Chronic Osteomyelitis With Proliferative Periostitis of the Mandible in a Child

Report of a Case Managed by Immunosuppressive Treatment

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Background: Osteomyelitis with proliferative periostitis is a relatively uncommon inflammatory condition of the jaws, mainly characterized by periosteal formation of reactive bone. It primarily affects children and adolescents, also referred to as Garre’s osteomyelitis, more frequently involving the molar region of the mandible. Cases lacking an obvious source of infection may have an immunologically mediated etiopathogenesis, falling under the spectrum of primary chronic osteomyelitis or chronic recurrent multifocal osteomyelitis (CRMO).

Case report: Herein, we present a case of chronic osteomyelitis in a 6.5-year-old girl, who suffered from recurrent painful episodes of swelling of the mandible for the last 2 years, previously requiring hospitalization and administration of intravenous (IV) antibiotics and NSAIDs with limited responsiveness. The biopsy showed features consistent with osteomyelitis with proliferative periostitis. The patient was initially managed with an IV combination antibiotic regimen with only partial improvement. The possibility of an autoimmune mechanism in the context of primary chronic osteomyelitis or CRMO was considered, and immunosuppressive therapy (TNF inhibitor etanercept along with corticosteroids and methotrexate) was administered, resulting in clinical resolution.

Conclusions: Osteomyelitis and its childhood variants are relatively rare and their management presents several challenges. Although typically treated with administration of antibiotics, possibly along with surgical intervention, other treatment modalities may be necessary for resilient and persistent cases. In a subset of cases, especially in the absence of local infectious factors, immunologically mediated mechanisms may play an important role and appropriate immunosuppressive therapy may be effective.

Key words: osteomyelitis with proliferative periostitis, primary chronic osteomyelitis, chronic recurrent multifocal osteomyelitis, immunosuppressive therapy, anti-TNF

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OSTEOMYELITIS

Osteomyelitis is an inflammatory disease of the cortical and cancellous bone, which may affect the jaws and more frequently the mandible.1,2 Several etiologic and predisposing factors have been associated with the development of osteomyelitis, including odontogenic infections of pulpal or periodontal origin, fractures, and surgical trauma, for example, extractions, although the etiology for some cases remains unknown.1,2 According to the clinical course and the predominant type of inflammation, osteomyelitis can be characterized as acute or chronic: the latter has a longer duration (arbitrarily set as exceeding 1 month), sometimes exhibiting a very protracted course. Although the classification remains a matter of debate, chronic osteomyelitis is divided into several types: chronic suppurrative (or secondary chronic) osteomyelitis is the chronic counterpart of acute suppurative osteomyelitis and, similar to it, is considered of bacterial origin and characterized by suppuration and sequestration.3 Other forms of osteomyelitis of the jaws include: diffuse and focal sclerosing osteomyelitis, primary chronic osteomyelitis (PCO), and osteomyelitis with proliferative periostitis (or periostitis ossificans or Garre’s osteomyelitis).3-3 The latter was first described in 1893, when the Swiss surgeon Carl Garre first reported on a type of osteomyelitis, which was clinically characterized by distention and thickening of bone, in the lack of suppuration, sequestration, or fistula formation.1,4 In the past, various names have been used for this entity, including Garre’s osteomyelitis, periostitis ossificans, nonsuppurative ossifying periostitis, osteomyelitis with proliferative periostitis, nonsuppurative sclerosing osteomyelitis, and chronic sclerosing inflammation of the jaw.5,6 This entity has been primarily described in children and adolescents. The predilection for younger individuals has been attributed to high periosteal activity along with increased resistance in microbes.1,7 Radiographic investigation typically shows bone laminations parallel to each other and to the cortical surface of the involved bone (resembling “onion skin”).3 However, several authors have proposed that the term “Garre’s osteomyelitis” should be abandoned, because it likely corresponds to several forms or complications of osteomyelitis and not to a single specific type of the disease.1

In the present article, a case of persistent chronic osteomyelitis in the right mandible of a 6.5-year-old girl is presented. The patient was unresponsive to antibiotic treatment but was successfully managed with immunosuppressive therapy. This case enhances the theory of immunologically mediated etiopathogenesis in the context of PCO, manifesting with clinical, radiographic, and histopathologic features of proliferative periostitis.

