CASE REPORT

© Borgis Nowa Stomatol 2018; 23(2): 72-77 https://doi.org/10.25121/NS.2018.23.2.72

Ewa Krasuska-Sławińska[1], *Paulina Piekarska[1], Piotr Gietka[2], Anna Wieteska-Klimczak[3], Mirela Wadecka[3], Anna Matosek-Rutkowska[1]

# Chronic mandible inflammation as the first symptom of chronic recurrent multifocal osteomyelitis (CRMO) – a case report

[1]Specialist Outpatient Clinic Complex: Dental Surgical Clinic for Children, Dental Surgery for Children and Adults, Children's Memorial Health Institute, Warsaw
Head Specialist Outpatient Clinic Complex: Agnieszka Pieniak, MSc
[2]Rheumatology of Evolutionary Age Clinic and Polyclinic, MD PhD Professor Eleanor Reicher National Geriatrics, Rheumatology and Rehabilitation Institute, Warsaw
Clinic Manager: Medical Sciences Phd Professor Lidia Rutkowska-Sak
[3]Department of Paediatrics, Nutrition and Metabolic Disorders, Children's Memorial Health Institute, Warsaw
Head of Department: Janusz Książyk, MD, PhD

**Keywords**

CRMO, mandible inflammation, diagnosis

**Summary**

Chronic recurrent multifocal osteitis (CRMO) is a rare disease of an unknown aetiology, occurring mainly in children aged 4-14 years. It is characterised by recurring episodes of osteitis, with no detectable cause, lasting from several months up to a few years. It usually affects the metaphysis of long bones. Primary lesions in the form of isolated focuses rarely occur in the mandible. The clinical symptoms of CRMO include ostealgia, soft tissue swelling (oedema), skin reddening, and mild fever. The diagnosis is difficult. It involves numerous laboratory and radiological investigations. In order to exclude infectious and neoplastic aetiology, it is advisable to perform a tissue biopsy. The disease is long-lasting with exacerbations and remissions. The prognosis is uncertain. Non-steroidal anti-inflammatory drugs and empirical antibiotic therapy are a recommended first-line therapy; if no improvement is observed, corticosteroids should be used.

The analysed case concerns a 10-year-old boy with mandible inflammation as the first symptom of chronic recurrent multifocal osteitis (CRMO).

Mandibular lesions may be the first symptom of chronic recurrent multifocal osteitis. The non-specific onset and variable clinical picture delay the diagnosis. Early diagnosis enables early treatment, which prevents complications.

## Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) was first described in 1972 by Giedion et al. (1). It is a rare disease with an unknown aetiology, which accounts for 2-5% of all bone inflammations (2). Although it usually affects children aged 4-14 years and young adults, cases of adult patients have also been reported in the literature. There is a significant predominance of female patients (5:1), while the incidence of CRMO is similar for all races (3, 4). CRMO is characterised by recurrent episodes of osteitis without a specific infectious agent. The disease lasts from several months up to several years with periods of exacerbations and remissions, as well as a self-limiting tendency of the inflammatory process (3). Although lesions may occur in any location, such as vertebrae, pelvic bones, metacarpus, metatarsus, sternum and clavicles, in most clinical cases they are found in the metaphysis of long bones, femoral and tibial bones in particular (5, 6). They are rarely found in the mandible, where they occur in the form of a single, isolated focal lesion (7, 8). Although the aetiology of the disease is not fully understood, the available literature devotes a lot of attention to

