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Multifocal Bone Pain, Recurrent Fevers and Anemia in a 15-Year-Old

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CASE REPORT

Multifocal Bone Pain, Recurrent Fevers, and Anemia Lead to Diagnosis of Chronic Recurrent Multifocal Osteomyelitis

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Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder that primarily affects children with recurrent episodes of sterile osteomyelitis. Patients usually present with recurrent bone pain, although CRMO is often a diagnosis of exclusion after patients undergo extensive workup.

Clinical Findings: A 15-year-old female presented with months of progressive multifocal bone pain, 22-pound weight loss, and recurrent fevers. Work-up as an outpatient included a positive screening assay and IgM Western blot Panel positive for Lyme disease, treated with a 28-day course doxycycline without symptom resolution. Her test results also revealed elevated inflammatory markers and normocytic anemia. She was admitted when her pain progressed and she had difficulty with ambulation.

Diagnosis, interventions, and outcomes: The patient was treated with ketorolac, which improved her pain. Her lab results were negative for underlying infection, autoimmune disease, or hematologic etiology. Spinal MRI (magnetic resonance imaging) revealed a compression deformity of her fourth cervical vertebra and multifocal signal abnormalities in her bone marrow. A percutaneous CT-guided core needle biopsy of the manubrium was consistent with CRMO. A bacterial culture from the biopsy grew *Cutibacterium (*formerly *Propionibacterium) acnes*, for which she was treated with antibiotics. She was prescribed naproxen and discharged with some improvement in her pain.

Conclusions: This case illustrates an unusual presentation of CRMO and emphasizes that the condition should be on the differential diagnosis for patients with ongoing bone pain, weight loss, and anemia. A multi-disciplinary approach is needed and early suspicion is important for determining appropriate diagnostic evaluation and targeted treatment.

Keywords: CRMO, multifocal bone pain, weight loss, recurrent fevers, anemia

CASE PRESENTATION

An otherwise healthy 15-year-old female presented to the hospital with progressive multifocal bone pain, 22-pound weight loss, and intermittent fevers. The pain began in her neck 3.5 months earlier, after she played pickleball. Later, her pain became multifocal, affecting her sternoclavicular area, right periscapular area, and left hip radiating down into her left leg. She was initially given a diagnosis of Lyme disease based on a positive ELISA (enzyme-linked immunosorbent assay) screen and immunoglobulin M (IgM) Western blot with 2 bands. She was treated with doxycycline for 28 days, without resolution of her symptoms. She was admitted for further workup when her pain progressed in her lower extremities and she had difficulty with ambulation.

When examined, the patient appeared thin and uncomfortable. She had 4/5 muscle strength in her left upper extremity and bilateral lower extremities. Her patella reflexes were brisk with 1-2 beats of bilateral clonus, though her toes were downgoing. Her cervical spine was tender, with limited range of motion due to pain. The broad musculature in her periscapular region was also tender. Pain was elicited at the left sternoclavicular joint with palpation and abduction. She had tenderness with left hip external rotation in the gluteal region, diffuse tenderness around the left knee, and tenderness

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down the anterior tibial bone shaft without bony irregularity or palpable warmth. She ambulated using crutches and, in general, moved slowly.

Her lab results revealed progressive normocytic anemia over the last 2 months (13.4 to 10.8 g/dl) and elevated inflammatory markers [erythrocyte sedimentation rate (ESR) 54 mm/hr, C-reactive protein (CRP) 15 mg/L]. Her low prealbumin, increased haptoglobin, and polyclonal gammopathy were thought to be due to an acute-phase reaction, supporting underlying inflammation. Otherwise, her lab tests did not reveal underlying infection [normal white blood count and negative blood cultures, syphilis immunoglobulin G (IgG), HIV, and stool cultures], autoimmune disorder [normal antinuclear antibodies (ANA), extractable nuclear antigen panel, anti-double-stranded DNA, and urinalysis with spot urine protein to creatinine ratio], or hematologic etiology [normal lactate dehydrogenase (LDH), uric acid, and platelets; and no blasts on peripheral smear).

