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# Garrè's Osteomyelitis – regarding a clinical case and literature review

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**Abstract**

Garrè's osteomyelitis is a rare inflammatory disease with an unclear aetiology. It mainly affects the mandible in young children and adults under 30 years old. The goal of the treatment is to control the symptoms. However, the most appropriate management remains unclear. There are reports of off-label use of antiresorptive drugs, namely bisphosphonates, in patients with refractory disease, with favourable outcomes. In this article we present a literature review about Garrè's osteomyelitis and a case report of a patient with this diagnosis, refractory to conventional treatments and symptomatic over the previous five years, who was effectively treated with zoledronic acid.

## Highlights

- Garrè's osteomyelitis is a rare inflammatory disease with an unclear aetiology.
- The mandible is the most common stricken area, while young children and adults under 30 years, mainly men, are the most affected age groups.
- The most appropriate therapeutic approach remains unclear, but antiresorptive drugs, particularly bisphosphonates, in patients with refractory disease, seem to be effective.
- This article presents a literature review and a case report of a patient effectively treated with zoledronic acid.
- The use of bisphosphonates should be considered for refractory cases of Garrè's Osteomyelitis.

## 1. Introduction

Garrè's osteomyelitis is a rare inflammatory disease usually affecting the jaw, which aetiology remains unclear, characterized by an insidious onset, localized pain with episodic nonprogressive nature, without suppuration or sequestra formation [1–4]. Young children and adults aged below 30 years are the most affected, frequently men [1, 4]. The duration is variable and may persist for several months to years [1]. Between crises, several patients are asymptomatic [5].

It was first described by Carl Alois Philipp Garrè in 1893, as a thickening of cortices of long bones without abscess or sequestra. Initially it was only reported in long bones, particularly in the tibia, until 1948, when Berger described a case involving the mandible [6]. It is very rare and difficult to diagnose, usually mentioned in sporadic case reports [1].

Garrè's osteomyelitis diagnosis is made usually based on the patient's history and conventional radiographic methods or computed tomography (CT) images [1–4, 7]. The most appropriate treatment remains unclear [1]. Reported modalities include antimicrobial therapy, glucocorticoids, occlusal splint and physiotherapy, hyperbaric oxygen therapy, antiresorptive medications, targeted biologic therapy or surgical resection [1, 5].

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The most accepted treatment is antibiotic administration and extraction of teeth with inflammatory lesions or decay, which leads to lesion regression and bone remodeling over a period of 6 to 8 months [1, 7]. However, in most cases these treatments fail in achieving a long-lasting reduction of the recurrent pain, trismus and swelling [2]. In these refractory cases, bisphosphonates can be useful to achieve symptom control [2].

## 2. Case Report

A 20-year-old woman was referred due to pain and swelling of the right jaw over the last five years. Her personal and family background was unremarkable and she wasn't taking any medication. In 2016, after an endodontic treatment of tooth 4.6 (mandibular right first molar), the patient started experiencing pain and swelling of the right mandible region (Figure 1 A). The tooth was extracted, but the patient persisted with pain and a swollen jaw, the reason why she did several cycles of antibiotic therapy and analgesics.

In 2018 she underwent a second molar extraction (Figures 1 B and 1 C). Intraoperatively, dense bone was observed with areas of osteoid material and periosteal reaction and biopsy revealed a chronic inflammatory process. She started high dose prednisolone (initially 40 mg per day, then slowly reduced to 10 mg) that was kept for three years. A CT of the jaw in 2019 revealed an exuberant periosteal reaction with cystic areas and progressive ossification of the right mandibular body (Figures 1 D and 1 E).

After prednisolone dose reduction she had recurrence of symptoms with doses lower than 7.5 mg per day. She underwent hyperbaric chamber treatments, without improvement. A new jaw CT in 2021 revealed layered bone sclerosis with periosteal reaction control, resulting in a double contour of the mandible and facial asymmetry, which confirmed the diagnosis of Garrè's osteomyelitis (Figures 1 F and 1 G).

