

CASE REPORT

Nagoya J. Med. Sci. 77. 493 ~ 500, 2015

Skull involvement in a pediatric case of chronic recurrent multifocal osteomyelitis

Toru Watanabe¹, Hiroyuki Ono¹, Yoshitaka Morimoto², Yoshiro Otsuki³, Masami Shirai¹, Akira Endoh¹, Masaaki Naito⁴, Yoshiya Inoue⁵ and Teruaki Hongo¹

¹Department of Pediatrics, Iwata City Hospital, Iwata, Japan

²Department of Orthopedics, Iwata City Hospital, Iwata, Japan

³Department of Diagnostic Pathology, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

⁴Department of Diagnostic Radiology, Iwata City Hospital, Iwata, Japan

⁵Department of Surgery of Bone and Soft tissue tumor, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

ABSTRACT

An 11-year-old boy was diagnosed with chronic recurrent multifocal osteomyelitis (CRMO) and presented with right sacro-femoral and occipital lesions. Initially, a tumor was suspected. However, the bone biopsy showed osteomyelitis with a negative bacterial culture. Bone scintigraphy revealed inflammatory changes on multiple bone lesions. The slight elevation in inflammatory markers such as C-reactive protein was of little clinical value. He was diagnosed with CRMO by sacral biopsy, and the clinical course progressed, with the presence of a new occipital lesion observed after the 1-year follow-up. The administration of non-steroidal anti-inflammatory drugs successfully improved his clinical symptoms. The presence of a skull lesion in the occipital bone of a pediatric patient with CRMO has not been previously reported.

Key Words: auto inflammatory diseases, bone pain, chronic nonbacterial osteomyelitis, non-steroidal anti-inflammatory drugs, skull

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO), a disorder that primarily affects children and adolescents, is characterized by episodic osseous pain over several years.¹⁾ CRMO is an idiopathic, aseptic, auto-inflammatory disease with no uniformly effective treatment.²⁾ The long bones of the lower extremities are frequently affected, and skull involvement is rare. Although in the majority of patients with CRMO, symptoms resolve post-puberty, the bone pain that accompanies the active disease is severe. CRMO can be difficult to diagnose as it often presents nonspecific imaging findings. The critical factors leading to its diagnosis are patient demographics, clinical course, and lesion localization. We report a very rare case of CRMO with skull involvement.

CASE PRESENTATION

At the time of symptom onset, an 11-year-old boy initially reported right coxalgia at rest,

Received: October 8, 2014; accepted: February 17, 2015

Corresponding author: Toru Watanabe

Department of Pediatrics, Iwata City Hospital, 512-3, Iwata City, Shizuoka, 438-8550 Japan

Telephone: +81-538-38-5000, FAX: +81-538-38-5052, Email address: brightsirius@msn.com

point, the radiologist suggested the possibility of CRMO. The differential diagnoses were chronic osteomyelitis and bone malignancy with metastasis.

A course of antibiotics was administered for 14 days but did not alter the disease course. The non-steroidal anti-inflammatory drug (NSAID) ibuprofen was started at 200 mg/day and the symptoms improved, but complete relief was not attained. Three months later, a bone biopsy was performed to rule out the possibility of malignant bone tumors, such as an osteosarcoma. Upon pathologic examination, mild, mainly lymphocytic, inflammatory cell infiltration indicated chronic osteomyelitis, without suppurative infection (Fig. 2). There was no yield from the bone tissue culture. One year later, the patient developed occipital headaches, accompanied by a decrease in

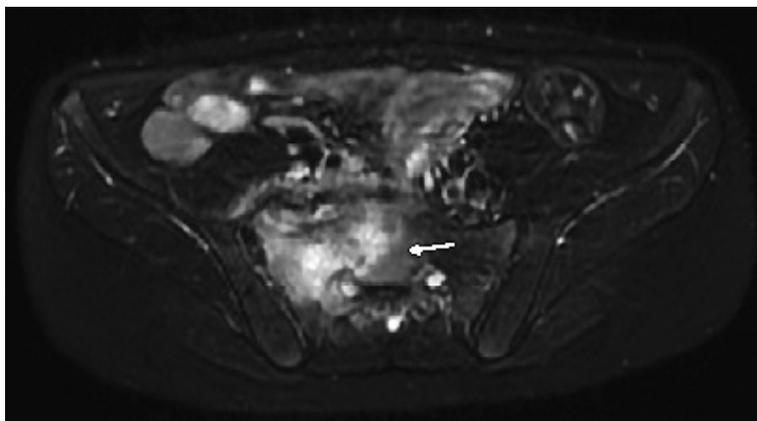


Fig. 1 Fat suppressed T2-weighted magnetic resonance images show a heterogeneous high intensity area on the right side of the sacrum (white arrow). There is no abscess formation.

