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Case Report

Chronic secondary orofacial pain as the first symptom of chronic non-bacterial osteomyelitis in the mandible: a case report and literature review

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Abstract: Chronic non-bacterial osteomyelitis clinically manifests with pain, swelling and limitation of movement. When it affects the jaw, it can cause pain, similar to other orofacial conditions, requiring a correct differential diagnosis. The objective of this study was to report a clinical case of chronic secondary orofacial pain as the first manifestation of an inflammatory bone disease located in the mandible, in addition to discussing the diagnostic hypotheses, the pathophysiological aspects and the therapy. A 21-year-old male patient came to the service complaining of pain in the mandible, preauricular and temporal regions bilaterally with one year of evolution, associated with anterior open bite and psychological impairment. So, it was chronic orofacial pain secondary to non-bacterial osteomyelitis with a high rate of bone remodeling. Elevation of pro-inflammatory cytokines can lead to an increased power cycle of nociceptive signaling, chronic inflammation, and bone loss. Pro-inflammatory cytokines that originate in neuronal and glial cells can trigger effects such as chronic hyperexcitability, changes in the phenotypic expression of nociceptors and abnormal processing of noxious signals. The patient is still undergoing treatment and without pain. Careful assessment, ordering tests and multidisciplinary investigation are essential in the care of patients with chronic and complex orofacial pain.

Keywords: Osteomyelitis; Inflammation; Facial pain.

1. Introduction

Diagnosis is an essential part of the dentist's activity. Despite the systematic evaluation, which includes a detailed medical history, and a proper physical examination, imaging and laboratory tests should be used to help in the diagnosis, always at the clinical judgment [1]. Considering the complexity involved in the diagnosis of pain, the International Association for the Study of Pain (IASP) suggests a classification of chronic pain, in which pain can be considered the disease itself or a secondary symptom of an underlying condition [2]. Chronic orofacial pain comprises a diverse group of extraoral and intraoral painful manifestations, which can include dental, muscular, and joint pain (involving the temporomandibular joint), as well as neuralgias and post-traumatic neuropathies. In ad-

dition to the potential negative impact on patients' quality of life, these conditions are often associated with other comorbidities, such as primary headaches, fibromyalgia, neck pain, and other conditions [3-5].

An inflammatory bone condition that can involve the jaw and typically presents as pain and swelling is osteomyelitis, which can be either primary (non-infectious) or secondary (infectious). Several clinical aspects differentiate these conditions, but a biopsy with microbiological culture examination is essential for determining the type. Chronic non-bacterial osteomyelitis (CNO) may have a cyclic nature, requiring long-term data collection to identify disease patterns and treatment response, given its high recurrence rate [6]. It is a non-infectious autoinflammatory bone disease that can be part of a syndrome or constitute an isolated pathological entity. It primarily affects children and adolescents and is characterized by a clinical spectrum of monofocal or multifocal bone inflammation that can be self-limited and mild or chronic and recurrent [7].

It is considered rare and is typically associated with periods of exacerbation, with clinical resolution that can last for years. It mainly affects the sternum, clavicle, ribs, spine, pelvis, and peripheral long bones, but craniofacial involvement is not uncommon, affecting the jaw in up to one-fifth of cases [8]. It is worth noting that this is an exclusion diagnosis, established by clinical presentation, imaging studies, and negative bone biopsy culture [8, 7]. Therefore, the dentist should be familiar with the possible manifestations of these conditions and be able to differentiate them from other types of orofacial pain, as they may present with features similar to more prevalent orofacial conditions. Thus, the aim of this clinical case report was to present the case of a patient with chronic orofacial pain secondary to a non-bacterial chronic osteomyelitis of the mandible. The patient authorized the writing and publication of the case through the signing of an informed consent form (ICF).

