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CASE REPORT

Pharmacological Treatment of Primary Chronic Osteomyelitis: A Case Report

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Abstract:

Introduction: Chronic primary osteomyelitis (CPO) is a rare disease, defined as a chronic inflammatory process involving cortical and medullary bone. In the maxillofacial region, it mainly affects the mandible, with a predilection for females in a wide age range, with unknown etiology or defined treatment protocol. **Objective:** The objective of this article is to report a case of the rare disease Chronic Primary Osteomyelitis, focusing on its clinical, radiographic, and histopathological characteristics, and to discuss the nomenclature for differential diagnosis while comparing with other osteomyelitis. **Case Report:** MLP patient, 53 years old, female, leukoderma, was admitted at the Maxillofacial Surgery and Traumatology Service of the University Hospital of USP referred from another service and reported of severe pain and swelling in the face for approximately 1 .5 year. On clinical examination, he presented edema 1+/4+ in the lower third of the right hemiface, sensitive to palpation, trismus, lower lip paresthesia, no evidence of infectious odontogenic focus, increased volume or intraoral secretion. The patient was submitted to an incisional biopsy, computed tomography and scintigraphy, which showed an sclerotic pattern and increased uptake in the mandible, respectively. After months of antibiotic therapy with no results, the patient was initially submitted to 20mg of Prednisone with regression up to 5mg and two doses of 60mg of Pamidronate which resulted in remission of pain, edema and trismus. Until the publication of this article, the patient had no recurrence of the symptoms, totalizing 6 years of follow up. **Conclusion:** CPO is a rare and challenging diagnosis disease. Prednisone was effective to edema and trismus decreasement and Pamidronate for pain control, however more studies are necessary to determine a definitive treatment for this condition.

Keywords: Osteomyelitis; Pamidronate; Treatment Outcome.

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INTRODUCTION

Osteomyelitis is defined as an inflammatory process involving cortical and cancellous bone. A variety of classifications have been proposed based on different aspects, such as clinical evolution, histological findings and/or radiological characteristics, etiology and pathogenesis[1]. Acute osteomyelitis differs from chronic osteomyelitis by the arbitrary time limit of 4 weeks after the onset of clinical symptoms[1,2,3]. Chronic infectious osteomyelitis may show a suppurative course with abscess formation, fistula and sequestration[1,2,3]. In some cases, however, osteomyelitis can appear as a chronic inflammation of the jaw with no underlying cause[1,3]. The first type is classified as secondary secondary osteomyelitis, while the second was defined as primary chronic osteomyelitis[1,3].

The literature is vast in reports using the term "sclerosing osteomyelitis" as a synonym for primary chronic osteomyelitis (PCO), referring to the same nosological entity[1,2]. However, this term represents a description of a strictly radiographic aspect and can be found in several processes, including primary or secondary chronic osteomyelitis, chronic periostitis and ossificans or Garré's periostitis[1,2,3].

Eyrich et al proposed a classification for an osteomyelitis of the jaw, mainly based on the clinical appearance and course of the disease, as well as radiological characteristics. This classification distinguishes three main groups of osteomyelitis: acute osteomyelitis, secondary chronic osteomyelitis (SCO) and primary chronic osteomyelitis (PCO)[3].

Such variation in terms of classification has led to confusion and difficulties in comparative studies[1,3].

The etiology of PCO is unknown, but the possible causes are: infection, vascular deficiency (localized endoarteritis), autoimmune disease, genetics and muscle hyperfunction[1,2,3,4].

Due to the rarity of the pathology, difficulty in classifying it and of unknown etiology, the treatment of this disease is challenging and does not have an established treatment[1,3,4,5,6,8].

Several treatment methods have been described, from invasive methods such as segmental resections of the manxillomandibular complex to exclusively pharmacological approaches[3,7,9].

Among the approaches, decortication is the most mentioned method in the treatment for OCP[9].

Aggressive surgical approaches are contraindicated for young patients, given the considerable incidence of this pathology in this group[9].

Antibiotic therapy is widely used as a treatment approach, and the main reason for it is not the success of its results, but the difficulty in diagnosing the disease and because the literature has not been strategically discarded due to the infectious fact[5,6].

The use of anti-inflammatories has varied results, and due to their association with the SAPHO syndrome, they are widely used[5,8].

