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A Rare Case of Chronic Recurrent Multifocal Osteomyelitis with Undifferentiated Juvenile Idiopathic Arthritis, Uveitis, and Psoriasis

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Abstract

We report here a 17-year-old boy with a complicated presentation of undifferentiated juvenile idiopathic arthritis, vision-threatening uveitis and chronic recurrent multifocal osteomyelitis (CRMO) in the pelvis. His severe iritis needed subtenon injections and only responded to infliximab after failing multiple biologics. Unfortunately he later developed infliximab-associated psoriasis. A combination of infliximab and ustekinumab induced remission of his arthritis, osteomyelitis, uveitis and psoriasis without experiencing severe infections.

Keywords

Juvenile Idiopathic Arthritis, Uveitis, Psoriasis, Chronic Recurrent Multifocal Osteomyelitis, Infliximab, Ustekinumab

1. Introduction

Chronic recurrent multifocal osteomyelitis is a rare condition [1] that may coexist with ankylosing spondylitis [2] [3], psoriasis [4] [5], and inflammatory bowel disease (IBD) [4] [6]. Patients usually present with persistent bone pain. It is a diagnosis of exclusion and X ray is usually the first imaging modality. However, X rays lack sensitivity compared to bone scan and whole-body MRI [7] [8]. Whole-body MRI [9] is the most sensitive modality to identify involved areas because symmetrical lesions commonly occur near growth plates that bone scan fails

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to detect. Focal MRI is helpful to evaluate affected sites with more details when whole-body MRI is not available. When CRMO is suspected in appropriate clinical setting, it is important to obtain further imaging when affected sites are difficult to assess.

Acute anterior uveitis is most commonly seen in children with enthesitis-related arthritis [10]-[12] and presents with eye pain, redness and photophobia. Steroid eye drops are the first-line treatment. But often systemic medications such as methotrexate and/or monoclonal anti-TNF agents are necessary to induce inactive disease and preserve vision [13]-[16].

Despite their therapeutic effectiveness, anti-TNF agents may cause worsening or new onset of psoriasis in adults and children. The mechanism is not well defined, but this has been seen in patients taking anti-TNF agents for a variety of conditions including inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis [17]-[21]. The current recommendation when psoriasis develops is to discontinue or switch to another anti-TNF agent when the affected skin area is greater than 5% of total body or palmar plantar psoriasis has developed [21]. For patients with refractory uveitis, monoclonal anti-TNF agents are reported to have the best efficacy [13]-[16]. When patients have complications with anti-TNF associated psoriasis, it poses a practical challenge to their care.

2. Case Background

In 2009, at age 10 years 11 months, a Caucasian male presented with pain and swelling in his fingers, knees, ankles, toes, and pain in his hips, mid back and temporomandibular joints (TMJs) accompanied by greater than 2 hours of morning stiffness. He also had a thickened crusty rash on his scalp which was consistent with seborrheic dermatitis. He was treated with prednisone by his primary pediatrician; with taper to 5 mg daily, his symptoms recurred. He was seen by pediatric rheumatology in August 2009 and was taking prednisone 10 mg daily, iron 325 mg daily, ibuprofen 400 mg twice daily. At birth, he had apnea but went home on the same day as his mother. At age of 2, he had intoeing and was diagnosed with anterior tibial torsion. At age of 4, he had a mildly displaced distal tibial and fibular fracture due to injury, which healed after casting. His review of systems was positive for headaches, joint swelling, joint pain, poor sleep, weight loss, and the scalp rash. His family history was positive for asthma (his brother), rheumatoid arthritis (cousin) and polyarteritis nodosa and renal transplant (cousin). On his physical exam, his weight was 46.7 kg (90.7th percentile) and height was 1.40 m (32.3th percentile) with normal temperature, blood pressure and pulse. His exam was notable for swelling, tenderness and warmth in right 2nd to 4th metacarpophalangeal joints (MCPs), right 1st to 4th distal interphalangeal joints (DIPs), left 1st, 2nd, 3rd, and 5th DIPs and left 2nd, 3rd, 5th MCPs, knees, ankles, and subtalar joints and decreased mouth opening (2.5 cm) without deviation. He was unable to make a fist or do a squat. He had tenderness over the greater trochanter areas bilaterally. There was no leg length discrepancy. Modified Schober test was 21 cm. His skin was clear except a very thick crusting patch on his scalp. He did not have nail pitting or dactylitis. His initial laboratory testing revealed normal white blood cells (WBC), hemoglobin, hematocrit, platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, c reactive protein (CRP) 8.73 mg/dL (normal < 0.28), erythrocyte sedimentation rate (ESR) 45 mm/hr (normal < 10), negative urine analysis, positive p-ANCA, negative PR3 and MPO, rheumatoid factor, anti-cyclic citrullinated peptide antibody (anti-CCP), and positive HLA-B27 with antinuclear antibody (ANA) 1:320. Bilateral knee and ankle X rays showed mild osteopenia without signs of erosion or joint space narrowing. No MRI was obtained at diagnosis because there was no concern of chronic osteomyelitis at that time.