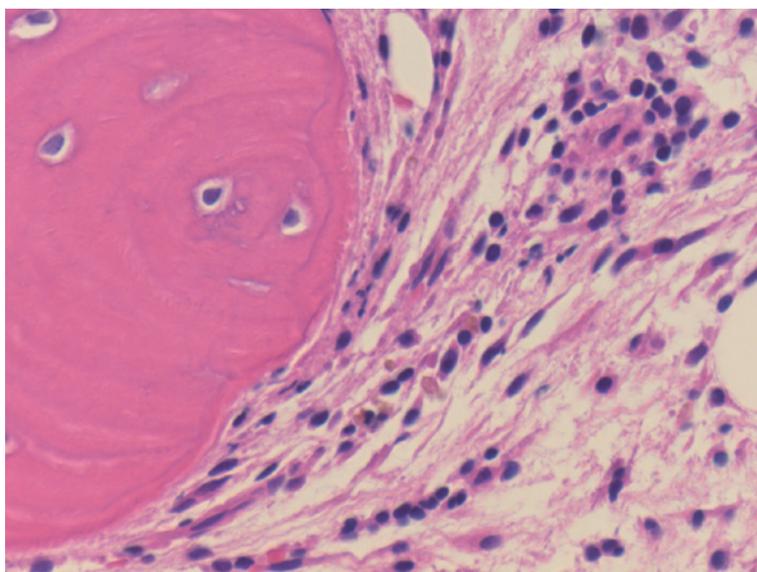


Fig. 2 Photomicrograph of the sacral bone biopsy, demonstrating connective tissue with mild infiltration by mononuclear inflammatory cells.

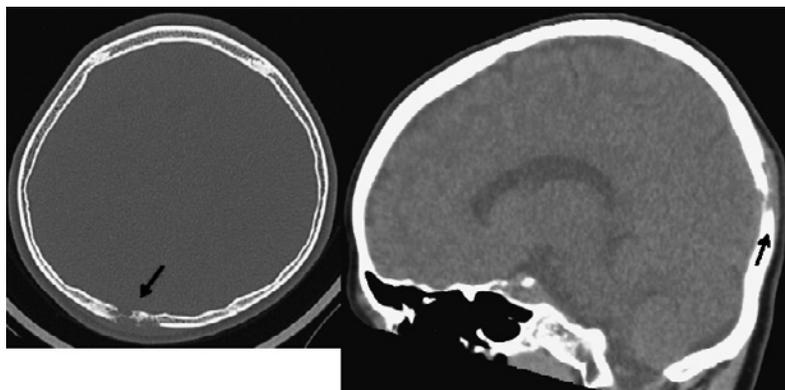


Fig. 3A Head computed tomography showing osteolytic lesions in the occipital bone (arrow). Axial view (left). Sagittal view (right).

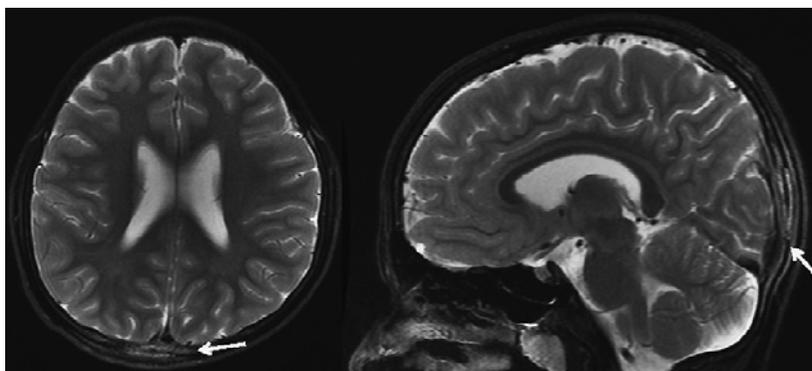


Fig. 3B Fat-suppressed T2-weighted images. Axial (left) and sagittal (right) fat-suppressed T2-weighted images demonstrate a focus of increased signal intensity on the occipital bone. The area of increased intensity extends into the epidural space and scalp.