The drug class with the best results are Bisphosphonates. the non-metabolizable anabolic of metabolic organic cells has an action on bone metabolism, with unscheduled osteo resorption[5,10,11,12,13].

Several classes of bisphosphonates have been used as treatment for PCO, since the non-nitrogenous 1st generation to the 3rd generation phosphonates that have their action potentiated, both showing satisfactory results[10,12].

Treatment modalities and their controversies will be better presented in the discussion of this article.

OBJECTIVE

The objective of this article is to report a case of the rare disease Chronic Primary Osteomyelitis, focusing on its clinical, radiographic, and histopathological characteristics, and to discuss the nomenclature for differential diagnosis while comparing with other osteomyelitis.

CASE REPORT

53-year-old female patient, leucoderma, was admitted at Maxillofacial Surgery and Traumatology Department of the University Hospital of USP relating severe pain and swelling in the face for approximately 1.5 years. According to the reported on anamnesis, she was submitted to a residual root extraction of the element 45 in 2012, and this procedure gave onset to severe pain in the region. Despite the endodontic retreatment of the canal and subsequent removal of the tooth 44, and endodontics of the tooth 47, the pain persisted. He used several medications (Amoxicillin, Levofloxacin, Ciprofloxacin, Clindamycin, Miosan, Dorflex, Tylex, Tandrilax, Dipyrone) with little or no effect. On clinical examination, he presented a 1+/4+ volume increase in the lower third of the right hemiface, sensitive to palpation, limited mouth opening, lower lip paresthesia, no evidence of infectious odontogenic focus, increased volume or intraoral secretion. Computed tomography was requested and revealed a mixed pattern of sclerosis

and osteolysis at body region and mandibular angle on the right side, with a periosteal reaction. (Figure 1) Clinical examination showed swelling 1+/4+ at the lower third of the right hemiface, flushing and associated heat, oral pain, limited mouth opening and paresthesia of the lower lip, absence of infectious teeth, swelling or purulent discharge on the intraoral aspect. Computed tomography was requested, which revealed a mixed pattern of sclerosis and osteolysis at the region of body and mandibular angle on the right side, with periosteal reaction. Laboratory tests (leucogram, ESR and CRP) were within normal standards. The patient was submitted an intraoral biopsy under general anesthesia, and the intraoperative appearance was of a slightly sclerotic bone close to normal, without sequestrums or other alterations. Histological analysis demonstrated chronic inflammatory reaction and growth of Streptococcus salivaris bacteria in the specimen culture. The diagnosis of OCP was established by the sum of the findings and Clindamycin 300mg/4x a day and Prednisone 20mg/1x a day orally were prescribed. The mitigation of signs and symptoms were observed after 11 days, at the follow-up consultation. The antibiotic was maintained to prevent infection secondary to the surgical approach and suspended after 2 weeks. After 30 days, corticoid weaning began. However, due to the recurrence of pain in the 3rd week with a daily dose of 5mg, a dosage of 10mg per day was adopted. It was maintened for 5 months and remission of symptoms was achieved. After another failure in the attempt to discontinue Prednisone, a new therapeutic scheme was adopted, using Pamidronate 60mg diluted in 500ml of saline solution administered under slow infusion. The next day, the patient returned to the service relating pain all over her body, which was a side effect of the new medication regimen. Oxycodone 20mg per day was prescribed, with pain remission within 24 hours. Corticosteroid therapy with Prednisone 10mg/day was maintained in association with bisphosphonates, with several unsuccessful attempts of anti-inflammatory suspension due the continuous reports of pain. A new infusion of Pamidronate with the same dosage was performed 6 months after the first dose (May/2015), and the corticoid was maintained at a dosage of 10mg with subsequent weaning 6 consecutive months (Nov/2015), which resulted in total regression of painful symptoms and the volume increseament of patient's mandibular body. The new computed tomography revealed an alteration of the previous pattern, demonstrating greater osteosclerosis and regression of the previously presented periosteal reaction (figures 2 and 3). In follow-up at this service until the moment, the patient relates the absence of any painful symptom and refers to have not used any medication in the last 6 years and 9 months (figure 4).