3. Clinical Course

Detailed course was illustrated in **Figure 1**. He was diagnosed with undifferentiated juvenile idiopathic arthritis based on duration of arthritis longer than 6 weeks, the age of onset of arthritis in a male > 6 years, positivity of HLA-B27, possible psoriasiform scalp rash and acute anterior uveitis based on International League of Associations for Rheumatology (ILAR) criteria [22]. He was treated with subcutaneous methotrexate at 25 mg per week and prednisone at his first visit. Fluocinonide was prescribed for his scalp rash. His scalp rash resolved at his return visit in November 2009. Multiple joint injections were performed due to persistent arthritis until etanercept was started at 50 mg weekly in September 2010. Heself discontinued methotrexate two months later.

In April 2011, he developed florid uveitis in his right eye that was treated with prednisolone eye drops. On his eye exam in June 2011, he still had 1 - 2+ injection, 3 - 4+ cells in anterior chamber, posterior synechiae, 1+ cell

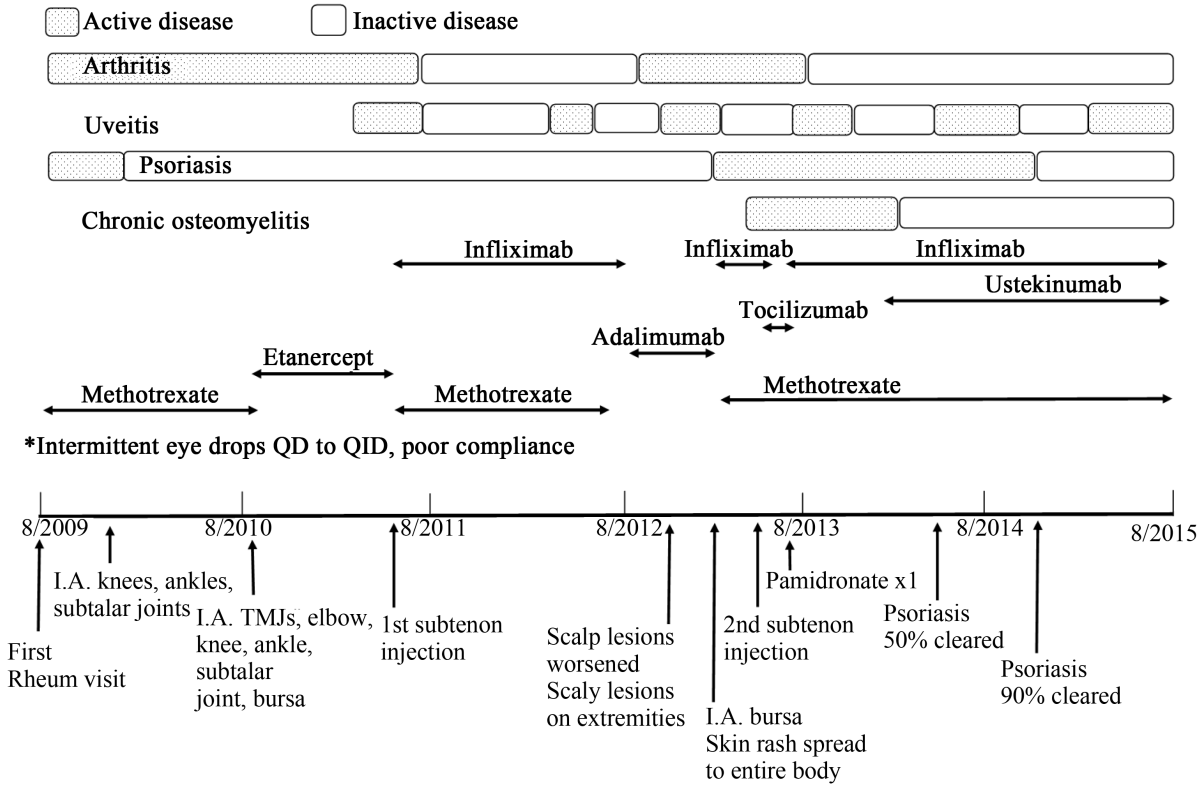

Figure 1. Clinical course including the onset and progress of arthritis, uveitis, psoriasis, and chronic osteomyelitis is shown. Major procedures including intraarticular corticosteroid injections and subtenon injection as well as systemic medications usage are listed.