Ultrasound and X-rays of her sternoclavicular joints and left hip revealed no focal abnormalities or effusions. X-rays of her left tibia and knee were normal. An X-ray of her cervical spine and an MRI (magnetic resonance imaging) of her cervical and thoracic spine showed a compression deformity of her fourth cervical vertebra and multifocal signal abnormalities in her bone marrow, including C4, T1, T4-T10, L5, L2, and L3, without spinal cord impingement. To better determine the extent of her disease, a bone scan was obtained and showed increased uptake at the C4 vertebral body and manubrium. To prepare for a biopsy, an MRI of her chest was obtained to better see manubrium abnormalities (Figure 1). A percutaneous CT-guided core needle biopsy of the manubrium was performed, and the pathology was consistent with chronic recurrent multifocal osteomyelitis (CRMO) (Figure 2). Bacterial culture from the bone biopsy grew *Cutibacterium (*formerly *Propionibacterium) acnes* after 6 days.

The patient's differential diagnosis included CRMO with *C. acnes* contaminant vs *C. acnes* osteomyelitis. She was prescribed naproxen (500 mg, twice per day) and discharged. She was then given ceftriaxone for 2 weeks, followed by oral clindamycin due to growth of *C. acnes*. After starting nonsteroidal anti-inflammatory drugs (NSAIDS), her pain and mobility initially improved, though it was still significant and limited her functioning. Approximately 2 months after her initial hospital admission, she received oral methylprednisolone and started oral methotrexate. Due to continued pain, she was transitioned to adalimumab. During this time, her anemia resolved, her ESR/CRP normalized, and she gained weight. Her mobility also improved, though she has not returned to her baseline due to neck and back pain. She visited the emergency room 1 time for exacerbation of chest pain before starting adalimumab.

DISCUSSION

CRMO is an autoinflammatory disorder of bone that primarily affects children with recurring episodes of sterile osteomyelitis. Its peak onset is at 10-years-old, and it affects females 2 to 4 times more often than males.[1,2] Patients with CRMO generally present with insidious onset of recurring bone pain, most often involving the metaphases of long bones, clavicle, vertebral bodies, and pelvis.[1,2] Early in the disease, plain radiographs may appear normal and positive findings are similar to osteomyelitis.[1,2] Fever may also be associated with symptoms of CRMO.[2] Laboratory results may be normal or indicate non-specific markers of inflammation, such an elevated ESR, CRP, and leukocytosis.[1,2]

Most patients who are ultimately given a diagnosis of CRMO undergo extensive laboratory, radiologic, and invasive procedures to rule out bacterial osteomyelitis. They are often exposed to antibiotics during this time.[3] Cultures are ultimately sterile and CRMO is believed to be a non-infectious autoinflammatory disorder.[1,2] CRMO is often described as the pediatric presentation of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis).[2,4] The first line of treatment for CRMO is NSAIDs.[2]

This patient's clinical and radiologic presentation fit most consistently with CRMO, though her anemia and weight loss were not typical for the disease. While she did meet the Jansson criteria and Bristol criteria for CRMO, she did not meet the minor Jansson criteria, including normal blood counts and general good health. Also, all patients used to define the Bristol criteria for CRMO had normal complete blood counts.[3,5] Progressive anemia could be explained by a systemic autoimmune process due to the suppressive effects of the bone marrow from non-malignant inflammation. However, there was initial concern that the anemia could indicate

