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Chronic nonbacterial osteomyelitis - A diagnostic quandary

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO) is an aseptic inflammatory disorder of unknown cause occurring in children and adolescents. CRMO is a diagnosis of exclusion based on the clinical, radiological and pathological criteria. Like other inflammatory osteomyelitis, CRMO has no infectious sources such as retained roots, periodontitis, or pathology in the oral cavity. The early diagnosis of CRMO in the jaw will prevent unnecessary and prolonged antibiotic usage or unnecessary surgical intervention.

The purpose of this article was to present our experience with five cases of CNO of mandible in the age group of 9 - 16 years. The specific aim was to document the clinical characteristics, radiographic findings, and histologic features of CNO.

Keywords: CNO, CRMO, CT.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO), or chronic nonbacterial osteomyelitis (CNO), is a very rare idiopathic non-infectious inflammatory disorder, characterised by bone lesions with pain and swelling, and periods of exacerbations and remission, in different locations, over the course of several months to years [1,2]. The disease was first described by Giedion et al in 1972 and the term chronic recurrent multifocal osteomyelitis was coined by Bjorksten et al.

CNO can occur as an isolated lesion or can be multifocal. The term chronic recurrent multifocal

osteomyelitis (CRMO) is used to describe the multifocal form of CNO.[4]

CNO primarily affects children, with a female-to-maleratio of 4:1, and the mean age at onset is 10 years.[5,6]

Mandibular lesions are found in 1.5–3% of disease foci in patientswith CRMO [7] and the bone most commonly affected by unifocal disease is the mandible [8].

Although the etiology of these diseases is unclear, it has been classified as an auto inflammatory disorder which is known as an immune system hyper activation without high titers of autoreactive lymphocytes and auto antibodies [9].

Case 1

A 9 year old girl was referred to our institution with complaint of pain and swelling in the right face. She had no previous history of trauma or any systemic disease. Clinical examination revealed a facial asymmetry with a diffuse swelling in the right lower face which was extending anteroposteriorly from the parasymphysis to body region of mandible. The skin over the swelling was erythematous compared to surrounding skin. On palpation a local rise in temperature with tenderness in the lower border of mandible was noted. Margins were diffused. One enlarged level 1b submandibular lymph node on right submandibular region was present, which was tender on palpation, soft in consistency and mobile. On intra oral examination no active dental of foci infection was noted.

An Orthopantomograph showed an altered trabecular pattern with increased density in right parasymphysis-body region of mandible in relation to 83 to 46. Indistinct cortical margin of developing follicles of 43, 44 and 45.

A multi slice CT examination was then performed and revealed cortical irregularity and thinning of cortex with medullary sclerosis involving right body of mandible. Surrounding periosteal reaction noted. Adjacent soft tissue thickening noted. Enlarged submandibular lymph nodes noted on right side.

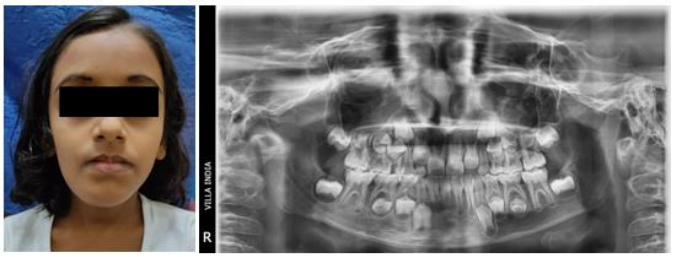


Figure 1: Panoramic radiograph

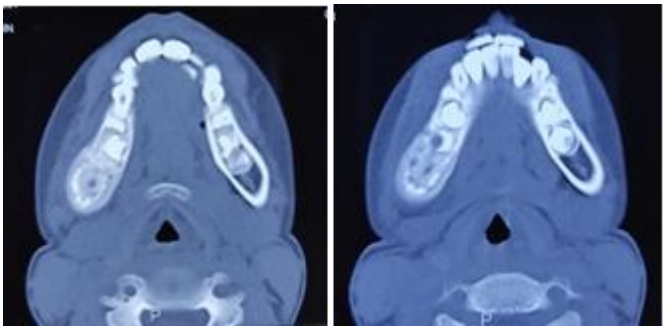


Figure 2: CT Axial Sections

Case 2

12 year old girl with complaint of a swelling in the left side of face. Clinical examination revealed a mild facial asymmetry due to diffused swelling in the left lower face region. On palpation tenderness noted in the left canine region. On intra oral examination no active of foci infection was noted.