genetic, autoimmune and bacterial factors (3). The clinical manifestations of CRMO include gradually increasing bone pain, local tenderness, soft tissue oedema, skin reddening and mild fever. Severe pain may limit patient's activity and is a frequent reason for hospital stay (4). Although CRMO usually occurs as a single disease, there are cases of chronic recurrent multifocal osteomyelitis coexisting with inflammatory diseases showing signs of autoimmunisation, e.g. ulcerative colitis or Crohn's disease (9-11). According to the latest literature data, it is believed that CRMO is a paediatric variant of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) in adults, which produces symptoms such as synovitis, acne, pustular psoriasis of the hands and feet, bone hypertrophy and inflammation (3). Due to the unclear clinical picture and the course of disease, the diagnosis of CRMO is difficult and requires differentiation with bone neoplasias, infectious and autoimmune diseases (3). The diagnostic process involves a series of laboratory (serology, microbiology) and imaging (radiology, including the whole body skeletal scintigraphy, CT and MRI) investigations. Tissue biopsy is necessary to exclude infectious and neoplastic processes (12-14). CRMO is treated empirically. Despite an aseptic course of the disease, long-term antibiotic therapy is usually used, which does not bring the expected result, but supports the treatment (15). Non-steroidal anti-inflammatory drugs are recommended as first-line agents. If no improvement is observed, systemic glucocorticosteroids are included. Currently, high hopes are pinned on bisphosphonate therapy, particularly in cases of multifocal lesions. Intravenous, cyclic infusions of pamidronic acid are used in children. It was found that the compound causes rapid and significant pain alleviation, reduces serum inflammatory markers, as well as induces regression of inflammatory lesions in the bones, as confirmed in MRI (16).

## Case report

A 10-year-old boy was admitted to the Department of Paediatrics, Nutrition, and Metabolic disorders of the Children's Memorial Health Institute in January 2015 due to fever during the treatment of the third episode of left parotid salivary gland inflammation. It was found from medical history that the child was born from the third pregnancy (second delivery) complicated with haemolytic anaemia treated with steroid administration in the mother and terminated via C-section. The newborn received an Apgar score of 10. After birth, a murmur over the heart was detected. A small atrial septal atrial aneurysm was diagnosed based on echocardiography with no obvious secondary signs of leakage. The boy has a history of asthma and allergic rhinitis since 2004. He was diagnosed in the Department of Gastroenterology of the Children's Memorial Health Institute for suspected Hirschsprung's disease due to chronic constipation with negative findings. The boy's mother suffers from Sjögren's syndrome. In September 2014, the boy complained of pain in the region of the left mandibular branch, which was accompanied by the swelling of the left cheek, trismus and increased body temperature. Based on the clinical picture and an ultrasound of the parotid and submandibular glands, left parotid gland inflammation was diagnosed by an otolaryngologist. The boy received combination antibiotic therapy (azithromycin, penicillin, clindamycin), which led to pain and oedema regression. Another episode of the disease with raised temperature, oedema and pain in the left parotid gland was observed in December 2014. Clindamycin and metronidazole were prescribed by the otolaryngologist; general and local improvement was achieved. In January 2015, the patient again developed severe pain and oedema in the left parotid gland accompanied by high body temperature (39°C). The boy was again administered penicillin, but the therapy did not improve the general or local condition. On day 6 of antibiotic therapy, the boy was admitted to the Department of Paediatrics, Nutrition, and Metabolic Disorders of the Children's Memorial Health Institute (CMHI) for extended diagnosis. Laboratory findings revealed increased inflammatory markers (leukocytosis, CRP, ESR). Antibiotic therapy was maintained, and non-steroidal anti-inflammatory drugs (ibuprofen) were included, resulting in short-term relief of pain and significant reduction of oedema. A slight distention of the alveolar part of the mandible persisted in the region of the left mandibular angle. Considering the family history, a decision was made to perform laboratory testing for autoimmune diseases. No parameters suggesting an autoimmune disease were found. During his stay in the Department of Paediatrics, the boy was referred to the Dental Clinic for Children (Children's Memorial Health Institute) for dental consultation. Extraoral clinical examination revealed facial asymmetry: swelling of the left cheek; hard oedema of the left parotid gland tender on palpation. Bilaterally enlarged submandibular lymph nodes were also fund. Intraoral examination revealed a palpable thickening in the mandibular branch. A suspicion of osteitis was raised by a dental surgeon. Due to an unclear, recurrent clinical picture of the disease, imaging testing was performed – a panoramic radiograph (fig. 1),