During follow-up the patient progressively reduced the prednisolone dose over six months, until its discontinuation in September 2021. By this time, laboratory tests showed high levels of inflammatory parameters - C-reactive protein (CRP): 2.17 mg/dl and erythrocyte sedimentation rate (ESR): 50 mm. Whole-body bone scintigraphy with head SPECT/CT showed focal hyperfixation in the right jaw (Figures 1 H, 1 I, and 1 J).

Since the patient maintained recurrent complaints of pain, at least one crisis per month, she accepted treatment with zoledronate 5 mg, single IV administration, with resolution of the symptoms and improvement of inflammatory parameters (CRP 1.09 mg/dl; ESR 29 mm). After a 28-month follow-up period, the patient remains clinically in remission, with no analgesic therapy required (Figure 2).

## 3. Discussion

Garrè's osteomyelitis is a rare inflammatory disease of chronic nature [1]. It is also known as Garrè's sclerosing osteomyelitis, chronic osteomyelitis with proliferative periostitis, ossifying periostitis or nonsuppurative chronic sclerosing osteomyelitis [1].

It mainly affects the jaw, but in rare cases, the metaphysis of long bones can be affected [1]. Young children and adults are the most affected among population, and it is commonly seen in men aged below 30 years [1, 2].

Clinically it is characterized by insidious onset, localized pain with episodic and nonprogressive nature. When the mandible is the affected area, swelling of the cheek with facial asymmetry and trismus, without suppuration or sequestra formation is seen [1–3]. However, it has sometimes been described a fistula extending from the affected tooth to the buccal mucosa, detected on CT scan [2]. The size of the bone lesion can go from a few centimeters to the whole length of the mandible, and can expand as much as 2 cm laterally [6]. Pain is not a characteristic finding, although severe pain can occur if the lesion is secondarily infected. Other possible symptoms include lymphadenopathy and mild fever [2, 6].

The aetiology is still unclear, but some authors believe it is related to a microbial stimulus, even though cultures are generally negative. In this hypothetical model, chronicity would be preceded by an acute infection with phlogistic signs, maintained by a low-virulence infection, and then extended after the infection has been treated [1, 7]. Others authors have introduced chronic periostitis as an additional possible contributing factor, because it usually occurs in the mandibular body of children and adolescent patients who have higher periosteal osteoblastic activity [2, 3].

Radiographic manifestations are dependent on the injury's duration and the progression of ossification. During the early period, a thin crust-like-convex layer appears over the cortex and a combination of sclerotic areas and cystic areas could be observed in the region of the lesions. During exacerbations, as the event continues, the cortex is thickened and loss of medullary canal occurs. As a result of successive new bone deposits, an "onion skin" appearance can be detected, characterized by the presence of lamellae of newly formed subperiosteal bone overlying the cortex [1–3, 7].

Panoramic radiographs and CT-scans show areas of sclerosis, occasionally osteolysis and periosteal bone formation, widening of the lamina dura, and the diffuse border of the mandibular canal. Technetium-scans (Tc-scans) show increased uptake in the lesion's area due to increased bone turnover [2, 3, 7].

Laboratory blood tests may show increase in acute-phase inflammatory markers such as CRP and ESR, as well as leukocytosis, but this increase is not marked [1].

Clinical history, combined with conventional radiography or CT imaging, typically suffices to establish the