Panoramic radiograph showed lytic lesion involving the left mandibular body region with ill-defined margins and irregular borders extending from 33 to 36 and to the lower border of mandible. Increase in the thickness of the lower border of the mandible noted in the left parasymphyseal region.

A multi slice CBCT examination showed lytic lesion with multiple separate radiopacities (sequestra) within the lesion. Alteration of normal trabecular pattern extending from the left of midline to distal of 36. Proliferative periostitis (Onion peel appearance) noted

on the buccal cortex in the parasymphysis. A breach of buccal cortical plate noted at multiple sites. Coronal section shows increased buccolingual width of mandibular body compared to night side from midline to the region of 36.

WB-MRI showed cortical thickening and STIR hyper intensity in body of left hemi mandible (39mm) and right tibia diaphysis in middle third shows STIR hyper intensity measuring 36 mm, findings are nonspecific, could indicate involvement by CRMO.

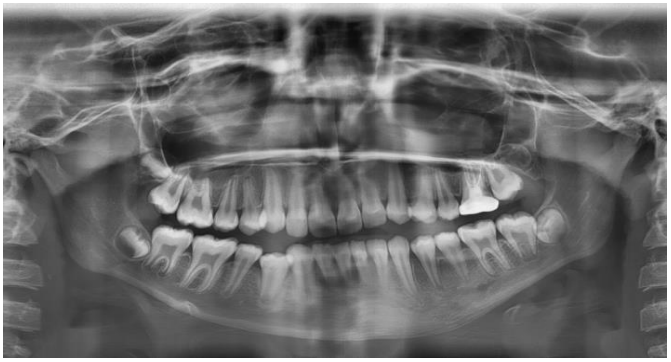


Figure 3: Panoramic radiograph

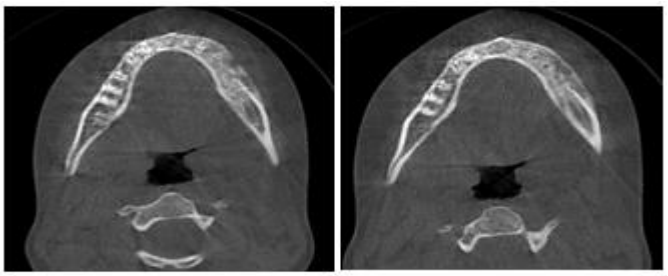


Figure 4: CBCT axial sections

Case 3

A 13 year old male patient presented with a complaint of pain and swelling on left side of mandible since last 4 days with a history of pain and fever 1 week back. On clinical examination a diffused swelling noted in the left posterior body of mandible. Tenderness was present on palpation along the inferior border of mandible.Enlarged level 1b submandibular lymph node present on left submandibular region which was tender on palpation. Intraorally no visible caries was present in relation to 24, 25, 26, 27 34, 35, 36 and 37, Erupting 33 and 37 noted.

In panoramic radiograph radiolucent lesion noted in the left body-ramus region of mandible in relation to 36,37 and 38 region, extending antero-posteriorly from the mesial aspect of 36 to the left mid ramus region and superior-inferiorly from alveolar crest distal to 37 to 2.96mm superior to the lower border of mandible. Interdental crestal bone loss noted between 35,36 and 36,37.

Multi slice CBCT showed a uniformly hypodense lesion in the left body-ramus region of mandible in relation to 36, 37& 38 region, measuring antero-posteriorly 25 mm, bucco-ligually 18 mm and 17 mm supero-inferiorly. Extending from the mesial aspect of 36 to left mid ramus region. Thinning and breach of buccal and lingual cortical plate in relation to 36,37& 38 region noted. Left inferior alveolar canal could not be traced. Loss of lamina dura noted in relation to 37.