CASE PRESENTATION

A 6.5-year-old Caucasian female child was referred to the Oral Medicine Clinic due to a symptomatic swelling in her right mandible. The girl’s mother reported recurrent painful episodes of swellings in the right mandible and face for the last 2 years. The
child had been hospitalized several ("5–6") times in the past elsewhere. Based on a clinical diagnosis of Garre’s osteomyelitis, these previous episodes had been managed with intravenous (IV) administration of antibiotics (including clindamycin, and amoxicillin and clavulanic acid) for approximately 7–10 days each time, followed by per os antibiotic coverage for another week, along with NSAIDs (including ibuprofen and mefenamic acid). According to the mother, treatments resulted only in partial and temporary improvement of the swelling. During these previous hospitalizations, an incisional biopsy of the jaw swelling was performed without rendering a specific diagnosis, but showing features “reminiscent of Garre’s osteomyelitis versus fibrous dysplasia.” According to the mother, the frequency of painful swelling episodes was very high (recently approximating almost 2 episodes per month), accompanied by chills but not fever. Also, with the progression of time, the swelling had increased in size and, despite fluctuations, never completely resolved. In addition, trismus had developed. A vague history of an episode of injury in the area due to falling at age 3.5 years old was also mentioned.

Regarding medical history, the young patient was healthy with no known systemic illnesses or allergies and did not receive any medications, apart from the frequent use of antibiotics and NSAIDs for the painful episodes of jaw swelling. There was not any significant family history.

On clinical examination, a large swelling of the right mandible was noticed, which, extraorally, was causing a noticeable facial asymmetry (Fig. 1A). Intraoral examination revealed a swelling of the right body of the mandible with buccal expansion, which was hard in consistency and covered by normal mucosa (Fig. 1B). The rest of clinical examination of the head and neck was unremarkable.

Panoramic radiograph revealed an extensive mixed lesion with a diffuse radiopaque appearance containing radiolucent zones at the body and ramus of the right mandible, with significant periosteal reaction (Fig. 2A). A Cone Beam Computed Tomography (CBCT) scan of the mandible showed a diffuse mixed sclerotic-lytic pattern with ill-defined borders in the right mandible, extending from the premolar area to the condyle and accompanied by periosteal reaction with osteoid deposition in the molar area, the lower border, and the ramus, as well as perforation of the cortical bone of the lower border of the right mandible (Fig. 2B,C).

On the basis of the clinical and radiographic findings, the preliminary diagnosis of chronic osteomyelitis with proliferative periostitis (Garre’s osteomyelitis) was set. To further corroborate the diagnosis, an incisional biopsy of the right mandible was performed under local anesthesia. Microscopic examination revealed trabeculae of compact bone of variable size and shape, which, in some areas, were arranged in parallel or perpendicular to the surface or were interconnected forming a meshwork (Fig. 3A). The bone trabeculae were surrounded by partially loose and edematous fibrous connective tissue with foci of mild chronic inflammation. Prominent reversal lines and occasionally empty bone lacunae were also discerned (Fig. 3B). These microscopic features were consistent with the diagnosis of osteomyelitis with proliferative periostitis (Garre’s osteomyelitis).

During the intrabony biopsy, a culture specimen was also taken; culture was positive for streptococcus oralis (abundant colonies) and coagulase-negative staphylococci (rare colonies), while no pyocytes were present. An antibiogram for the aforementioned cultured bacteria was also performed showing sensitivity in several antibiotics.