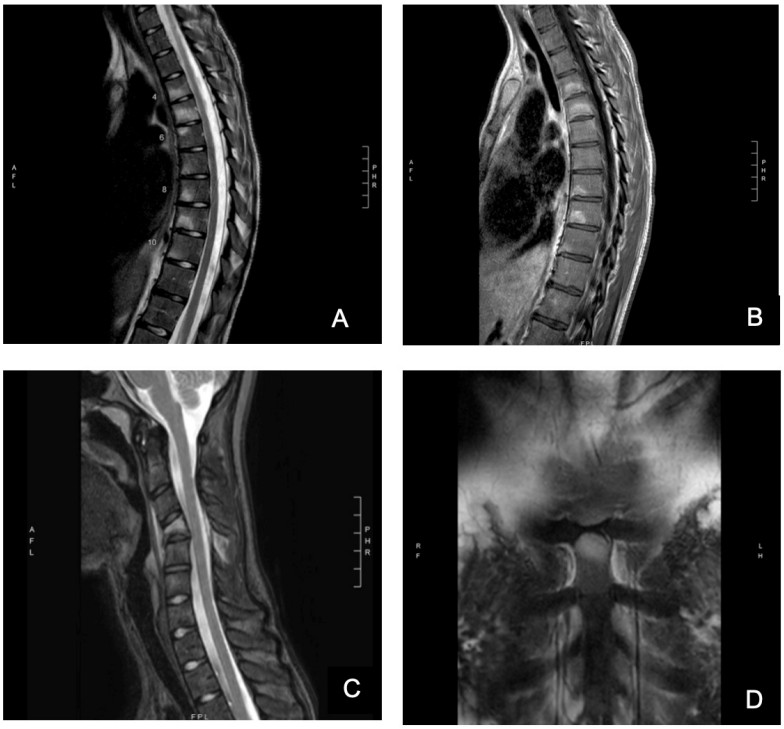

Figure 1. MRI of cervical and thoracic spine. A) Axial T2–weighted sequencing demonstrating multifocal signal abnormalities of the bone marrow in the thoracic spine. B) Post-contrast enhanced imaging demonstrates associated abnormal enhancement of affected areas. C) Gross signal abnormality involving the C4 vertebral segment, demonstrating moderate compressive deformity. D) MRI of the chest demonstrating multifocal abnormalities within the manubrium and sternum. The largest lesion occupied the superior two-thirds of the manubrium, measuring 4.4 cm x 2.6 cm x 1.4 cm in size. MRI, magnetic resonance imaging.

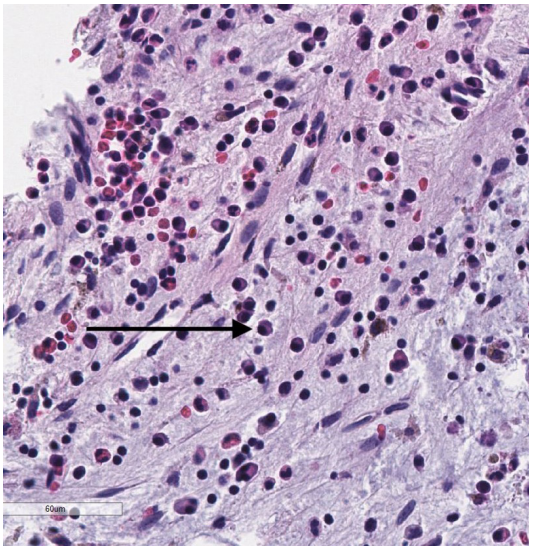

Figure 2. Pathology of bone biopsy. Results predominantly show plasma cells without morphologic features of Langerhans cells, consistent with CRMO. Plasma cells are identified by the basophilic cytoplasm and eccentric nuclei with perinuclear clearing (arrow). CRMO, chronic recurrent multifocal osteomyelitis.

an underlying malignancy. Ultimately, infiltrative process of the marrow was considered less likely given her other lab and bone biopsy results, resolution of anemia, and weight gain.