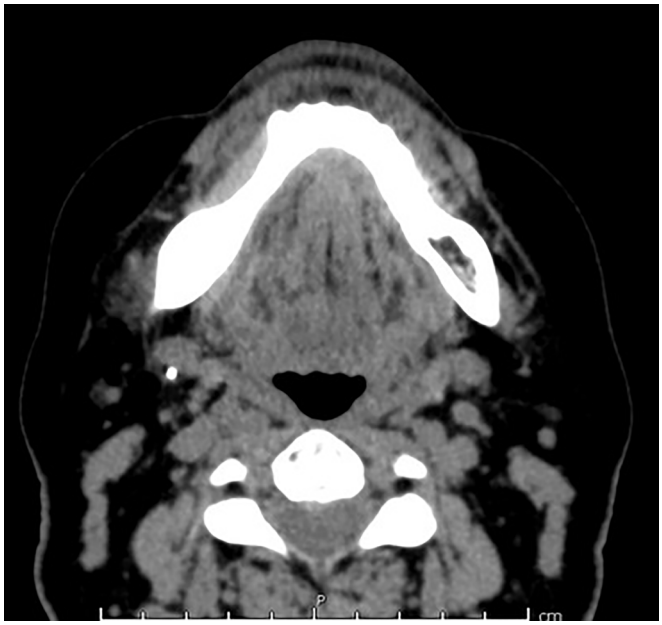

Figure 1. Computed tomography in its axial section demonstrating the sclerosis of the body of the mandible on the left side compared to the contralateral side, which presents a normal aspect of the tomographic density of the medullary bone.

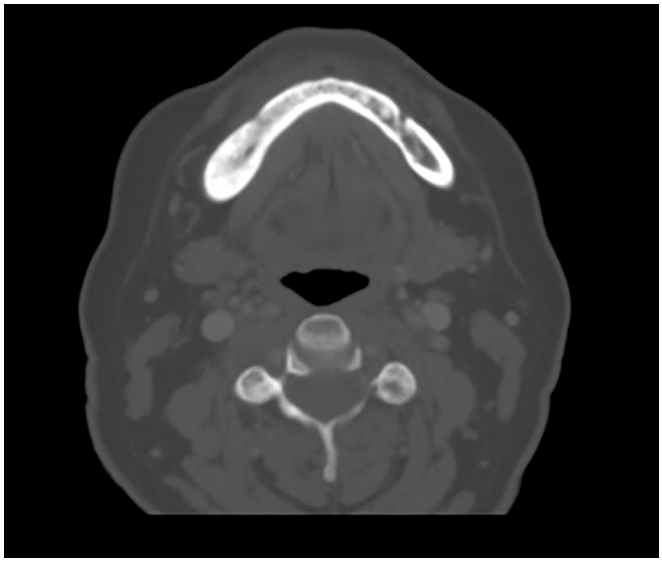

Figure 2. Computed tomography in its axial section 6 months after the second dose of pamidronate showing the maintenance of mandibular sclerosis, however the patient is asymptomatic.

DISCUSSION

The total remission of PCO have still not been reported, and the disease remains without definitive

Figure 3. Computed tomography in its coronal section 6 months after the second dose of pamidronate showing the maintenance of mandibular sclerosis affecting the region of the body and ramus, however the patient is asymptomatic.

Figure 4. Control panoramic x-ray after 05 years of treatment showing the sclerotic mandible body but with stability of the imaging parameters.

treatment protocol, making the management of PCO quite challenging[11]. Several strategies have been used, including conservative methods such as antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), corticoids, hyperbaric oxygen therapy, muscle relaxants and bisphosphonates, and surgical approaches (decortication, resection)[2,5,9].

Many retrospective studies and case series refer to surgery as a therapeutic option for this disease. However, the high rates of failure and recurrence, added to the great morbidity, lead surgeons to make this decision very cautelously[3].

Decortication is one of the most common surgical procedures used to treat osteomyelitis. Its advocates premise that the pathology may be related to the bone's altered or reduced blood supply, which may explain why the location is exclusively in the mandible versus the maxilla which has a much richer collateral blood supply. Furthermore, if the central blood supply (alveolar artery) is compromised, and if the pathology is deep in the bone marrow (as is often the case in other forms of osteomyelitis), then it would make sense to try to improve the marrow's blood supply. Decortication removes the cortical barrier between the rich blood supply of the periosteum and adjacent soft tissues, and the deeper medullary spaces, providing more irrigation to these sites. The "natural defenses" can then be delivered to medullary spaces altered by the disease[2,5,9].