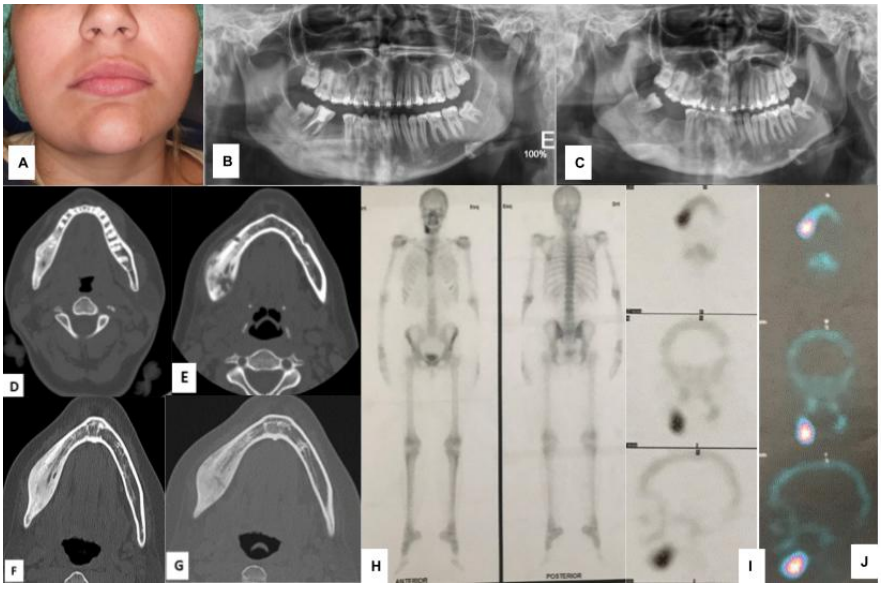


**Figure 1.** A - Right mandible region swelled. B and C - Orthopantomography before and after second molar extraction. D and E - Jaw Computer Tomography revealing exuberant periosteal reaction with progressive ossification of the right mandibular body. F and G - Jaw Computer Tomography revealing a layered bone sclerosis, resulting in a double contour of the mandible and facial asymmetry. H, I and J - Whole-body bone scintigraphy with head SPECT/CT showed focal hyperfixation in the right jaw.

diagnosis [2, 3]. In atypical cases with a negative history of chronic abscesses, deep carious lesions or trauma to the area, bone biopsies are recommended to rule out several disease entities. Biopsy shows chronic, nonspecific osteomyelitis, and both blood and tissue cultures are generally negative [2]. The numerous clinical symptoms and lack of laboratory abnormalities make diagnosis and assessment of disease activity challenging. A sensitive or specific biomarker is not currently available [5].

The main histological characteristic of Garrè's osteo myelitis is the new bone formation, or osteoid tissue, with bordering osteoblasts and some areas of bone resorption. Lymphocytes are commonly seen in marrow spaces. All histologic examinations revealed young reactive bone formation, arranged as trabeculae of lamellated bone separated by connective tissue. All findings included the presence of diffuse chronic inflammation with infiltration of lymphocytes and plasma cells. Authors agree that the reaction is destructive in the early stage when osteoporosis can be observed in the adjacent medullary bone. However, as the layers of new bone arrange themselves around the lesion, the lytic lesions become more sclerotic [6].

A multifocal sclerosing bone reaction with clinical, radiological and histological characteristics similar to Garrè's osteomyelitis may be encountered in several other diseases, which make a differential diagnosis with Garrè Osteomyelitis. In order to reach a definitive diagnosis, it is essential to take a careful clinical history, carry out blood tests and imaging exams such as X-rays and CT scans.

The goal of Garrè's osteomyelitis treatment is symptom relief and the most appropriate treatment for this chronic condition remains unclear [1]. Treatment modalities reported so far are presented in Table 2 and include antimicrobial therapy; glucocorticoids; analgesic medication; non-steroidal anti-inflammatory drugs (NSAIDs); muscle relaxants; conservative therapy with occlusal splint, physiotherapy to stabilize the muscles and the temporomandibular joint; hyperbaric oxygen therapy; antiresorptive medications (bisphosphonates and denosumab), targeted biologic therapy or surgical resection [1, 5].

**Table 1.** Characteristics of jaw Garrè's osteomyelitis main differential diagnosis

| Garrè's osteomyelitis | Main differential diagnosis |
|---|---|
| Affects young children and adults below 30 years. Usually it is unifocal and unilateral. Characteristic "onion skin" appearance in X-rays, with new bone formation arranged as trabeculae of lamellated bone. | Fibrous dysplasia: affects young patients, shows a "ground glass appearance", thickening of the inner bone and thinning of the cortex in radiologic exams. Not related to dental infections. Osteosarcoma: mostly affects males between 10 and 25 years. It is a sclerosing form, with a sun-rays appearance on X-rays. |

The most promising results seem to originate from conservative treatment options, even if the studies have low quality and include a limited number of patients [8]. The most commonly accepted treatment is the administration of antibiotics and the extraction of the infected tooth. Some patients respond to analgesics while others respond to antibiotics, although the exact mechanism remains unclear [1].