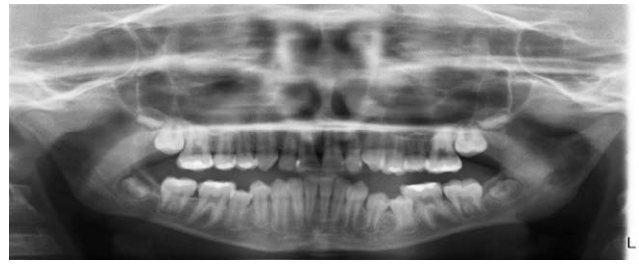

**Fig. 1.** Panoramic radiograph

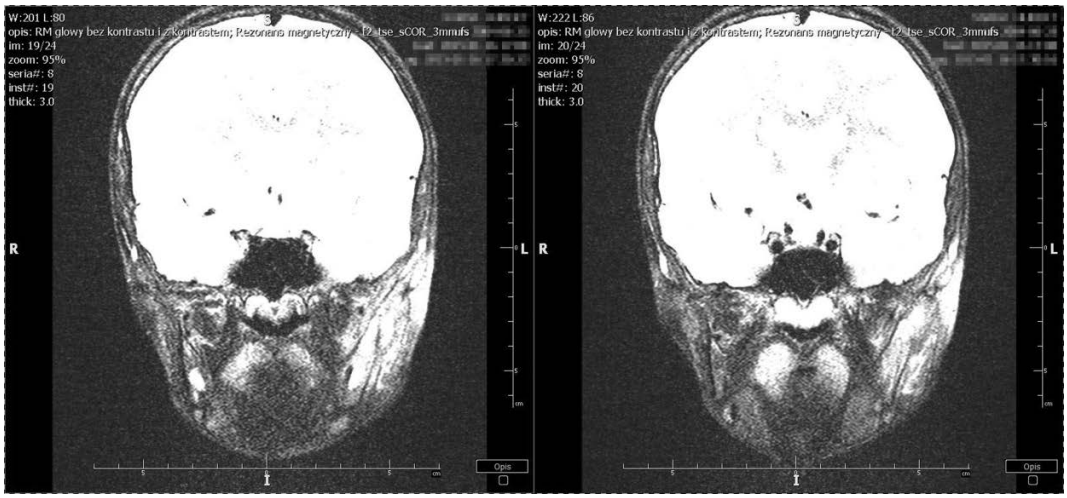


**Fig. 2.** MRI – a ruptured cortical bone layer in the mandibular branch with infiltration of the myeloid cavity, the lesion involves the masseter and the lateral portion of the lateral medial pterygoid

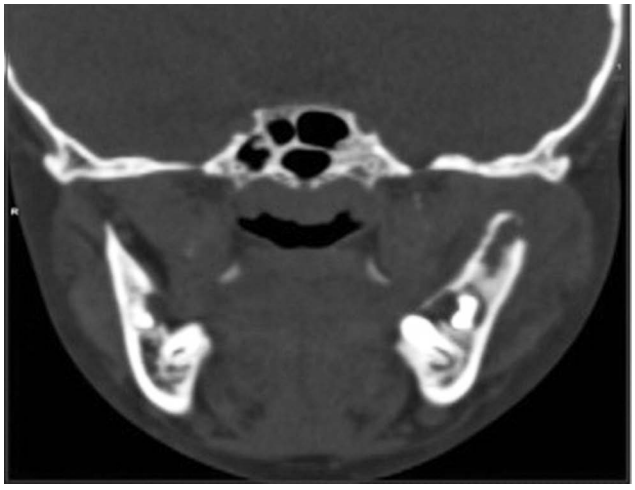

**Fig. 3.** CT – multiple osteolytic foci in the left mandibular branch, condyloid process, coronoid process and the head of the mandible

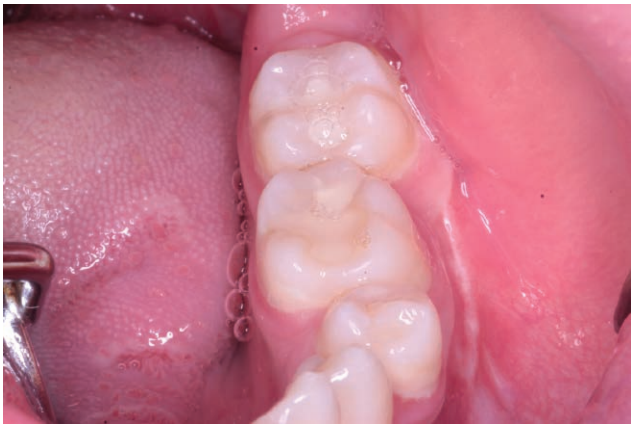

**Fig. 4.** An intraoral photograph after the biopsy (a scar on the mucosa in the vestibule of the mouth near the tooth 36)