Following per os administration of amoxicillin and clavulanic acid, which resulted only in temporary improvement of the painful swelling, the patient was admitted to a specialized infectious disease clinic in a Children’s Hospital. A complete bone scintigraphy scan showed increased uptake diffusely in the right mandible but did not reveal any other lesions in the skeleton. A triple antibiotic scheme, that is, daptomycin, rifampicin, and ertapenem, was administered IV for 1 month; only mild improvement with subsequent stabilization of the jaw swelling was noticed. Due to the lack of sufficient response to antibiotics, the involvement of a possible autoimmune mechanism was considered, in the context of PCO. Therefore, immunosuppressive therapy was initiated. First, the patient received prednisolone 30 mg daily along with ranitidine for gastroprotection, resulting in prompt significant improvement of the painful swelling, with subsequent progressive tapering of prednisolone by approximately 2.5 mg every 2 weeks for a total of 4 months. In addition, the patient received methotrexate, that is, 5 mg twice a week, accompanied by folic acid supplementation, while IV administration of etanercept, a tumor necrosis factor (TNF) inhibitor (25 mg once a week), was also introduced. With this regimen, a stable marked improvement of the swelling was noticed; the painful episodes and the trismus were eliminated.

At a follow-up visit, approximately 1 year after the first visit, the swelling was resolved (Fig. 4A,B) and the mouth opening

**FIGURE 1.** Clinical findings at presentation: (A) Extraoral examination showing facial asymmetry due to swelling of the right mandible. (B) Intraoral view of the swelling of the right mandible, which is covered by normal mucosa and causes expansion of the buccal cortical plate.
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was within normal limits (Fig. 4C). A new panoramic radiograph revealed significant improvement of the trabeculation pattern of the right mandible (Fig. 5). The patient remains under follow-up without any further episodes of swelling.

DISCUSSION

Our patient demonstrated several demographic, clinical, radiographic, and histopathologic characteristics, which were consistent with osteomyelitis with proliferative periostitis. The entity
is an inflammatory disease primarily affecting children and adolescents with a mean age of 13 years. The affected periosteum forms several rows of reactive bone, which clinically may manifest as extraoral swelling causing facial asymmetry, as seen in the present case; the overlying skin is usually normal. Intraorally, a hard swelling may also be obvious, covered by normal mucosa. The lesion may be asymptomatic or painful; the latter may be persistent or intermittent in nature. In the present case, multiple and frequent painful episodes were reported, having an adverse effect in the quality of life and psychology of the young patient and her family. Other neurologic symptoms, such as paresthesia in teeth, skin, and lip, may infrequently occur, while trismus is present in approximately 60% of the cases, including ours. In some cases, lymphadenopathy, fever, and weakness may also develop.

Appropriate radiographs, such as panoramic and occlusal, and CBCT imaging show radiopaque laminations of bone that roughly parallel each other and the underlying cortical surface. The radiographic examination of our patient showed clear evidence of new periosteal bone formation, as well as diffuse involvement of the right mandible with ill-defined borders, also causing perforation of the mandibular cortex. The clinical and radiographic features may elicit a differential diagnosis which, besides osteomyelitis, encompasses fibro-osseous lesions. In a pediatric patient, the latter mainly include fibrous dysplasia and juvenile ossifying fibroma. Neoplastic entities, such as osteosarcoma and Ewing’s sarcoma, should be also considered, especially taking into account the ill-defined border, the prominent periosteal reaction and the painful symptomatology. Histopathologic examination will exclude the aforementioned neoplastic entities showing features consistent with proliferative periostitis, similar to our case. The main histopathologic finding is the presence of trabeculae of cellular woven bone typically arranged parallel to each other, perpendicular to the surface or in an interconnecting meshwork; inflammation and bone sequestration is usually limited. Nonetheless, the microscopic findings may overlap with those of some fibro-osseous lesions (eg, fibrous dysplasia), necessitating careful correlation with the clinical and imaging characteristics.