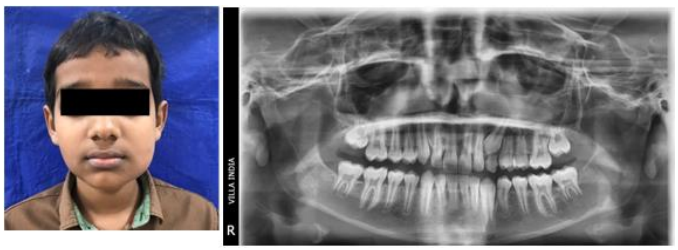


Figure 5: Panoramic radiograph

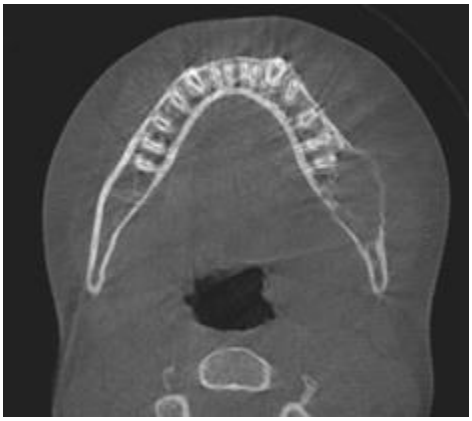


Figure 6: CBCT axial section

Case 4

A 15 year old male patient presented with a complaint of pain and swelling on left side of the jaw for last 11 months.History of palmar plantar pustular skin lesion.

On examination a mild diffuse swelling on the left side of jaw noted. Mouth opening was within normal limits but painful on wide opening. Swelling was tender on palpation. A palpable firm, mobile non tender level 1b lymph node on left submandibular region was present.

Panoramic radiograph showed a lytic lesion with irregular margins on the left posterior body and ramus region of mandible of size approximately 22 mm x 13 mm involving the left inferior alveolar canal and mandibular foramen.

In multi slice CBCT increased width of left ramus with medio-lateral measurement of 17.6 mm compared right ramus measurement of 9.20 mm. Irregular lytic lesion with periosteal reaction noted in the left ramus. Discontinuity noted on the medial and lateral cortical border of left ramus.

In CT diffused widening of ramus of left mandible with loss of normal density and adjacent edema in the masseter muscle and soft tissues noted. Subtle periosteal reaction noted in the lateral aspect.

No other abnormal, focal or diffuse, tracer concentration seen in the whole body bone scan.

