasis after discontinuing TNFi therapy in many patients. This phenomenon is not specific for CRMO, but some children with CRMO may have a higher predisposition to TNFi-induced psoriasis. In our series, all children were girls, were white, and had multiple bone lesions including pelvis (5 cases), long bones (5 cases), and spine (3 cases). Only 1 case had positive human leukocyte antigen (HLA)-B27, which suggests low likelihood of a role of HLA-B27 in this phenomenon.

The characteristic and pattern of TNFi-induced psoriasis in these 5 cases was strikingly similar in that all 5 cases had significant scalp involvement with alopecia and presented with annular and plaque type psoriasis. Two cases also presented with additional pustular variant of psoriasis with sterile pustules studding the psoriasis plaques, and 2 cases had palmoplantar psoriasis. These findings were consistent with those of previous reports. Perman et al[8] reported 5 cases of pediatric patients with juvenile idiopathic arthritis or IBD who had scalp psoriasis after initiation of TNFi therapy.[8] Time between initiation of TNFi and psoriatic scalp involvement was 2 to 26 months. In our case series, psoriasis developed between 2 and 5 months after initiation of TNFi.

Treatment of TNFi-induced psoriasis varies depending on the extent and severity of psoriasis.[9] Collamer et al[9] proposed the following algorithm. In patients with psoriasis affecting less than 5% of body surface area (BSA), topical treatments such as corticosteroids, keratolytics, and vitamin D analogs are recommended while continuing TNFi. If greater than 5% BSA is affected or there is palmoplantar psoriasis, topical therapies with palm/sole occlusive, ultraviolet phototherapy,

methotrexate, cyclosporine, or acitretin are recommended. If the psoriasis is severe or patients prefer, TNFi should be discontinued and the patient may be treated with topical agents. In our patients, four of five patients in our series had greater than 5% BSA involvement, and 2 had palmoplantar psoriasis. Patients 1, 2, 3, and 5 all experienced significant improvement in their psoriasis after discontinuation of TNFi therapy, as did patient 4 when they were switched to another TNFi and infliximab was discontinued. All were treated with topical corticosteroids. Patient 4 switched to adalimumab at a lower-than-normal dose (every 3 weeks vs every 2 weeks) and had good response. Patient 1 had a very recalcitrant course of her CRMO that required continuation of infliximab; therefore, ustekinumab was added and successfully improved her psoriasis without causing serious infections. Subsequent switch from infliximab to golimumab resulted in resolution of psoriasis. A systemic review by Brown et al[10] found a significant difference in TNFi-induced psoriasis based on medication used with fewest cases reported with golimumab (0.5%) versus infliximab (63%) and adalimumab (22%), which were the most common offenders.

Further research is needed to elucidate the prevalence of new-onset psoriasis after TNFi therapy in pediatric CRMO patients. Additionally, physicians should be aware of this potential side effect and treat the psoriasis accordingly if induced.

TNFi may cause psoriasis in children with CRMO. Discontinuation of the TNFi and topical medications are very effective in treating the psoriasis. In patients who required continuation of the TNFi for their CRMO, switching to another TNFi, offering an alternative or lower dosing regimen, or adding another biologic agent such as ustekinumab may be considered.

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