2. Case Report

A 21-year-old male patient with fair skin color attended to the Orofacial Pain Ambulatory at Clinics Hospital of the School of Medicine at the University of São Paulo (HCFMUSP) in March 2021, complaining of pain in the bilateral mandibular and pre-auricular region with a duration of one year and two months. The patient reported daily, and constant pain rated at 8 out of 10 on the visual analog scale, and during flare-ups, it reached a level of 10. The pain was described as pressure, throbbing and mainly 'inflamed,' and it was worse during the nighttime. The pain was reported to be spontaneous, with no identified triggering factors. As aggravating factors, the patient re-ported talking, poor sleep, stress, and consumption of tough foods. There were also reports of intermittent swelling in the jaw area. As factors that improved the condition, the patient mainly identified the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Previous unsuccessful treatments included the use of an occlusal splint, laser therapy sessions, and the use of carbamazepine and gabapentin due to a previous diagnosis of trigeminal neuralgia. The patient reported significant financial losses due to job loss shortly after the onset of the painful condition. He also mentioned discontinuing physical activities, resulting in a six-kilogram weight loss over the past year, as well as isolating from his social circle. Additionally, there was a deterioration in sleep quality and a severe impact on the quality of life. He also reported a change in his bite over the past two years, as well as feeling a tired face upon waking up and self-perception of teeth clenching during sleep.

The extraoral physical examination showed facial symmetry, facial skin with a high degree of acnes and mouth opening of 45 mm. In the physical examination, palpation of the temporomandibular joint (TMJ) and muscles caused hyperalgesia but did not reproduce the patient's complaint. Dental patient in both upper and lower arches, with no pain upon vertical and/or horizontal dental percussion during intraoral physical examination,

anterior open bite, and intact and normally colored oral mucosa (Figure 1). The requested panoramic radiograph showed normal findings (Figure 2).

Figure 1. Intraoral assessment (anterior open bite).

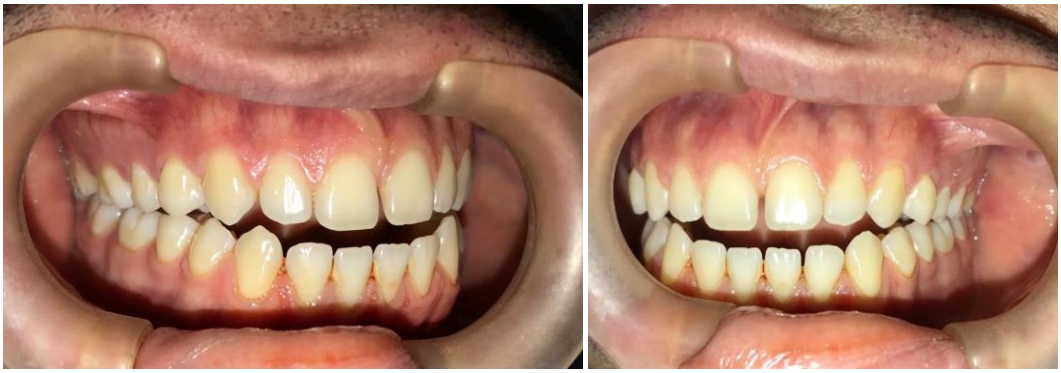
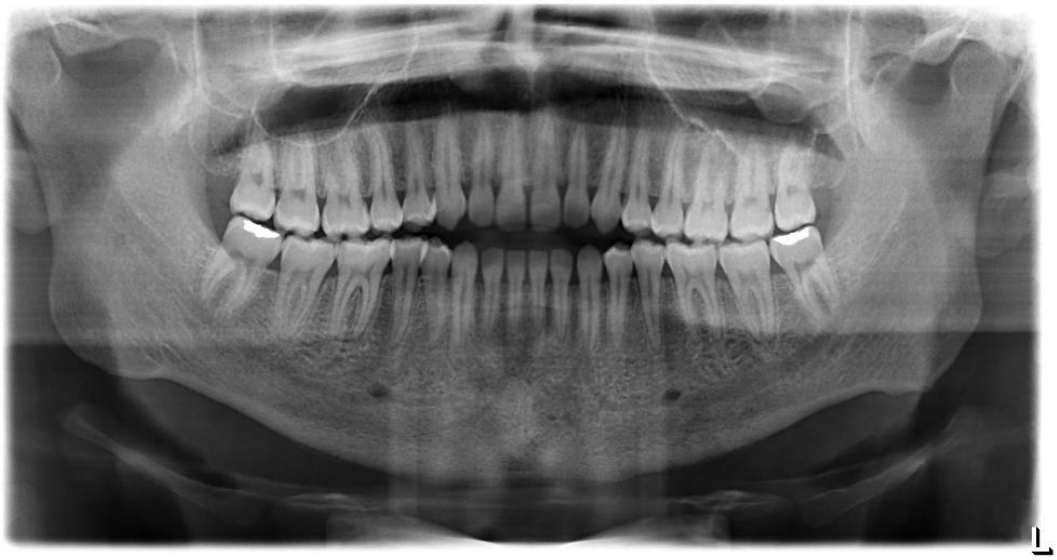