It should be emphasized that osteomyelitis in children, including proliferative periostitis, is a relatively rare entity and several of its aspects, ranging from terminology to etiology and, most importantly, management, remain controversial and challenging. Regarding nomenclature, the term Garre’s osteomyelitis has been frequently used in the literature and is still commonly applied, despite the fact that several authorities have advocated against its use, mainly because of the realization that the original entity described by Carl Garre in 1893 was rather obscure and not supported by radiographic and histopathologic findings. Instead, the term osteomyelitis with proliferative periostitis has been advocated as a more appropriate term, emphasizing a prominent feature of osteomyelitis, especially in children, namely the periosteal deposition of new bone. Our case was also characterized by periosteal

FIGURE 4. Clinical findings at 1 year follow up: Significant improvement of the extraoral (A) and intraoral (B) swelling and normal mouth opening (C).

FIGURE 5. Radiographic findings at 1 year follow up: A panoramic radiograph demonstrated significant improvement in the trabeculation pattern of the right mandible.
reaction resulting in new bone formation along the cortical plate of the right mandible at various sites, which was clinically observable as hard tissue swelling. However, it should be noted that activation of periosteum resulting in new bone deposition occurs in many conditions of variable origin; besides inflammatory diseases, malignant neoplasms (such as osteosarcoma, chondrosarcoma, and Ewing sarcoma) may also frequently cause a similar pattern of periosteal reaction.\textsuperscript{11,17} Although specific radiographic patterns have been described (eg, the periosteal reaction associated with Garre’s osteomyelitis typically presents with an onion skin-like appearance, also seen in Ewing’s sarcoma, while osteosarcoma and chondrosarcoma more characteristically cause a sun-ray pattern), significant overlap in the imaging features of periosteal reaction caused by diverse entities may exist.\textsuperscript{13,17}

The most common cause of proliferative periostitis, and jaw osteomyelitis in general, is odontogenic infection mainly of periapical and, less frequently, periodontal origin; trauma and fractures have been also implicated.\textsuperscript{18–20} Several other hypotheses on the etiopathogenesis of osteomyelitis have been proposed in the literature, including hyperactive immunologic response to infection and bacterial toxins, endogenous bacterial infection, and reactive hyperplasia of bone because of chronic tendinitis caused by muscular overuse.\textsuperscript{21–23} In our case, no periapical or periodontal pathoses were noticed; a vague history of trauma in the area at age 3.5 years was reported and could have been a possible etiologic factor. Despite the fact that a culture and sensitivity test was performed under aseptic conditions, showing positivity mainly for streptococcus oralis, the possibility of contamination exists.\textsuperscript{24–27} More importantly, the lack of response to repeated antibiotic regimens, including IV administration and combination schemes, raised significant doubt on the potential bacterial etiology. Therefore, other possibilities, including a hyperactive immune response, were entertained.

Primary chronic osteomyelitis (PCO) is an entity of non-infectious etiology, which should be distinguished from chronic suppurative osteomyelitis.\textsuperscript{1,2,28} It is usually a localized phenomenon affecting the mandible of both adolescents and adults.\textsuperscript{8} It commonly manifests with painful bone swelling, which may be accompanied by trismus and regional lymphadenopathy, in the absence of an obvious source of infection; in addition, fever, purulence or sequestration are typically lacking.\textsuperscript{1,2,28} Chronic recurrent multifocal osteomyelitis (CRMO) is an entity affecting mainly children, characterized by periods of exacerbations and remissions over many years. It presents with painful swellings in multiple bones, including the extremities and the jaws, and may be viewed as a disseminated variant of PCO.\textsuperscript{1,2,28,30} It may be also accompanied by dermatologic manifestations in the form of neurotrophic cutaneous diseases, while it appears to be closely related to SAPHO syndrome (ie, synovitis, acne, pustulosis, hyperostosis, and osteitis).\textsuperscript{1,2,30} It is not associated with bacterial infection and is not responsive to antibiotics. Radiographically, PCO and CRMO are commonly characterized by a mixed radiographic appearance with scattered osteolytic areas within a diffusely sclerotic bone, along with periosteal bone formation.\textsuperscript{1,30}