pelvic pain. The headaches were intermittent and sometimes woke him during the night. There was palpable edema in the occipital lesion, and the size of the swelling was 3 cm. Head CT showed osteolytic lesions in the occipital bone (Fig. 3A). Axial and sagittal fat-suppressed T2WI demonstrated a focus of increased signal intensity in the occipital bone, with the area of increased intensity extending into the epidural space and scalp (Fig. 3B). The previous osteolytic lesion improved, but another lesion appeared as an osteolytic change in the occipital bone (Fig. 4). Technetium-99m-hydroxymethylene diphosphonate (^{99m}Tc -HMDP) scintigraphy showed increased uptake in the occipital bone and the right side of the sacrum, leading to a diagnosis of CRMO, which was controlled using ibuprofen (200 mg/day). We ruled out Langerhans cell histiocytosis (LCH) after considering the sacral biopsy and radiological findings, and because the head lesion appeared recently. The bone pain and swelling of the occipital lesion gradually improved with NSAID treatment over one year. One year and 4 months later, diffusion-weighted MRI imaging showed a new, asymptomatic region on the left (opposite) side of the sacrum. The serum cytokine profiles at this time were almost normal; the values are as follows (normal values in parentheses): IL-6 was <3 pg/mL, neopterin was 3.9 nmol/L (<5), soluble tumor necrosis factor

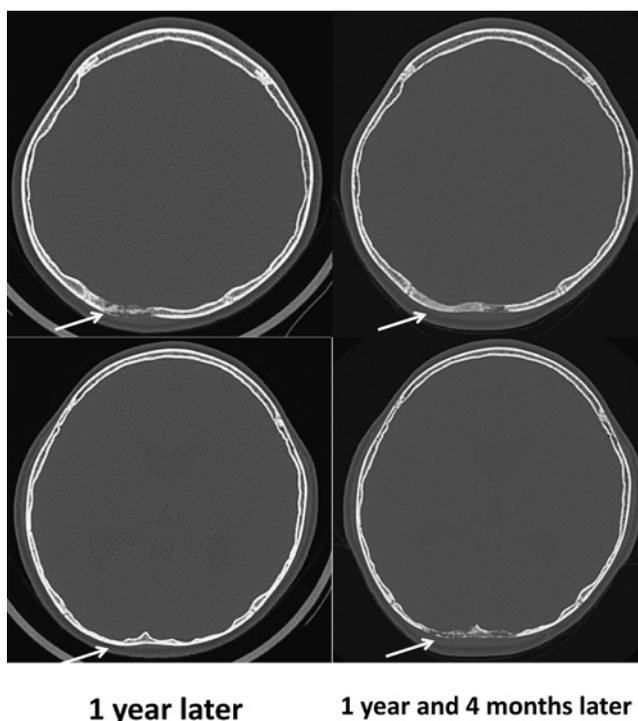


Fig. 4 Head CT shows that the previous osteolytic lesion improved (upper), but a new lesion appeared as an osteolytic change (lower).

receptor (sTNF-R)1 was 940 pg/mL (484–1,407), sTNF-R2 was 2,630 pg/mL (829–2,262), and IL-18 was 300 pg/mL (<500). Over the following two years, there were no cutaneous findings. An LPIN2 mutation seen in Majeed syndrome was not detected in our patient.

DISCUSSION

CRMO is a skeletal auto-inflammatory disorder of unknown cause that primarily affects children and adolescents.¹⁾ The disease is a rare, nonpyogenic bone inflammation that was first described by Giedion *et al.*³⁾ in 1972 as “an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis.” The prevalence of CRMO is estimated to be less than 1/1,000,000.⁴⁾ A 5-year follow-up study revealed the mean age of onset to be 10 years (range 4–14 years).⁵⁾ Symptoms include pain, local swelling, and warmth in the absence or presence of fever. CRMO mainly affects the metaphyses of the long bones, the pelvis, shoulder girdle, and, less commonly, the spine and skull. Skull involvement, as described in this report, is very rare. Therefore, it is important to explore the etiology of CRMO and the reason for its primary localization to the metaphyses and epiphyses of the long bones, which are areas involved in bone growth in children and adolescents. It is likely that osteoclast cells or cytokines at the lesion sites in CRMO are associated with the etiology.⁶⁾ For this patient, we could not evaluate the state of disease using the serum inflammation data, including the cytokine profiles. We speculated about the reason for the onset of this rare skull involvement in this patient. He may

have had some triggering factors, such as prior infection or vaccination.⁷⁾ Our patient's father had idiopathic bilateral femur head necrosis, suggesting that an examination of the genetic mutations common to them may be worthwhile, although there are no data to support the concept that CRMO is a monogenic disease. Our patient demonstrated bone pain and swelling on the back of the head in the absence of fever. Reports of CRMO involving skull lesions are scarce, and the well-documented cases involve flat bones such as the ilium and mandible.⁸⁾