Figure 2. Panoramic radiograph.



Due to the reported of open bite over the last two years, a bone scintigraphy was requested due to the initial diagnostic hypothesis of a non-specific chronic inflammatory condition in the mandible as a possible cause of the occlusal alteration. The bone scintigraphy showed symmetrical radioisotope uptake in typical TMJ projections, indicating normality of the TMJ bone structures. However, a diffuse and moderate concentration of the radioisotope was observed in the mandible, suggestive of diffuse bone remodeling, particularly noticeable bilaterally in the mental and mandibular body regions, with slight asymmetrical uptake, more pronounced on the left side (Figure 3). In the evaluation of the facial CT scan, diffuse bone marrow sclerosis was observed in the anterior and body regions of the mandible in axial sections, along with mild thickening of the bone cortex (Figure 4).

In the evaluation of Magnetic Resonance Imaging (MRI) of the mandible, heterogeneous signal alterations in the bone marrow were observed, affecting the chin, mandibular bodies, angles, and lower portions of the mandibular branches bilaterally and symmetrically. These alterations were characterized by hyperintensity on T2, hypointensity on T1, and with heterogeneous enhancement following contrast administration, without signs of significant inflammatory changes or collections in the regional myoadipose planes. These findings led us to conclude that they were nonspecific but likely of a chronic inflammatory

nature. Additionally, the MRI showed enlarged lymph nodes in the superficial lateral cervical chains, with preserved morphology, likely reactive (Figure 5).

Figure 3. Bone scintigraphy showing changes in the mandible.

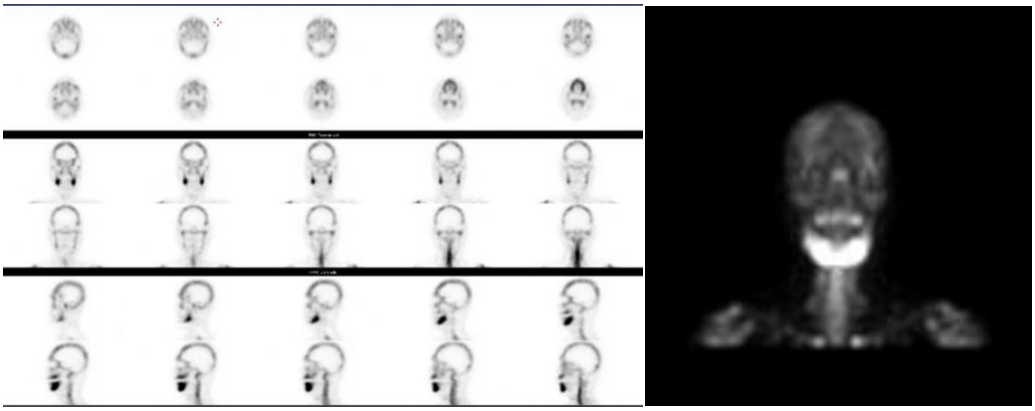


Figure 4. Axial sections of face CT scan showing mandibular bone changes.