MRI (fig. 2) and CT (fig. 3). The panoramic radiograph of the left mandibular branch showed a focus of irregular shadowing without a visible osteosclerotic capsule. Computed tomography revealed multiple small osteolytic foci in the left mandibular branch, condyloid process, coronoid process and the head of the mandible. At the largest focus (10 mm in diameter), there was a ruptured cortical bone layer and an adjacent thickened, inhomogeneous masseter. Parotid and submandibular glands unremarkable. Magnetic resonance imaging confirmed the presence of a lesion 5 x 2.5 cm in diameter, with ruptured cortical bone layer in the mandibular branch and infiltration of the myeloid cavity, in the left mandible. A follow-up ultrasound of the parotid and submandibular glands was performed, but did not reveal any focal lesions. Mandibular and masseter biopsy was performed to exclude malignancy after dental, otolaryngological, oncological and maxillofacial surgical consultations (fig. 4). The procedure was performed in the Department of Surgery of Children and Adolescents of the Institute of Mother and Child. Cancer diagnosis was extended with CT and chest X-ray, which showed no abnormalities. Mandibular and masseter biopsy revealed chronic inflammation with no signs of neoplastic process. Microbiological analysis of wound samples was performed; *Corynebacterium species* and *Eubacterium limosum* were grown. Targeted antibiotic therapy (clindamycin + metronidazole) was used for 6 weeks. Another relapse occurred in March 2015. A follow-up facial CT was performed at that time. An osteolytic lesion with a size of 5 x 2.5 cm, with ruptured cortical bone layer in the mandibular branch and multiple small osteolytic foci was found in the left mandible. The picture was similar to the findings reported in January 2015. Continuation of antibiotic therapy for further

3 months (penicillin, metronidazole) was advised. In order to extend the diagnosis, the patient was referred to the National Institute of Geriatrics, Rheumatology and Rehabilitation for a full-body MRI scan, which showed swelling of the left masseter muscle and small foci of oedema in the distant metaphyses of both tibial bones and the distal part of the left tibial shaft. Furthermore, slightly increased amount of fluid was detected in the left elbow. The course of disease and the diagnostic findings did not allow for a final, unambiguous diagnosis. However, due to the presence of several pathological lesions in the bones in the full-body MRI scan, chronic recurrent multifocal osteitis (CRMO) was diagnosed. In addition to antibiotics and NSAIDs, sulfasalazine was included, which led to general and local improvement. Currently, the boy is under constant care of the CMHI. Disease recurrences with pain and oedema of the left cheek in the region of the mandibular angle with periodical trismus are observed every 3-6 months. The patient regularly receives sulfasalazine and NSAIDs (ibuprofen), vitamin D and $B_6$, as well as antibiotic therapy (clindamycin) during exacerbations. In July 2016, a follow-up full-body MRI scan was performed during the boy's stay in the CMHI. The presence of persistent inflammatory lesion in the left mandibular branch with no other pathological osseous or articular foci was confirmed. The treatment was maintained. A follow-up blood testing (blood cell count, CRP, ESR) is performed every 2 months. From November 2016 to the present (October 2017), the child's condition is stable with no disease recurrence.