in vitreous of his right eye. Because of persistent active uveitis, he received his first subtenon injection to the right eye at the end of June 2011. In addition, his left knee and TMJs were injected on the same day for active arthritis. Infliximab 5 mg/kg (300 mg) along with low dose methotrexate (7.5 mg po weekly) were initiated in July 2011 to better control his uveitis.

His uveitis responded to this treatment regimen within a month. Infliximab dose was increased from 5 mg/kg (300 mg) to 6 mg/kg (400 mg) after a uveitis flare. Due to poor intravenous access, infliximab was switched to adalimumab 40 mg every other week in September 2012. His uveitis became active in November 2012 and continued to worsen despite using difluprednate eye drops 2 - 6 times a day. Switching back to infliximab with a surgical port quickly resolved his uveitis.

In November 2012, he developed skin lesions diagnosed as psoriasis on his scalp, behind the right ear and on the left upper arm. In February 2013, his left greater trochanter bursa was injected with glucocorticoid. The psoriasis spread to his entire body with diffuse lesions on his trunk, arms and legs and hyperkeratotic fissured plaques on his palms and soles (**Figure 2**). Topical treatments including ketoconazole 2% shampoo, tar and salicylic acid shampoos, fluocinonide 0.05% scalp oil for the scalp and topical clobetasol 0.05% ointment, calcipotriene 0.005% cream or protopic 0.1% ointment for the body were not successfully though he was not compliant consistently. Oral cyclosporin at 4 mg/kg was started. His diffuse body rash cleared, but the scalp, palm and sole plaques persisted. Cyclosporine was eventually discontinued due to hypertension.

In March 2013, MRI of pelvis with and without contrast was performed due to persistent hip pain. This revealed edema in the right ilium at the posterosuperior aspect of the acetabulum. He was switched to tocilizumab infusion 8 mg/kg (600 mg) every 2 weeks due to persistent infliximab-associated psoriasis. However, his uveitis flared in June 2013 and required a second subtenon injection in his right eye. In July 2013, tocilizumab was switched back to infliximab at 6 mg/kg (500 mg) every 4 weeks due to inadequate control of uveitis and arthritis.

In July 2013, pelvis MRI was repeated and revealed increased bone edema in acetabulum and new edema in proximal femurs consistent with chronic recurrent multifocal osteomyelitis (CRMO) (**Figure 3**). Due to the