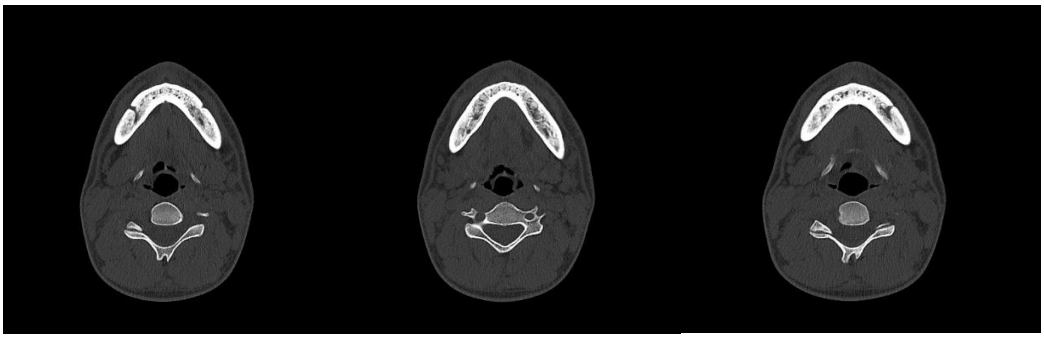
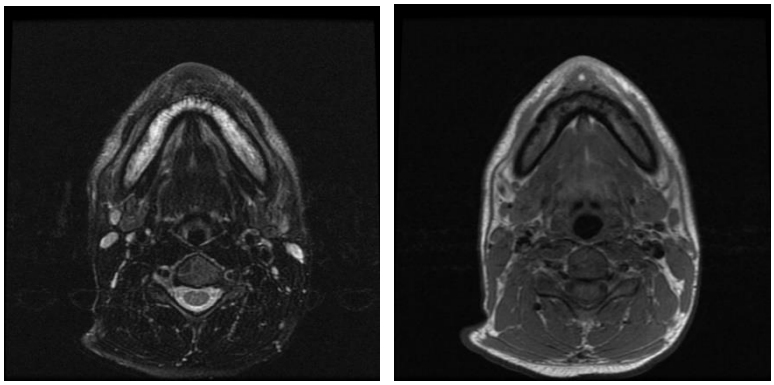


Figure 5. Hyperintensity on T2 and hypointensity on T1 in the MRI of the mandible.



The patient then underwent an incisional biopsy in the mandibular symphysis region under local anesthesia, and two bone fragments, each approximately 4-5 mm in size, were sent to the histopathology laboratory at HCFMUSP to investigate the initial diagnostic hypothesis established with the oral and maxillofacial team of non-bacterial chronic osteomyelitis of the mandible (Figure 6). The anatomopathological result of the obtained bone fragments indicated the presence of bone tissue with prominent ossification lines, without osteoclastic/osteoblastic activity. Additionally, the result of the aerobic culture found coagulase-negative Staphylococcus and Streptococcus sanguis, while the anaerobic culture was negative.

At this point, the Rheumatology team at HCFMUSP became involved in the case and opted to perform hematological tests, which showed values of N-terminal propeptide of type 1 procollagen and C-terminal telopeptide of type 1 collagen above the reference values (Table 1), suggestive of intense bone remodeling. Subsequently, to assess possible multifocal involvement, a sacroiliac MRI was performed, which revealed no abnormalities (sacroiliitis). Thus, the diagnostic hypothesis of chronic non-bacterial osteomyelitis (CNO) of the mandible was indeed established.

Figure 6. Surgical site and bone fragments obtained.