Both PCO and CRMO are characterized by a lack of an obvious source of infection; although their etiology remains obscure, an immunologically mediated mechanism has been suggested, possibly an autoimmune-type response stimulated by exposure to low-virulence microorganisms. Patients with CRMO show an underproduction of anti-inflammatory cytokines (IL-9, IL-10, IL-18) and overproduction of proinflammatory cytokines (IL-1β, IL-6, TNF-α).\textsuperscript{29,30,33} This imbalance has been proposed as a mechanism responsible for osteoclast activation leading to the bone manifestations of the disease.\textsuperscript{29} Recently, the coexistence of CRMO with inflammatory bowel disease (IBD) was identified in pediatric patients. Although the etiologic link needs further investigation, this coexistence might further strengthen the hypothesis that an autoimmune process is implicated with possible predisposing genetic factors.\textsuperscript{30,36} In several articles, a possible nosologic relationship between PCO and CRMO with diffuse sclerosing osteomyelitis and chronic tendinitis of the jaws (an entity attributed to parafuncional overuse of the masticatory muscles) has been also postulated.\textsuperscript{37–39}

In our case, bone scan did not reveal any other lesions in the skeleton; additionally, symptoms compatible with IBD were lacking. Nonetheless, an autoimmune mechanism in the absence of a detectable source of infection was considered probable and was supported by the clinical response in the administered immunosuppressive medication. Overall, our case had the clinico-pathologic features of osteomyelitis with proliferative periostitis, while, in terms of etiology and treatment responsiveness, it appeared to fit within the context of PCO (or a localized variant of CRMO).

The management of osteomyelitis in general and proliferative periostitis in particular is frequently challenging.\textsuperscript{1,6} If there is an obvious source of infection, for example, a periapical lesion associated with a necrotic tooth, its elimination may be sufficient to induce regression of the osteomyelitis. Short courses of antibiotics are used for alleviating acute cases; in chronic osteomyelitis, anti-biotic treatment is less effective and may require long-term, even IV and high dosage, administration.\textsuperscript{27} In nonresponsive to medical treatment cases, surgical intervention may be indicated, including curettage, sequestrectomy, decortications, or sauerization, possibly with bone transplantation, or even resection and reconstruction in more severe cases.\textsuperscript{40–44} Hyperbaric oxygen (HBO) has been also used as an adjuvant therapy, especially in recurrent cases.\textsuperscript{4,2} Cases that lack an obvious source of infection and may be associated with a possible autoimmune mechanism (eg, in the context of primary chronic osteomyelitis or CRMO) frequently show unresponsiveness to antibiotic or even surgical and HBO treatment. In these cases, immunosuppressive therapy, such as corticosteroids, methotrexate, and TNF-α antagonists, are frequently used with satisfactory response rates; other attempted interventions include the use of NSAIDs and bisphosphonates, such as pamidronate.\textsuperscript{29,30,34,42} In a series of pediatric patients with chronic nonbacterial osteomyelitis of the mandible from a single center, full response rates to anti-TNF therapy (60%) and pamidronate (67%) far surpassed those to NSAIDs (11%).\textsuperscript{42} Pabulert suppression therapy with a gonadotropin-releasing hormone analogues was also recently reported to result in restored bone anatomy and complete relief of symptoms in a pediatric patient with PCO.\textsuperscript{44} In our case, etanercept administrated IV along with corticosteroids and methotrexate resulted in significant and sustained improvement by clinical and radiographic criteria.

In conclusion, osteomyelitis in pediatric patients, frequently presenting as proliferative periostitis, can be attributed to many etiologic factors and is typically treated with elimination of a detectable source of infection, frequently in combination with administration of antibiotics and sometimes along with surgical intervention, such as decortication of the affected area. In a subset of cases, it is possible that immunologically mediated mechanisms may play an important role, either in the context of CRMO (especially with involvement of multiple bones) or as a localized phenomenon (in the form of PCO). Our case appears to fit in the latter category, considering the lack of an obvious source of infection, the unresponsiveness to long-term combination antibiotic treatment and the very good therapeutic result with immunosuppressive therapy. Publication of more cases of jaw osteomyelitis in children with thorough diagnostic work-up and emphasis on treatment responsiveness should be encouraged.
REFERENCES