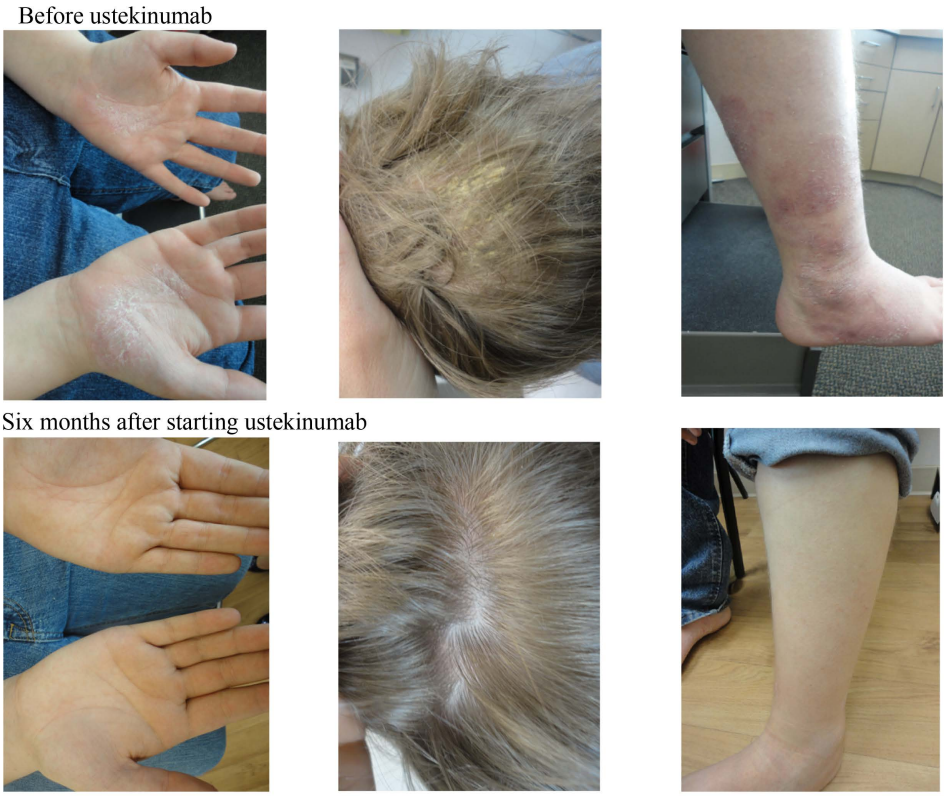

Figure 2. Psoriatic skin lesions in scalp, palms and lower extremities are shows on the top panel prior to starting ustekinumab. Near complete resolution of psoriatic lesions 6 months after starting ustekinumab are shown on the bottom panel.

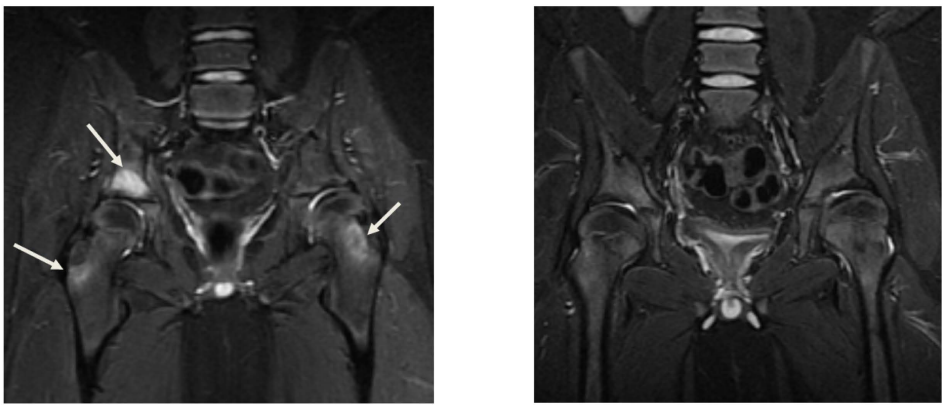

Figure 3. Coronal short tau inversion recovery (STIR) sequence of pelvic MRI in July 2013 (left panel) and December 2013 (right panel) are shown. Arrows indicate active bone inflammation with hyperintense signals.

classic chronic course, multifocal bone lesions, and associated psoriasis, it was felt that bone biopsy was not needed. In September 2013, his Infliximab dose was increased from 6 mg/kg to 10 mg/kg every 4 weeks. He received one dose of 70 mg (1 mg/kg) pamidronate for his CRMO and had severe reactions including dysuria and headache. He has been consistently given infliximab every 4 - 6 weeks at 10 mg/kg (800 mg) since October 2013. Whole-body MRI was not available so a repeat MRI of pelvis was obtained in December 2013 and showed resolution of previously seen bone edema (**Figure 3**).

An attempt to resolve the psoriasis was made by decreasing frequency and dosing of infliximab between March and September 2014 but did not help. Additionally, he had a mild flare of uveitis during this period which resolved quickly with short courses of difluprednate eye drops. His palmar, plantar psoriasis and scalp psoriasis persisted. In June 2014, ustekinumab 45 mg was initiated and has continued every 3 months. Four months later his skin had cleared by greater than 50%. Six months after starting ustekinumab, his skin lesions were 90% clear (**Figure 2**).

He had another uveitis flare in September 2014. His infliximab dose was increased to 12.5 mg/kg (1000 mg) for 2 doses and his difluprednate eye drop was restarted at 1 drop twice daily for 3 weeks, which quickly resolved his uveitis. His infliximab dose was decreased back to 10 mg/kg (800 mg) every 4 weeks since November 2014. Another follow-up MRI of pelvis was done in December 2014 and showed no recurrence of bone inflammation.

He did not follow up with an ophthalmologist until April 2015 when he was found to have 1+ cell in right eye. Difluprednate eye drop was restarted at 1 drop twice daily while keeping infliximab at 800 mg every 4 weeks. In September 2015, he had eye pain and photosensitivity in his right eye and self-initiated difluprednate1 drop twice daily until he saw ophthalmologist at the end of September 2015. At that exam, there were 1 - 2+ cells in his right anterior chamber. His posterior subcapsular cataract is mild and stable. Visual acuity corrects to 20/20.