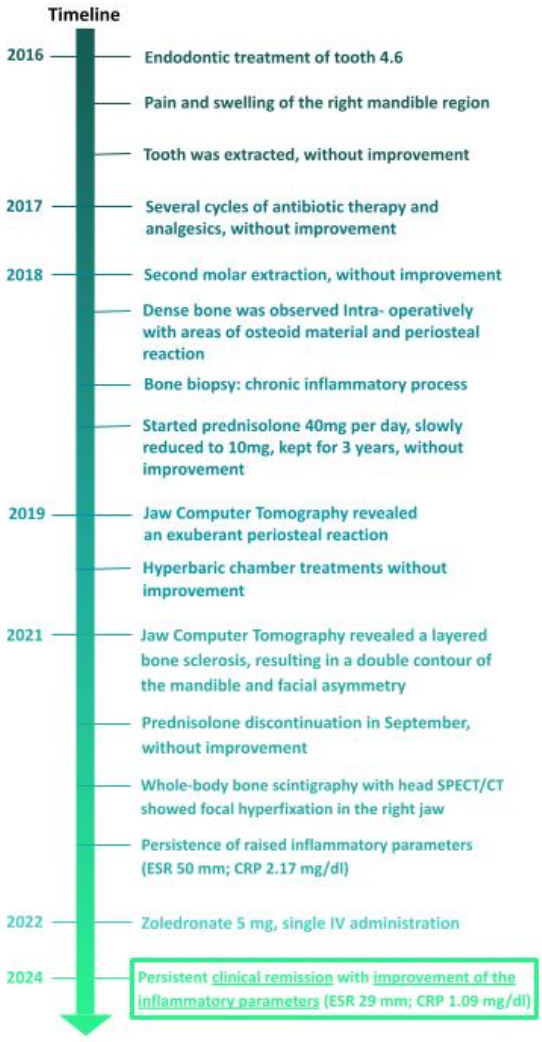


**Figure 2.** Chronological progress chart with the main clinical features of the patient.

## 4. Conclusion

Garrè's osteomyelitis has a favourable prognostic [4]. With the removal of the etiologic factor, a regression of the lesion with subsequent bone remodeling in six to eight months is expected [4, 6]. Chronic osteomyelitis presents low mortality but high morbidity [7]. The collaboration between stomatologists and rheumatologists for assistance with medical management should be encouraged to improve outcomes and to allow for continued study and overall improvement in the management of this difficult disease [5].

We have presented a report of a patient with Garrè's Osteomyelitis, refractory to conventional treatments and symptomatic over the previous five years, who was effectively treated with zoledronic acid. The use of bisphosphonates, particularly zoledronic acid, should be considered for refractory cases of Garrè's Osteomyelitis.

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**Data Availability Statement:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Table 2.** Therapeutic options for the management of Garrè's osteomyelitis

| Therapeutic strategy | Purpose |
|---|---|
| Antibiotic therapy | First option. Garrè's osteomyelitis is usually related to the manipulation of a tooth. It rules out an infectious cause. Some patients respond to antibiotics, but the exact mechanism is unclear. |
| Extraction of the infected tooth | Aims to control the inflammatory process. After the teeth extraction, the regression of the lesion with subsequent bone remodeling occurs in 6 to 8 months. |
| Analgesic medication | Aims to control the pain. Some patients respond to analgesics, but the exact mechanism is unclear. |
| Non-steroidal anti-inflammatory drugs (NSAIDs) | Aims to control the pain and swollen tissues. Some patients may respond. |
| Glucocorticoids | Some patients may benefit from corticosteroids, with a temporary improvement, for pain and swollen control. |
| Occlusal splint and physiotherapy | Aims to stabilize the muscles and the temporomandibular joint. |
| Hyperbaric oxygen therapy | Aims to improve blood supply and allow antibiotics and analgesics to penetrate more effectively into the tissues. |
| Antiresorptive medications | Bisphosphonates (pamidronate or zoledronate) and Denosumab: inhibit bone resorption, bone turnover and renewal through inhibition of the osteoclasts. Usually given once. |
| Targeted biologic therapy | Anti-Tumour necrosis factor (TNF) therapy, as infliximab, with the aim of curbing the local inflammatory process. |
| Surgical resection | If the symptoms are uncontrollable. Fenestration and curettage of the affected site is firstly used, if it doesn't work a bone resection can be done. |

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