Another factor in this case was the biopsy culture positive for *C. acnes*, as CRMO biopsies are by definition sterile. In this case, *C. acnes* may simply be a contaminant, as other reports have shown it is a common contaminant, especially with percutaneous surgical biopsies due to bacterial colonization of the sebaceous glands.[6] However, several reports of CRMO and SAPHO describe bone cultures, some obtained by open biopsy, that are positive for various organisms, including *C. acnes*. In the CRMO literature, these organisms are often discounted as contaminants, while in the SAPHO literature there is increasingly more data that the bacteria may be an infectious immunologic trigger.[7] A literature review conducted by Assmann and Simon found that 42% of 90 SAPHO bone cultures were positive for *C. acnes*, suggesting that *C. acnes* should be considered an immunologic trigger in SAPHO.[4,8] In another literature review, Zimmermann and Curtis found that 48% of 98 cases of autoinflammatory bone disorders had bone biopsies positive for *C. acnes.* They concluded that *C. acnes* might be a pathogen rather than a contaminant in CRMO/SAPHO, and that patients with simultaneous skin manifestations might have a genetic predisposition to impaired clearance of *C. acnes*.[9]

Our patient developed acne 6 months before hospital admission, around which time she also felt left jaw pain. While this pain resolved before her admission, she had some mild facial asymmetry with left mandibular hypertrophy when examined. Treatment of patients with CRMO and bone cultures positive for *C. acnes* with antibiotics, such as doxycycline, has appeared to improve symptoms in some patients. However, it is not clear if this improvement is due to the antibacterial or anti-inflammatory properties of these antibiotics.[7] Based on her history of developing acne before her pain, and the potential benefit of antibiotics, she was treated with antibiotics.

This case illustrates an unusual presentation of CRMO and emphasizes that CRMO should be on the differential diagnosis for patients with ongoing bone pain, weight loss, recurrent fevers, and anemia without an infectious source. A multi-disciplinary approach and close collaboration among subspecialties is needed, and early suspicion is important for determining the appropriate diagnostic evaluation and targeted treatment.

REFERENCES

1. Ferguson PJ, Laxer RM. Autoinflammatory Bone Disorders. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, eds. *Textbook of Pediatric Rheumatology (Seventh Edition)*. Philadelphia: Saunders; 2016:627-641. doi:10.1016/B978-0-323-24145-8.00048-X.
2. Sarwark J, Labella C. Chronic Recurrent Multifocal Osteomyelitis. In: *Pediatric Orthopedic and Sport Injuries*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014. https://www-r2library-com.mainehealth.idm.oclc.org/Resource/detail/1581108478/ch0007s0111. Accessed October 16, 2019.
3. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO) – advancing the diagnosis. *Pediatr Rheumatol Online J*. 2016;14(1):47. doi:10.1186/s12969-016-0109-1.
4. Rukavina I. SAPHO syndrome: a review. *J Child Orthop*. 2015;9(1):19-27. doi:10.1007/s11832-014-0627-7.
5. Jansson A, Renner ED, Ramser J. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology (Oxford). 2007;46(1):154-160. doi: 10.1093/rheumatology/kel190.
6. Heckmann N, Sivasundaram L, Heidari KS, et al. Propionibacterium acnes persists despite various skin preparation techniques. *Arthroscopy*. 2018;34(6):1786-1789. doi:10.1016/j.arthro.2018.01.019.
7. Sharma M, Ferguson PJ. Autoinflammatory bone disorders: update on immunologic abnormalities and clues about possible triggers. *Curr Opin Rheumatol*. 2013;25(5):658-664. doi:10.1097/BOR.0b013e328363eb08.
8. Assmann G, Simon P. The SAPHO syndrome – are microbes involved? *Best Pract Res Clin Rheumatol*. 2011;25(3):423-434. doi:10.1016/j.berh.2011.01.017.
9. Zimmermann P, Curtis N. The role of Cutibacterium acnes in auto-inflammatory bone disorders. *Eur J Pediatr*. 2019;178(1):89-95. doi:10.1007/s00431-018-3263-2.