Bone lesions can occur at any skeletal site except the neurocranium.⁹⁾ We believe that the skull lesions were caused by CRMO, although we could not examine the histopathological findings via skull biopsy because the patient experienced remission and exacerbation of his skull lesions. As one of the differential diagnoses, we had to consider LCH because our case had skull lesions, although we excluded malignancy and infectious osteomyelitis. We discovered a report of a child with a frontal and sphenoid bone lesion, which was the first case report of CRMO involving the skull.¹⁰⁾ To the best of our knowledge, this report provides the second description of skull involvement in a pediatric CRMO patient. The aim of publishing this case report is to indicate that CRMO should be considered when the skull is affected in pediatric osteomyelitis patients. CRMO is a self-limited disease, but sequelae of the disease occasionally occur. The clinical course is unpredictable, with considerable variation in the severity and time course. Exacerbations and spontaneous remissions, as well as inflammatory conditions of the skin and gastrointestinal tract, have been reported. Malignancy, pyogenic infections, and atypical presentation of juvenile arthritis need to be ruled out by correlating the history, clinical findings, and biopsy results. Pathogens are generally not cultured from the blood, bone, or joints of CRMO patients, but patients may report symptoms of psoriatic skin involvement, including palmoplantar pustulosis. Such patients are categorized as having synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome, which represents an inflammatory spectrum. This syndrome may or may not be associated with dermatological manifestations.¹¹⁾ To date, our patient has not presented skin lesions, but he will be followed to determine whether skin lesions appear in the future. Treatment typically involves NSAIDs, corticosteroids, tumor necrosis factor (TNF) inhibitors, and bisphosphonates.

Several observations suggest that genetic factors contribute to the etiology of CRMO. Mutations in *LPIN2* cause a syndromic form of CRMO known as Majeed syndrome, while mutations in *pstpip2* cause a murine form of the disorder.¹²⁾ Recent studies in murine chronic multifocal osteomyelitis, Majeed syndrome, deficiency of the interleukin-1 receptor antagonist (DIRA) syndrome, and SAPHO syndrome reveal abnormalities in innate immune system function.¹³⁾ IL-1 pathway dysregulation is present in several of these disorders, and blocking IL-1 therapeutically controlled the disease in DIRA, Majeed syndrome, and some cases of SAPHO and CRMO. IL-1 may be a key cytokine in disease pathogenesis. Laboratory findings are of little diagnostic value because they typically reveal nonspecific evidence of inflammation, such as altered ESR and CRP levels. Novel insights into the pathogenesis of CRMO suggest a link to the failure to produce IL-10 and the resulting imbalance of pro-inflammatory IL-6 and TNF-alpha levels, in conjunction with disease expression.¹⁴⁾ A diagnosis is supported by the presence of osteolytic lesions, with surrounding sclerosis apparent on radiographs; asymptomatic lesions frequently appear in nuclear scans. In our patient, MRI and CT revealed the involvement of the surrounding soft tissue, specifically the anterior soft tissue of the sacrum, the overlying scalp, and the underlying epidural space and dura mater of the head. At the time of our initial observation, the patient's bone alterations were limited to the occipital bone, but follow-up head CT scans revealed a new lesion in a different area of the occipital bone. In our patient, the bone scan readily detected lesions throughout the body. The demonstration of lesions at various typical sites is crucial for a correct diagnosis.

In a report involving 14 pediatric CRMO cases,¹⁵⁾ the mean age of symptomatic onset was 9.6 years and the mean disease duration was 5.3 years. NSAIDs were used in all 14 patients and glucocorticoid therapy was used in four. The long-term prognosis for CRMO patients is uncertain, but generally good.⁵⁾ However, in a study of 22 CRMO children, seven patients developed noticeable deformities and five had leg-length discrepancies lasting 2.5–20 years. The conclusion of the second study was that CRMO is not a benign condition, and if it is not followed to maturity, it can have disabling sequelae¹⁶⁾ that include physical and psychological complications. Therefore, periodic examination with CT or MRI is essential to monitor disease progression.