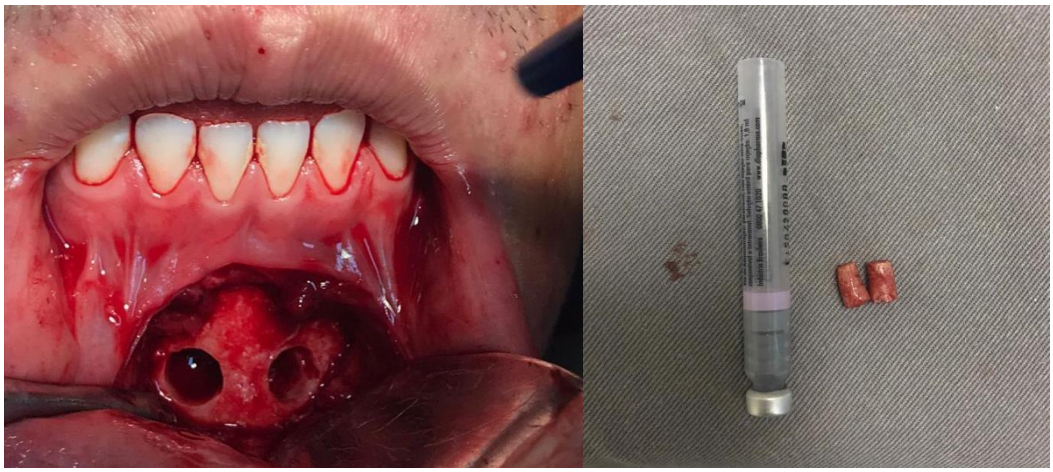


Table 1. C-terminal telopeptide of type 1 collagen and N-terminal propeptide of type 1 procollagen values.

	Result	**Reference values**
C-terminal telopeptide of type 1 collagen (CTX)	1,17 nanograms per milliliter	0,22-1,02 nanograms per milliliter
N-terminal propeptide of type 1 procollagen (P1NP)	91,23 nanograms per milliliter	27,2 – 87 nanograms per milliliter

Subsequently, in September 2021, the rheumatology service at HCFMUSP opted for the prescription of one intramuscular injection of betamethasone and continuous use of Celecoxib 200 mg every 12 hours. In follow-up assessments after three and five months, in December 2021 and February 2022, respectively, the patient reported an absence of pain, enabling his return to a new job, resumption of social relationships, and weight gain. Due to the return of painful symptoms in December 2022, methotrexate was added to the treatment, which had been used in conjunction with celecoxib up until the last assessment at the end of 2023, resulting in the current absence of painful symptoms. The patient continues treatment with the rheumatology and dentistry team at HCFMUSP.

3. Discussion and conclusions

According to the IASP, chronic orofacial pain is defined as pain that occurs for more than two hours per day on at least 50% of days for at least three months. Therefore, the case in question falls under the subgroup "Chronic secondary orofacial pain," as the patient's pain constitutes a manifestation of chronic orofacial pain secondary to an inflammatory bone disease localized in the mandible [2]. Siqueira et al. established diagnostic criteria by characterizing pain, which aids in the differential diagnosis of some orofacial pains, neuropathic, and nociceptive. Among them, pulpitis, pericementitis, alveolitis, and muscular myalgia stand out as pains that patients may characterize as throbbing and stabbing. These conditions have different etiologies but commonly involve the inflamma-tory

process and tend to show symptom reduction with the use of NSAIDs [1], as men-tioned by the patient in question during the anamnesis. Therefore, it can be stated that orofacial pains with inflammatory characteristics may manifest similarly in terms of characterization, given the common pathophysiology. So, the diagnostic process can be prolonged and complex, this is why it must be standardized and comprehensive, given that the etiological possibilities are diverse.

Osteomyelitis can be present in all bones, most commonly in children in the metaphyses and epiphyses of long bones, pelvic bones, shoulder girdle, and spine. Clinical signs of bone inflammation include heat and/or swelling and intense pain, which may manifest most severely and recurrently at night, as reported by the patient in the present case. X-rays typically show osteolytic lesions surrounded by sclerosis in later stages of the disease. The presentation of this condition in the mandible primarily occurs in adolescents and adults, but most studies involving such conditions are conducted in children [9-11]. It is worth noting that during the CT scan phase of the present clinical case, in June 2021, the patient was one year and six months into the onset of the painful condition, leading us to infer that the predominant aspect of sclerosis observed in the facial CT corresponds to the later stage of the disease due to the time elapsed since the onset of symptoms.

According to the literature, the prevalence of CNO varies, and the most recent estimates indicate 1-2 cases per million [12]. Pain is the most prominent and frequent characteristic, however, both increasing and decreasing complaints are typical. Due to the nonspecific clinical presentations, the diagnosis can be considerably delayed [6]. The cyclic course of CNO requires long-term data collection to identify disease patterns and treatment response, as the reported recurrence rate can vary from 16 to 83%. It is also considered a chronic disease that often shows favorable treatment outcomes in the first year, but with high rates of recurrence in long-term follow-up [13]. This corroborates the present findings since the patient managed the painful condition with celecoxib for over a year. However, there was a return of painful symptoms in December 2022, prompting the rheumatology team to introduce methotrexate. This underscores the importance of fol-low-up due to the high recurrence rate of the disease.