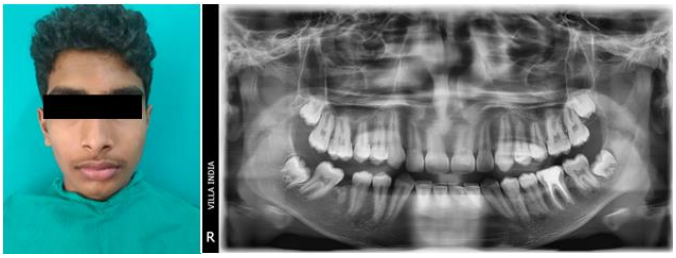


Figure 7: Panoramic radiograph

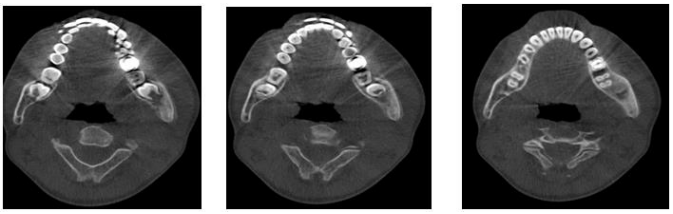


Figure 8: CBCT Axial Sections

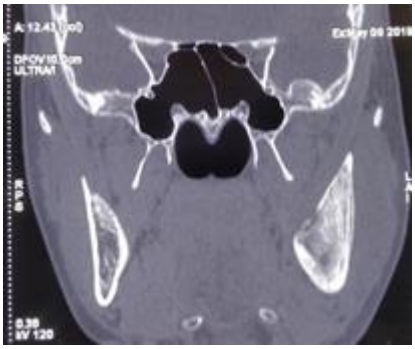


Figure 9: CT Axial Section

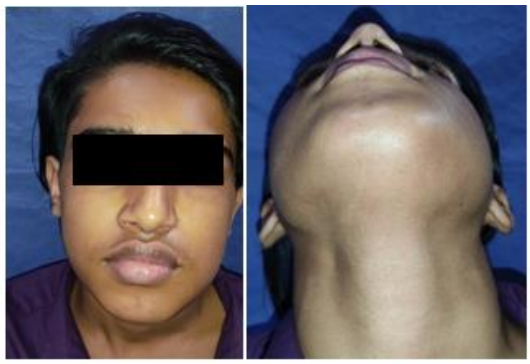
Case 5

A 16 year old male patient was referred to our institution with complaint of swelling in the left lower jaw since one year. He had no previous history of trauma or any systemic disease. Clinical examination revealed a facial symmetry with a diffuse swelling in the left lower third of face which was extending anteroposteriorly from the symphysis to body region of mandible. The skin over the swelling was tense compared to surrounding skin. Palpation revealed a bony hard swelling extending from the symphysis region to left body of mandible and a local rise in temperature with tenderness in the lower border of mandible was noted. Margins were diffused. One enlarged level 1b submandibular lymph node on left submandibular region was present, which was tender on palpation, soft in consistency and mobile. On intra oral examination caries exposed 16 was noted.

Panoramic radiograph showed altered trabecular pattern with multiple lytic areas in left para symphysis and body region of mandible. Loss of normal corticated border of left inferior border of mandible.

A multi slice CBCT examination showed lytic lesion with alteration of normal trabecular pattern extending from the right parasymphysis region of mandible to left body region. Proliferative periostitis (Onion peel appearance) noted on the buccal cortex in the parasymphysis. Coronal section shows increased buccolingual width of left mandibular body compared to

right. Thinning of corticated border of mandible in symphysis, left parasymphysis and body of mandible.



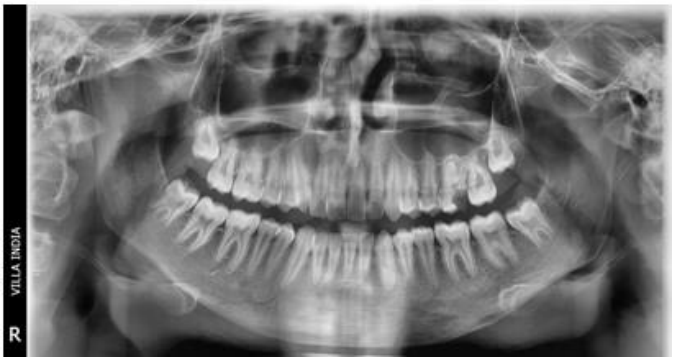


Figure 10: Panoramic radiograph

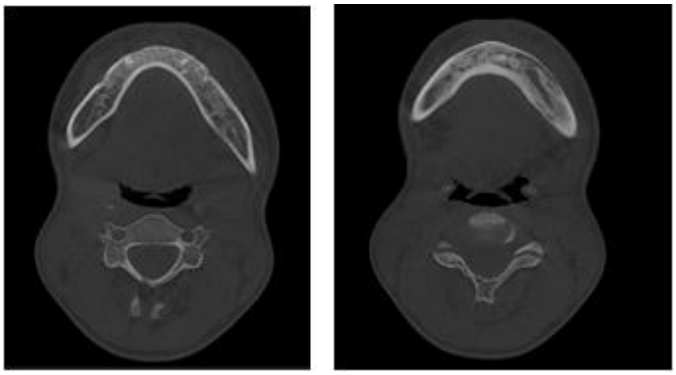


Figure 11: CBCT Axial Sections

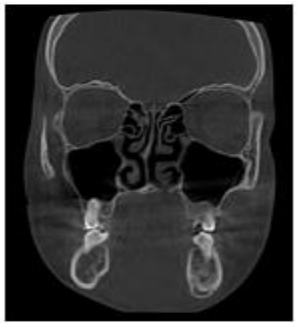


Figure12: Coronal Section

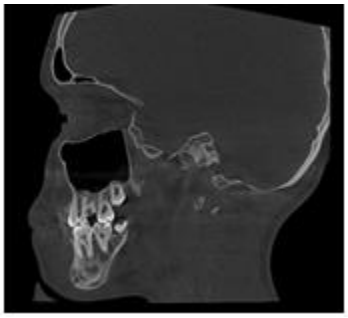


Figure 13: Sagittal Section

Radiographic summary

There were 13 images including Panoramic Radiograph (n = 5), CBCT (n = 4), CT (n = 2), WBMRI (n = 1), and 99mTc methylene diphosphonate isotope bone scans (n =1).