## Discussion

The diagnosis of chronic recurrent multifocal osteitis (CRMO) is difficult and ambiguous. According to the literature (17), the diagnosis should be based on the following diagnostic criteria: the presence of 2 or more bone focal lesions with clinical manifestations, radiological confirmation of the lesions, symptoms persisting for at least 6 months, lack of improvement after antibiotic therapy and the lack of other explanatory causes of the lesions. In our case report, the diagnosis of CRMO was based on the following clinical manifestations and investigations: 3 focal lesions (mandible, tibial bones and the left elbow), as confirmed by a whole-body MRI, facial CT and panoramic radiograph. Three years have passed since the onset of first symptoms. Antibiotic therapy did not bring any significant improvement in the general or local condition. Neoplastic diseases were excluded based on pathological examination of the lesion. In most cases, the primary focal lesion of CRMO is found in upper extremities, followed by the pelvis and, rarely, the clavicle (3). Mandibular lesions observed in our patient are rarely described as the primary focal lesion of CRMO in the literature. Due to similar initial clinical manifestations, recurrent mandibular inflammation is often misdiagnosed as parotid gland inflammation (3). Our patient was also initially diagnosed with left parotid gland inflammation. Although no specific laboratory markers for CRMO have been identified so far, many authors point to increased erythrocyte sedimentation rate, slightly increased CRP and leukocytosis in the affected patients. Shifts in the panoramic radiograph are also observed (2, 18). Similar laboratory findings were reported in our patient (WBC: 12.3 cells/μL vs 4-12 of norm; ESR 62 mm/h vs 1-10 of norm CRP 1.97 mg/dL vs < 0.5 of norm). According to the literature, microbiological and serological tests to diagnose bacterial, viral and fungal infections are negative in patients with CRMO. Negative oral and nasal swabs in our patient correspond to the findings reported by other authors. Tissue biopsy, which allows to exclude infectious and neoplastic aetiology of lesions, should be a diagnostic standard in CRMO. Pathological examination of mandibular and masseter material obtained from our patient revealed chronic inflammation with no signs of neoplastic proliferation. Radiological confirmation of the presence of disseminated, often symmetrical lytic, sclerotic or mixed lesions at different stages and at sites typical for specific (bacterial) osteitis is one of diagnostic criteria for CRMO. The lesions may be accompanied by periosteal reactions. The above clinical picture is not pathognomonic for CRMO and always raises suspicion of neoplastic process (13, 19); therefore histopathological diagnosis is necessary. Imaging testing (both panoramic radiograph and facial CT) performed in our patient confirmed the presence of an inhomogeneous osteolytic lesion with ruptured cortical bone layer and a size of 5 x 2.5 cm, with thickened masseter and multiple osteolytic foci in the mandibular branch, condyloid process and coronoid process, in the region of the mandibular angle. A full-body MRI, which is also considered a sensitive diagnostic method in CRMO by many authors, was also performed in our patient. This technique may be also used to monitor therapeutic progress (19). So far, no guidelines for therapeutic regimen in CRMO have been developed in the literature. Both in literature and in our case, the treatment usually begins with empirical antibiotic therapy, which shows only limited efficacy due to the absence of infectious aetiology, but supports the therapy and slightly improves the general condition of patients. Some authors postulate the use of azithromycin, an antibiotic with potential anti-inflammatory and immunomodulatory effects (20). Non-steroidal anti-inflammatory drugs, which were also used in our patient, are recommended as first-line therapy in CRMO. Systemic corticosteroids are included in patients with poor clinical improvement. There is also an ongoing research on the use of methotrexate, sulfasalazine, TNF-alpha blocker, gamma interferon, immunoglobulins and calcitonin in CRMO, which has already shown some positive effects (2). Sulphosalazine was also included in our patient, which led to significant local and general improvement. Currently, high hopes are pinned on bisphosphonate

therapy, particularly in cases of multiple focal lesions (16). If pharmacotherapy is impossible, surgical treatment is implemented. The diagnosis of chronic recurrent multifocal osteitis requires an interdisciplinary approach and the exclusion of a number of other diseases producing similar symptoms. During the diagnostic process, our patient was consulted with paediatricians, oncologists, rheumatologists, otolaryngologists, maxillofacial and dental surgeons from different healthcare centres.

## Conclusions

The described case shows that the diagnosis of CRMO is very difficult. Final diagnosis was based on the clinical manifestations, laboratory and radiology findings, biopsy of the inflammatory lesions and following the exclusion of infectious and neoplastic aetiology. Early diagnosis allows for early treatment onset, which is of key importance for the course of treatment, the comfort of the patient's life and prevention of possible complications. According to literature data, the disease resolves spontaneously, and the active phase of disease typically lasts more than 5 years.

During the inactive phase, patient's general condition is monitored. During the active phase, pharmacotherapy is necessary due to severe pain and acute inflammation.