It is observed that in CNO of the mandible, there may be pain, swelling, local hardening, and limited mouth opening during active periods of the disease, as well as possible regional lymphadenopathy. In the clinical case in question, the patient reported intense pain and episodes of mandibular swelling, and in the jaw MRI, reactive cervical lymph nodes were observed. Overall, the predominant radiographic alteration was medullary sclerosis, a pattern invariably observed in affected patients, as was evident in the facial CT scan. Bone scintigraphy also demonstrates significant uptake restricted to the affected re-gion [14], this is consistent with the findings of the present case, where the initial bone scintigraphy showed changes restricted to the mandible.

The laboratory tests CTX and P1NP are reference biomarkers related to bone resorption. When these values are above the reference range, as in the present case, they indicate an exacerbated process of bone resorption/formation, which was consistent with other findings related to the mandible observed in complementary exams such as scintigraphy, MRI, and CT [15]. Then, all these findings contributed to the diagnosis process of CNO.

Substantial evidence indicates that the imbalanced expression of immunoregulatory cytokines (IL-10 and IL-19) and pro-inflammatory cytokines (IL-1β, IL-6, TNFα, IL-20) leads to bone inflammation in CNO [16-19]. Furthermore, it is worth noting that IL-1β and other inflammatory mediators are also known to play important roles in neuronal pain perception. For example, IL-1β hypersensitizes peripheral nociceptors, causing a reduction in their threshold [20]. In autoinflammatory diseases like CNO, unlike the clearer inflammatory components, the neural components underlying pain still represent an open field of study. Considerable evidence indicates that numerous immune pathways mediated by glia (astrocytes and microglia), immune cells, pro-inflammatory cytokines, and chemokines alter neuronal communication leading to chronic pain [21]. Therefore, the

known inflammatory pathways involved in the pathophysiology of the disease explain the intense inflammatory-type pain reported by the patient. Additionally, according to the literature, the effects of these pro-inflammatory mediators on neuronal pain perception, combined with the role of glia-mediated immune pathways, appear to contribute to the development of chronic pain in these cases.

Monsour et al. [8] reported four cases of multifocal CNO with primary manifestation in the mandible, with subsequent identification of asymptomatic lesions in other bones, such as the acetabulum and metatarsals of the feet [8]. Therefore, it is essential to screen for other lesions and provide long-term follow-up. In our case, despite the medical investigation conducted, no other sites of involvement were identified, characterizing a unifocal CNO.

Some studies indicate that involvement of the mandible in CNO is rare. However, the likely underdiagnosis of this condition and the various other terminologies used to refer to the same condition hinder the acquisition of epidemiological data regarding jaw involve-ment. The population with mandibular involvement of CNO is typically adult, reporting pain, swelling, and consequently, loss of jaw mobility [22]. Additionally, lesions in the mandible are more frequently unifocal as opposed to the multifocal variant [23].

Especially in cases of single bone lesions, performing a biopsy is necessary to confirm the diagnosis and exclude any possibility of bacterial osteomyelitis or malignant diseases. Mixed anaerobic infections are common in infectious or secondary osteomyelitis, especially in skull infections, ranging from 33% to 93% of cases, with a higher prevalence of anaerobes than aerobes. In CNO, however, bone lesions, by definition, yield negative cultures [7]. In the present clinical case, the culture for anaerobes, which are more prevalent in infectious osteomyelitis, was negative. However, the culture for aerobes demonstrated coagulase-negative Staphylococcus and Streptococcus sanguis, common bacteria found in the oral microbiota. These bacteria can reach bone tissues through transient bacteremia, often occurring after surgical procedures or trauma, such as the bone biopsy itself [24].