Initial PAN (n = 5) examination showed altered trabecular pattern with increased density, Lytic lesion involving the affected region with ill-defined margins and irregular borders and increased thickness of the lower cortical border of the mandible. Lytic lesion with irregular margins involved the symphysis, parasymphysis, body and ramus region of mandible.

CT (n =2) examination showed cortical irregularity and thinning of cortex with medullary sclerosis of mandible. Diffuse widening of ramus of left mandible with loss of normal density and subtle periosteal reaction. Adjacent soft tissue thickening and edema in the masseter muscle along with enlarged submandibular lymph nodes.

CBCT (n=4) examinations typically showed foci of poorly defined lytic destruction with a lamellate periosteal reaction .The lytic foci involved the medullary space and/or cortex, sometimes thinning and breaching the buccal or lingual cortices as well as expansion of the affected mandible with sclerosis of the medullary space. Cases involved the symphysis, parasymphysis, body with also affecting the ramus of mandible. Bilateral mandibular lesions were continuous across the anterior mandible.

WBMRI (n=1) showed cortical thickening and STIR hyper intensity in body of left hemi mandible (39mm) and right tibia diaphysis in middle third shows STIR hyper intensity measuring 36 mm.

Bone scans (n=1) showed increased isotope uptake in the affected mandible. No other abnormal, focal or diffuse, tracer concentration seen in the whole body bone scan.

Follow-up PAN showed progression of mandibular disease, with increased sclerosis and altered trabecular pattern in all but one patient.

Discussion

In 1972, Giedion et al first described symmetric multifocal inflammatory bone lesions. In 2005, Girschick et al. [10] suggested the name, CNO, including CRMO, which also had a recurrent tendency because CRMO could be regarded as a severe form of CNO. The disease has been reported in children aged 25 months to 17 years, and 1.5 to 3% of children diagnosed with multifocal CNO have lesions in the mandible [4,7,13].

CNO is poorly characterized in the oral and maxillofacial surgery literature because of inconsistent terminology (eg, Garre osteomyelitis, diffuse sclerosing osteomyelitis, primary chronic osteomyelitis, juvenile mandibular chronic osteomyelitis) and lack of information about whether these patients have other bony foci and/or extraosseous lesions. [3]

Female patients are more commonly affected than male patients, and the disease course is highly variable. CNO lesions can be acute or chronic (persisting more than 6 months); can be solitary or multifocal; and may resolve, persist, or recur. [10, 11]

CNO most commonly develops in the metaphyseal plates of the long bones, vertebrae, and clavicles; however, any bone can be affected.[8,4] Mandibular lesions are found in 1.5 to 3% of disease foci in patients with CRMO,[7] and the most commonly affected bone with unifocal disease is the mandible.[8]

Wipff et al showed that most patients with unifocal disease eventually have progression to the multifocal type (CRMO); only 7% of patients had a persistent unifocal pattern after 4 years.[7]

CNO is currently thought to be in the spectrum of autoimmune and auto- inflammatory disorders. This is supported by the high rates of inflammatory conditions, particularly psoriasis and IBD, in patients and family members.[8] Extraosseous manifestations including palmoplantarpustulosis, psoriasis,Crohn's disease, and acne have led some authors to classify

CRMO as the juvenile form of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome.[7]

The differential diagnosis of mandibular CNO includes infectious osteomyelitis, malignancy (osteosarcoma and Ewing sarcoma), and Langerhans cell histiocytosis.[12]

The diagnosis of mandibular CNO is suggested by clinical features, including a history of random exacerbations of pain and swelling, the absence of acute systemic symptoms, an examination positive for swelling and tenderness over the mandible, the exclusion of primary dental disease by plain radiographs and panoramic films, and normal routine laboratory values (except for a possibly elevated sedimentation rate).[15]

Specific inquiry regarding other areas of bone pain or swelling and the presence of extra- osseous inflammatory lesions, as well as a family history of inflammatory and autoimmune conditions. [3]