### Conflict of interest

None

### Correspondence

*Paulina Piekarska
Poradnia Stomatologiczna dla Dzieci
Instytut „Pomnik – Centrum Zdrowia Dziecka"
Aleja Dzieci Polskich 20
04-730 Warszawa
tel.: +48 501-848-466
paulina.piekarska.stom@gmail.com

### References

1. Giedion A, Holthusen W, Masel LF, Vischer D: Subacute and chronic „symmetrical" osteomyelitis. Ann Radiol (Paris) 1972; 15: 329-342.
2. Chun CS: Chronic recurrent multifocal osteomyelitis of the spine and mandible: case report and review of the literature. Pediatrics 2004; 113: 380-384.
3. Patel R, Jacob R, Lee K, Booth TN: Parotid swelling and chronic recurrent multifocal osteomyelitis of mandible in children. Int J Pediatr Otorhinolaryngol 2015; 79(1): 47-52.
4. Korczowski B, Lonc B: Przewlekłe nawracające wieloogniskowe zapalenie kości i szpiku. Przegląd Medyczny Uniwersytetu Rzeszowskiego, Rzeszów 2010; 1: 7-13.
5. Prose NS, Fahrner LJ, Miller CR, Layfield L: Pustular psoriasis with chronic recurrent multifocal osteomyelitis and spontaneous fractures. J Am Acad Dermatol 1994; 31: 376-379.
6. Paller AS, Pachman L, Rich K et al.: Pustulosis Palmaris and Plantaris: its association with chronic recurrent multifocal osteomyelitis. J Am Acad Dermatol 1985; 12: 927-930.
7. Monsour PAJ, Dalton JB: Chronic recurrent multifocal osteomyelitis involving the mandible: case reports and review of the literature. Dentomaxillofacial Radiol 2010; 39(3): 184-190.
8. Borzutzky A, Stern S, Reiff A et al.: Pediatric chronic nonbacterial osteomyelitis. Pediatrics 2012; 130(5): 1190-1197.
9. Bousvaros A, Marcon M, Treem W et al.: Chronic recurrent multifocal osteomyelitis associated with chronic inflammatory bowel disease in children. Dig Dis Sci 1999; 44: 2500-2507.
10. Morbach H, Dick A, Beck C et al.: Association of chronic non-bacterial osteomyelitis with Crohn's disease but not with CARD15 gene variants. Rheumatol Int 2010; 30: 617-621.
11. Kobelska-Dubiel N, Ignyś I, Cichy W: Zmiany kostno-szpikowe w przebiegu wrzodziejącego zapalenia jelita grubego u 12-letniego chłopca – opis przypadku. Pediatria Współczesna Gastroenterologia, Hepatologia i Żywienie Dziecka 2007; 9: 203-204.
12. Girschick HJ, Huppertz HI, Harmsen D et al.: Chronic recurrent multifocal osteomyelitis in children: diagnostic value of histopathology and microbial testing. Human Pathology 1999; 30: 59-65.
13. Mortensson W, Edeburn G, Fries M, Nilsson R: Chronic recurrent multifocal osteomyelitis in children. A roentgenologic and scintigraphic investigation. Acta Radiologica 1988; 29: 565-570.
14. Khanna G, Sato TS, Ferguson P: Imaging of chronic recurrent multifocal osteomyelitis. Radiographics 2009; 29: 1159-1177.
15. King SM, Laxer RM, Manson D et al.: Chronic recurrent multifocal osteomyelitis: a noninfectious inflammatory process. Pediatr Infect Dis J 1987; 6: 907-911.
16. Simm PJ, Allen RC, Zacharin MR: Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. J Pediatr 2008; 152: 571-575.

17. Manson D, Wilmot DM, King S, Laxer RM: Physeal involvement in chronic recurrent multifocal osteomyelitis. Pediatr Radiol 1989; 20: 76-79.
18. Huber AM, Lam PY, Duffy CM et al.: Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr 2002; 141: 198-200.
19. Brown T, Wilkinson RH: Chronic recurrent multifocal osteomyelitis. Radiology 1988; 166: 493-496.
20. Wagner AD, Schilling F: Azithromycin: an antiinflammatory effect in chronic recurrent multifocal osteomyelitis. Rheumatology 2000; 59: 352-353.

**submitted:**
26.03.2018
**accepted:**
16.04.2018