CONCLUSIONS

This report describes the second case of skull involvement in pediatric CRMO, which occurred in an 11-year-old boy. Further research on this disease is needed, especially for children in Japan.

ACKNOWLEDGMENTS

We thank Akihiro Yachie, MD, Department of Pediatrics, Kanazawa University and Shunji Hasegawa, MD, Department of Pediatrics, Yamaguchi University, for measuring the serum cytokine levels.

Informed consent was obtained from the patient and his parents.

The authors declare that there are no conflicts of interest.

REFERENCES

- 1) Iyer R, Thapa M, Chew F. Chronic recurrent multifocal osteomyelitis: Review. *Am J Roentgenol*, 2011; 196: S87–91.
- 2) Miettunen PM, Wei X, Kaura D, Reslan WA, Aguirre AN, Kellner JD. Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO). *Pediatr Rheumatol Online J*, 2009; 12: 1–14.
- 3) Giedion A, Holthusen W, Masel LF, Vischer D. [Subacute and chronic “symmetrical” osteomyelitis] (in multiple languages). *Ann Radiol (Paris)*, 1972; 15: 329–342.
- 4) Costa-Reis P, Sullivan KE. Chronic recurrent multifocal osteomyelitis. *J Clin Immunol*, 2013; 33: 1043–1056.
- 5) Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, Cole WG, Kerr Graham H, Allen RC, Laxer RM. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. *J Pediatr*, 2002; 141: 198–203.
- 6) Park-Min K-H, Ji J-D, Antoniv T, Reid AC, Silver RB, Humphrey MB, et al. IL-10 suppresses calcium-mediated costimulation of receptor activator NF- κ B signaling during human osteoclast differentiation by inhibiting TREM-2 expression. *J Immunol*, 2009; 183: 2444–2455.
- 7) Arturo B, Sara S, Andreas R, David Z, Evan AS, Fatma D, Robert PS. Pediatric chronic nonbacterial osteomyelitis. *Pediatrics*, 2012; 130: e1190–e1197.
- 8) DiMeco F, Clatterbuck RE, Li KW, McCarthy EF, Olivi A. Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome presenting as a primary calvarial lesion. Case report and review of the literature. *J Neurosurg*, 2000; 93: 693–697.
- 9) Hedrich CM, Hofmann SR, Pablik J, Morbach H, Girschick HJ. Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO). *Pediatr Rheumatol Online J*, 2013; 11: 47. doi: 10.1186/1546-0096-11-47.
- 10) Wedman J, van Weissenbruch R. Chronic recurrent multifocal osteomyelitis. *Ann Otol Rhinol Laryngol*, 2005; 114: 65–68.
- 11) Mann B, Shaerf DA, Sheeraz A, Skinner JA, Saifuddin A. SAPHO syndrome presenting as widespread bony metastatic disease of unknown origin. *Rheumatol Int*, 2012; 32: 505–507.

- 12) El-Shanti HI, Ferguson PJ. Chronic recurrent multifocal osteomyelitis: a concise review and genetic update. *Clin Orthop Relat Res*, 2007; 462: 11–19.
- 13) Sharma M, Ferguson PJ. Autoinflammatory bone disorders: update on immunologic abnormalities and clues about possible triggers. *Curr Opin Rheumatol*, 2013; 25: 658–64.
- 14) Hedrich CM, Hahn G, Girschick HJ, Morbach H. A clinical and pathomechanistic profile of chronic nonbacterial osteomyelitis/chronic recurrent multifocal osteomyelitis and challenges facing the field. *Expert Rev Clin Immunol*, 2013; 9: 845–854.
- 15) Job-Deslandre C, Krebs S, Kahan A. Chronic recurrent multifocal osteomyelitis: five-year outcomes in 14 pediatric cases. *Joint Bone Spine*, 2001; 68: 245–251.
- 16) Duffy CM, Lam PY, Ditchfield M, Allen R, Graham HK. Chronic recurrent multifocal osteomyelitis: review of orthopaedic complications at maturity. *J Pediatr Orthop*, 2002; 22: 501–505.