CRMO is uncommon in the jaws, and on panoramic radiographs may be mistaken for fibrous dysplasia, chronic diffuse sclerosing osteomyelitis or periostitisossificans. Radiographs may show osteolysis in the early stages. Hyperostosis and sclerosis may be seen in later stages and periosteal reactions can occur at

any stage. This is consistent with multiple sites of acute and chronic osteomyelitis [16]

CT, which can be performed using a low-dosage technique, and cone-beam CT are the best diagnostic imaging tests because these provide adequate bone detail and visualization of soft tissues is not necessary. CT, cone-beam CT, or MRI can be used for follow-up. [3]

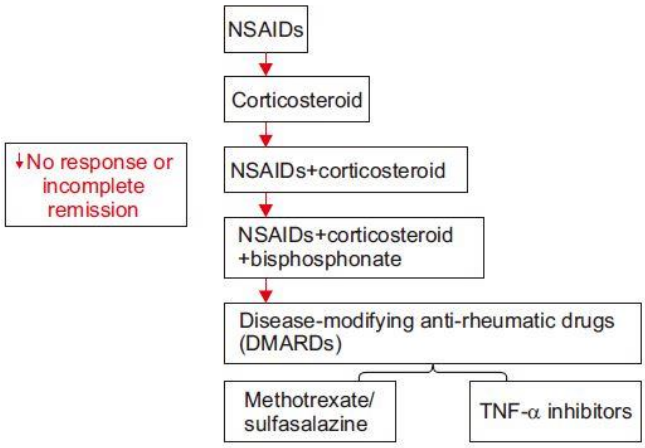
If the diagnosis remains in question, a biopsy specimen that includes cortical and cancellous bone can be obtained. This biopsy specimen should be obtained from an extraoral approach to avoid oral contamination and an erroneous diagnosis of an infectious etiology.[3]

The histology findings of CNO can vary and be similar to infectious osteomyelitis in the acute and chronic stages [3]. However, histologic results of CNO are known as sub-acute or chronic inflammation, with a lymphocytic or mixed inflammatory infiltrate, and marrow fibrosis [17].

Physicians not familiar with the disorder are influenced by biopsy and culture results to make the diagnosis of chronic infectious osteomyelitis. This leads to aggressive antibiotic regimens and surgical procedures which have minimal impact on the course of the disease.[3,10,12,13,14]

No standard treatment for CNO exists because there have been no randomized placebo-controlled trials. On the other hand, the use of Nonsteroidalanti inflammatory drugs (NSAIDs) for more than 6 months is recognized as a first choice. TNF blockers and bisphosphonates have also been used to treat CNO [3,17]. CNO has been reported to improve with surgical intervention and NSAID and bisphosphonate because of the relatively easy access to the mandible compared to other bones (clavicle, vertebrae, pelvis, tibia, fibula, and femur) [3].

CNO has been treated with a variety of anti-inflammatory drugs as well as metho-trexate, bisphosphonate, and anti-TNF-α agents as long-term medication for up to 12 years [17, 18]. Beck et al. [4] reported that 43% of patients showed improved clinical symptoms with naproxen medication for six months. In terms of the side effects, Stern and Ferguson [17] suggested that indomethacin might be more effective than Naproxen in the recurrence case. Bisphosphonate has a positive effect in preventing the symptoms and progression of CNO [19]. In a retrospective cohort study in 2012, Borzutzky et al. [9] estimated the drug-specific response probabilities of CNO as 57% for NSAID, 66% for sulfasalazine, 91% for methotrexate, and 95% for corticosteroids.



As CNO is a rare unknown disease, the standard medication therapy has not been established because there has not been any research with prospective randomized placebo-controlled trials for medication to treat CNO. Although positive results were reported with only medication, such as anti-inflammatory agents and bisphosphonates, recent study suggest bone biopsy on mandibular CNO [9].

Conclusion

CRMO in jaw must be diagnosed with the differentiation of chronic bacterial osteomyelitis, and a bone biopsy is essential. The early diagnosis of CRMO in jaw will prevent unnecessary and prolonged antibiotic usage and

unnecessary surgical intervention. The updated researches of several pathophysiological alterations in CNO/CRMO should be studied more for its exact causes and allow for the creation of target-directed treatment options.

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