Decortication and removal of necrotic tissue can be useful in the early stages of the disease[1,3]. However, due to the uncertain prognosis, excessive ablative surgery, such as resection, should be avoided, especially in young patients[1,3].

In a review study by M. M. Van de Meent et al, decortication of the affected mandibular side was reported in 27 articles, comprising 156 cases, and 54 of them had no description of the results. Out of 102 cases in the remaining 37 patients (36%) reported complete cure with no remaining symptoms[5].

Almost half of the 30 patients included in the study by Baltensperger et al were submitted to 2 to 6 major surgical procedures, with no demonstration of better outcome than patients who had only one surgical intervention, or those who received only conservative treatment[1].

Eyrich et al suggested that surgery must be carefully considered, as it results in relative or short-term success, recommending conservative treatment as the primary treatment strategy[3].

Several authors proposed conservative treatment with minimal surgical intervention, and emphasized the importance of frequent clinical/radiographic follow-up[5,9].

Additional therapeutic modalities, such as long-term antibiotics, hyperbaric oxygen therapy, NSAIDs and corticoids have been reported[1].

As the infectious etiology of PCO has not been ruled out, several patients were submitted to various modalities of antibiotic therapy with varied results[2,5,8].

In a literature review study, 94 patients were submitted to antibiotic therapy, and 43 of them experienced complete remission of symptoms after treatment. In this group, 25 patients were treated with a combination of surgery or hyperbaric oxygen, or both[5].

The use of NSAIDs and corticoids is also widespread as a treatment modality for PCO. In a study with 10 patients diagnosed with PCO, all of them were treated with anti-inflammatory drugs and only 1 had a response to the drug, while the rest of them showed a partial response[8].

In a review that included 94 patients who used NSAIDs or corticoids as a therapeutic modality, it was concluded that anti-inflammatory medication isolated showed a success rate of 2% and, when combined with other treatments, showed a higher success rate in 5% of cases[5].

Another pharmacological approach for the treatment of PCO is the bisphosphonates[5,7]. This class of drug showed better results compared to anti-inflammatory drugs and has been used for the past 17 years, with good results in controlling this condition and meeting the side effects reported in the treatment of suppurative osteomyelitis due to its prolonged use[5,12]. Bisphosphonates are organic pyrophosphate analogues that potentially inhibit osteoclastic bone resorption. Initially, these drugs have been widely used for the treatment of osteoporosis, Paget's disease, malignant hypercalcemia, bone metastases from solid tumors, and multiple myeloma[11,12]. Successful treatment of PCO with bisphosphonates was first reported in 2001 by Montonen et al, who infused disodium clodronate (300 to 900 mg) intravenously in 6 patients, with significant pain reduction 6 months after treatment[12]. However, the need for a second infusion of this medication and complementation with analgesics in almost all patients made their sample obtain an incomplete response[12,13].

Long-term effects cannot be estimated due to the short follow-up period. Yamazaki et al pointed out that doses should be low (30mg) and administered at a minimum interval of 3 months to avoid complications. They also highlighted the importance of long-term follow-up with bone scintigraphy. Such measures should be taken due to the risk of osteonecrosis of the mandible, reported in patients who received high doses of antineoplastic therapy and concomitant long-term intravenous bisphosphonate[13].

However, there is still no consensus regarding the therapeutic dose. In an observational clinical study that included 43 patients who underwent an infusion of 60mg of Pamidronate for 3 consecutive days, it was concluded that the treatment is effective and safe, and the patients evolved with reduced edema, pain and trismus. Among the 43 treated patients, only 2 cases repeated the cycle and another 4 cases presented recurrence of symptoms within the contemplated period, no side effects were reported, but is important to hightlight that the follow up lasted 18 months[14].

Alexander Just et al in their case report study reported that the use of Pamidronate 60mg, either in a single or multiple doses, at minimum intervals of 4 months, was more nephrotoxic and 3x less effective than Zoledronic acid in a 4mg dosage, which was the drug used in their case, with complete remission of the symptoms of clavicular OCP associated with SAPHO Syndrome[15]. Very high success rates have been reported, as observed in a review study of cases treated with bisphosphonates, 94% showed improvement, of which half had remission of symptoms, which means that only 6% showed no response[5].