Regarding the treatment of CNO, acute, recurrent, and chronic bone pain is primarily alleviated with NSAIDs and opioids [25]. Intense bone pain in patients affected by active CNO needs to be treated, as it worsens quality of life and can lead to bone deformities. NSAIDs are essentially the first-line treatment, with 80% of patients responding well. However, NSAIDs appear to be more effective in patients with limited disease (or unifocal) compared to individuals with multifocal CNO [12]. In clinical practice, NSAIDs are gen-erally used as first-line agents in patients without spinal involvement [26], As in the case in question, where NSAIDs were used as the first choice, achieving complete regression of the painful condition for over a year.

Patients who present with early structural damage, such as bone fractures, and fail to respond to treatments with NSAIDs and oral corticosteroids, should be treated more ag-gressively. Possible options include sulfasalazine, methotrexate, anti-TNF agents, anti-IL-1 agents, and bisphosphonates. Sulfasalazine and methotrexate are pharmacological agents that mediate the reduction of pro-inflammatory cytokine expression, potentially correcting the imbalance between pro- and anti-inflammatory signals in CNO [27]. There are also TNF antagonist agents, which specifically block TNF-α, restoring the balance between this pro-inflammatory cytokine and immunomodulatory cytokines [28]. In the present case, due to the return of painful symptoms after more than a year of control with NSAIDs, methotrexate was added to the therapy, achieving again complete regression of the painful condition.

Wang et al. [9] reported cases of three patients with CNO of the mandible where erroneous previous diagnoses led to partial mandibulectomy in one case and mandibular curettage in another, without therapeutic efficacy [9]. Another case report of CNO of the mandible involves a 14-year-old girl who was unsuccessfully treated with antibiotics for two years and underwent mandibular surgery. She only experienced symptom improvement after receiving the correct diagnosis and treatment with intravenous bisphosphonates [10]. Thus, the diagnostic challenge of these pathological conditions is emphasized,

which can lead to unnecessary, ineffective, and mutilating surgical treatments, underscoring the importance of correct initial differential diagnosis.

Regarding unnecessary treatments performed due to incorrect or delayed diagnosis of CNO, in the present case, the patient was initially subjected to continuous pharmacological therapy with carbamazepine and gabapentin, due to a diagnostic hypothesis of trigeminal neuralgia. Additionally, dental wear was performed on the third molars. Accurate diagnosis is essential because when erroneous, it results in irreversible and unnecessary procedures. For this reason, diagnosing patients with complaints of pain requires standardized evaluation. The complaint and details about the pain must be understood and organized to guide the diagnosis. This, coupled with multidisciplinary investigation involving oral pathology and rheumatology services, led us to the diagnosis of an autoinflammatory disease with a high rate of local bone remodeling.

The present clinical case was of utmost pedagogical value for the involved teams, particularly due to the rarity of the condition and the intricacies of the diagnostic process. It is important to emphasize, especially for dentists, that patient complaints should be taken into consideration even when initially there are no apparent symptoms or physical examination findings indicative of caries or temporomandibular disorder, for instance. In this case, the degree of patient distress coupled with the report of intense pain with an inflammatory characteristic and its coincidence with the onset of open bite were pivotal in hypothesizing a non-specific inflammatory mandibular condition. Thus, all details obtained during the anamnesis hold diagnostic significance.

Thus, we emphasize the importance of continued education for dentists, particularly regarding the diagnosis and treatment of patients with chronic orofacial pain, an area where it is necessary to understand and think beyond the confines of the stomatognathic system. Furthermore, more research is needed, especially longitudinal studies and clinical trials involving the diagnosis, treatment, and prognosis of mandibular CNO.

Despite the difficulty of obtaining anamnesis in patients with chronic pain, it is always necessary to value their complaints. As for the dentist, it is their primary task to investigate the possible causes of orofacial pain, even if unlikely or rare, or to make the appropriate referral. Thorough evaluation with detailed complaints, requesting complementary exams, and multidisciplinary investigation are essential in managing patients with chronic and complex orofacial pain. Thus, the differential diagnoses and consequent proposed treatments will be more effective and better directed.

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Conflicts of Interest: None.

Supplementary Materials: None.

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