In summary, his uveitis, arthritis and CRMO have been reasonably controlled by infliximab and his psoriasis almost resolved with the addition of ustekinumab.

4. Discussion

This case highlights the importance of imaging studies to detect CRMO. Our patient has features of Enthesitis-related arthritis (HLA-B27 positive, acute iritis, arthritis in a male older than 6) which has been reported to associate with CRMO [23]. In our patient, persistent pain raised concern of another associated condition, CRMO. MRI was useful to identify the active bone inflammation despite a normal joint exam. Comparing to other imaging modalities, such as bone scan and x ray, MRI is more sensitive in detecting bone lesions for CRMO [7] [9] and MRI remains an important disease-monitoring tool for CRMO [24] [25].

The treatment of CRMO comprises of a variety of medications including nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, sulfasalazine, anti-TNF agents and bisphosphonate [4] [24]-[27]. In a recent report, combination of methotrexate and infliximab with or without bisphosphonate has shown significantly decreased pain, inflammation marker and severity of bone edema in CRMO [25]. In our patient, a single dose of pamidronate and increasing dose of infliximab induced near resolution of bone inflammation 5 months later as confirmed by repeated MRI. His CRMO remained inactive with infliximab at 10 mg/kg every 4 - 6 weeks.

Psoriasis can be associated with CRMO as well as induced by TNF alpha inhibitors [17]-[21]. His psoriasis occurred after the initiation of monoclonal anti-TNF agents, infliximab and adalimumab. The timing of development of his psoriasis implied a role of anti-TNF agent to induce psoriasis. Anti-TNF agents have been associated with psoriasis in adults and children [17] [19] [28]. The mechanism is unclear but recent study in pediatric Crohn's disease population suggested a link of higher risk of anti-TNF associated psoriasis with homozygous polymorphism of IL23 receptor [28]. Unfortunately, infliximab was the most effective biologic for our patient's uveitis, which posed a practical challenge to the care of hispsoriasis. His psoriasis failed to respond to topical glucocorticoids (partly due to poor compliance). IL 23 is essential in the development of Th 17 lymphocytes [29] which is an important pathway driving the disease process in psoriasis. Ustekinumb, an IL12/23 blocker, has been shown effective in treating psoriasis for adults and approved by FDA [30]. It was reported as effective in children in a recent randomized clinical trial [31].

The combination of ustekinumab and anti-TNF agents has been used for refractory psoriasis in adult patients with psoriatic arthritis [32]. Based on 16.2 patient-years observation, psoriasis area severity index (PASI) decreased from between 11.2 and 30 to between 1.2 and 3 after adding ustekinumab to anti-TNF agent. Among 4 patients, one developed relapsing herpes zoster, one developed a skin infection both resolved after standard antibiotic treatments. Another patient developed a retrotonsillar abscess which resolved after incision and intravenous antibiotics.

Indeed, our patient responded to ustekinumab added to infliximab within 4 months with 50% clearance and further improvement of 90% clearance after 6 months of treatment. Combining two biologic treatments may potentially increase the risk of infection. Our patient has not had any infections for the 15 months of observation

while receiving a combination of anti-TNF alpha and anti-IL 12/23 agents. In an animal model for rheumatoid arthritis, bispecific antibody that blocks both TNF alpha and IL-17 improved joint inflammation more than any single blockade of these two cytokines [33] [34]. Thus, combining anti-TNF alpha and anti-IL 17 may provide a treatment option for complicated patient like ours with refractory uveitis, chronic arthritis, chronic osteomyelitis and severe psoriasis.

5. Conclusion

MRI should be considered to evaluate unexplained bone pain in children with JIA as chronic recurrent multifocal osteomyelitis can occur. When TNF alpha inhibitor-associated psoriasis fails to respond to topical therapy, combining ustekinumab with TNF alpha inhibitor may be considered when risks are assessed fully.

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Consent

This report was developed with approval by the institutional review board of Seattle Children's Hospital, Seattle and written informed consent was obtained from the patient's parents. Assent was obtained from the patient.

Competing Interests

The authors declare that they have no competing interest.

Authors' Contributions

YZ, SF, TM, MS, CAW collected and interpreted clinical findings. YZ, SF and CAW wrote the manuscript. All authors read and approved the final manuscript.

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Abbreviations

JIA, IBD, anti-TNF, CRMO, MRI.