Among the currently available bisphosphonates, pamidronate and alendronate are nitrogenous compounds that quickly relieved pain, in contrast to clodronate, a non-nitrogenous bisphosphonate with a late onset effect. The anti-resorptive potencies of pamidronate and alendronate are 100 and 1000 times, respectively, higher than that of clodronate, which may explain the difference in results with these bisphosphonates[7].

Soubrier et al reported 1 case treated with 2 infusions of 60 mg of pamidronate after failed attempts at antibiotic therapy and NSAIDs, with remission of symptoms for 3 years[10].

A total of 7 patients included in the study by Kuijpers et al were treated with an infusion of 15 mg pamidronate/day for 3 to 5 consecutive days. Depending on the improvement of the condition, this scheme was repeated after 3 months. There was a decrease in technetium 99 uptake on bone scintigraphy performed after 1 year in all cases. Considerable variation was found from one patient to another. The symptoms, which had been present for years, regressed considerably or even disappeared for a period of 28 to 46 months after treatment. Disease activity seemed to decrease in all patients[11].

Urade et al reported 1 case treated with a single infusion of 45 mg pamidronate, with no side effects, with complete resolution of signs and symptoms, and decreased radioisotope uptake on scintigraphy. Radiographically, the diseased bone started to have a homogeneous sclerotic appearance and, after three years, it assumed a pattern close to normal. The patient has been symptom free for 6 years[7].

Regarding patients with OCP associated with SAPHO Syndrome, treatment has not been standardized, although generally anti-rheumatic therapy with drugs such as NSAIDs, corticosteroids, sulfasalazine, methotrexate and cyclosporine are usually prescribed. Although NSAIDs are used to soothe early symptoms, they often fail to control this syndrome. In contrast, tumor necrosis factor alpha (TNF-alpha) antagonists such as infliximab have been shown to be effective, although their systemic side effects are significant[16]. Some authors, such as M. Julian et al recommend that health professionals must always consider the presence of SAPHO syndrome in patients who received the diagnosis of PCO[8].

The variation in terms of disease classification causes confusion in the literature, where authors suggest that the term "diffuse sclerosing osteomyelitis" is synonymous with "primary chronic osteomyelitis" and is related to the radiographic aspect[1,3]. Another terminology used is "juvenile primary osteomyelitis" which, according to Nadia et al, is the name given to the manifestation of PCO in childhood and this subdivision would not be necessary, as it makes comparative studies more difficult[9]. The term "tendoperiostitis" is classified as an aseptic inflammatory osteomyelitis as well as PCO, however, it is strictly related to parafunctional habits. However, according to Marieke M. et al, these terms are synonymous with no need for distinction and concluding that patients diagnosed with "diffuse sclerosing osteomyelitis" and "tendoperiostitis" benefit from treatment for temporomandibular disorders[17].

Marieke M et al treated 16 patients conservatively with temporomandibular dysfunction (TMD) therapy using occlusal splint, condition awareness, and physiotherapy with parafunctional habit reversal training, and/or muscle relaxation therapy. After 12 months of follow-up, four patients were completely pain free and eight patients had less pain and less frequent swelling in the jaw[17].

Since OCP is a rare disease, the small number of cases submitted to any therapeutic modality does not allow the establishment of significant statistical data that show its efficacy and its effects on the natural course of the disease[3].

To date, there is no cure for primary chronic osteomyelitis, as a result of little knowledge about the disease, especially about its etiology and natural progression of the disease[2,8,12].

CONCLUSION

The Primary Chronic Osteomielitis it is a rare disease with a challenging diagnosis and it is comprehended by different terms in literature, which limits the performance of comparative studies. The etiology and treatment of this disease have not been established yet. And it comes as a result of the lack of clinical, imaging and histological data. However, the conservative approach with the use of drugs has presented good results in literature. In this case, Prednisone was effective in decreasing edema and trismus while Pamidronate was effective in controlling pain. However more studies are needed to determine a definite treatment protocol and to give a complete understanding about this condition.

REFERENCES

1. Baltensperger M, Grätz K, Bruder E, Lebeda R, Makek M, Eyrich G. Is primary chronic osteomyelitis a uniform disease? Proposal of a classification based on a retrospective analysis of patients treated in the past 30 years. J Craniomaxillofac Surg. 2004 Feb;32(1):43-50.
2. Bevin CR, Inwards CY, Keller EE. Surgical management of primary chronic osteomyelitis: a long-term retrospective analysis. J Oral Maxillofac Surg. 2008 Oct;66(10):2073-85.
3. Eyrich GKH, Baltensperger MM, Bruder E, Graetz KW. Primary chronic osteomyelitis in childhood and adolescence: a retrospective analysis of 11 cases and review of the literature. J Oral Maxillofac Surg. 2003 May;61(5):561-73.
4. Frid P, Tornes K, Nielsen Ø, Skaug N. Primary chronic osteomyelitis of the jaw—a microbial investigation using cultivation and DNA analysis: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 May;107(5):641-7.
5. Van de Meent MM, Pichardo SEC, Appelman-Dijkstra NM, Van Merkesteyn JPR. Outcome of different treatments for chronic diffuse sclerosing osteomyelitis of the mandible a systematic review of published papers. Br J Oral Maxillofac Surg. 2020 May;58(4):385-95.
6. Cimolai N. Chronic multifocal osteomyelitis: is infectious causation a moot point? J Infect Public Health. 2011 Sep;4(4):157-68.
7. Urade M, Noguchi K, Takaoka K, Moridera K, Kishimoto H. Diffuse sclerosing osteomyelitis of the mandible successfully treated with pamidronate: a long-term follow-up report. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(4):e9-e12.
8. Amand MJS, Sigaux N, Gleizal A, Bouletreau P, Breton P. Chronic osteomyelitis of the mandible: a comparative study of 10 cases with primary chronic osteomyelitis and 12 cases with secondary chronic osteomyelitis. J Stomatol Oral Maxillofac Surg. 2017 Dec;118(6):342-8.
9. Theologie-Lygidakis N, Schoinohoriti O, Iatrou I. Surgical management of primary chronic osteomyelitis of the jaws in children: a prospective analysis of five cases and review of the literature. Oral Maxillofac Surg. 2011 Mar;15(1):41-50.

10. Soubrier M, Dubost JJ, Ristori JM, Sauvezie B, Bussière JL. Pamidronate in the treatment of diffuse sclerosing osteomyelitis of the mandible. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001 Dec;92(6):637-40.
11. Kuijpers SCC, Jong E, Hamdy NAT, Richard JP, Van Merkesteyn R. Initial results of the treatment of diffuse sclerosing osteomyelitis of the mandible with bisphosphonates. J Craniomaxillofac Surg. 2011 Jan;39(1):65-8.
12. Montonen M, Kalso E, Pylkkären L, Lindströrm BM, Lindqvist C. Disodium clodronate in the treatment of diffuse sclerosing osteomyelitis (DSO) of the mandible. Int J Oral Maxillofac Surg. 2001 Aug;30(4):313-7.
13. Yamazaki Y, Satoh C, Ishikawa M, Notani K, Nomura K, Kitagawa Y. Remarkable response of juvenile diffuse sclerosing osteomyelitis of mandible to pamidronate. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104(1):67-71.
14. Li X, Jia K, An J, Zhang Y. Application of pamidronate disodium for the treatment of diffuse sclerosing osteomyelitis of the mandible: a clinical study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Jul;130(6):616-24.
15. Just A, Adams S, Brinkmeier T, Barsegian V, Lorenzen J, Schilling F, et al. Successful treatment of primary chronic osteomyelitis in SAPHO syndrome with bisphosphonates. J Dtsch Dermatol Ges. 2008 Aug;6(8):657-60.
16. Hatano H, Shigeishi H, Higashikawa K, Shimasue H, Nishi H, Oiwa H, et al. A case of SAPHO syndrome with diffuse sclerosing osteomyelitis of the mandible treated successfully with prednisolone and bisphosphonate. J Oral Maxillofac Surg. 2012;70(3):626-31.
17. Van de Meent MM, Wetselaar-Glas MJM, Fiocco M, Appelman-Dijkstra NM, Van Merkesteyn JP. Non-surgical treatment of adults with chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible. J Craniomaxillofac Surg. 2019 Dec;47(12):1922-8.