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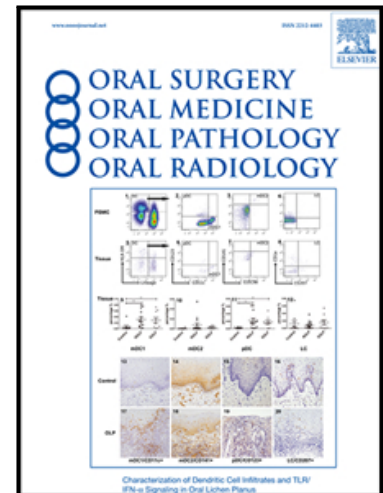
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Post-COVID steroid induced avascular necrosis of the jaw: emerging challenge in India

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Case report | Oral and Maxillofacial Pathology

Post-COVID steroid induced avascular necrosis of the jaw: emerging challenge in India

Post-COVID steroid induced avascular necrosis of the jaw

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Abstract

COVID-19 pandemic continues to evolve, spread with new variants of SARS-Cov-2 across the globe and also comes to clinical attention with several post-covid conditions. We report a post-COVID condition being observed by us at our tertiary care center: spontaneous de novo development of steroid induced avascular necrosis in patients who have recently recovered from COVID-19 following high dose steroid usage in a short span of time. Pre-covid published literature indicates that these lesions were seen very rarely in the jaws and were related to long-term usage of steroids and recent tooth extraction. They were considered under the broad spectrum of medication related osteonecrosis of the jaws (MRONJ). Present authors believe that the post-COVID-19 steroid induced avascular necrosis of the jaw is a distinct new entity. It is analogous to the avascular necrosis noticed in the femoral head of individuals recuperating from

COVID-19, a condition conventionally known to be strongly associated with steroid therapy. Rapid progression, associated morbidity and mortality and its possible differential diagnosis requires pathologists to be vigilant regarding the chance encounter of such cases in jaws. Further reporting of such cases is required to gain additional insight into its features.

Keywords

COVID; steroid; avascular necrosis; osteonecrosis; jaws

Introduction

COVID-19 pandemic continues to evolve and spread with the episodic appearance of new variants of SARS-Cov-2 spreading panic and alarm around the globe. The associated morbidity and mortality with the infection is continuously challenging the understanding of this disease among healthcare workers. In addition, several novel post-covid conditions have been reported in the literature due to the multi-organ damage induced by SARS-Cov-2, which further impedes the recovery and affects the quality of life of the patients for a prolonged period following recovery from COVID infection.¹ Herein, we report a post-COVID condition being increasingly observed by us at our tertiary care center: spontaneous de novo development of osteonecrosis (avascular necrosis) in the jaws in patients who have recently recuperated from COVID-19 and have received intensive steroid therapy in a short span of time.

Avascular bone necrosis is a degenerative bone disorder in which reduction or obstructed subchondral blood supply results in cellular bone necrosis.² It is also known as osteonecrosis, aseptic necrosis, and ischemic bone necrosis and has primarily been reported in the long bones. Several theories have been proposed to explain its etiology including use of glucocorticoids, chemical toxicity, radiation, thermal injury, smoking, bone fractures or recurrent traumas, blood vessel abnormalities, intra-osseous vascular compression or occlusion, etc.^{2,3}

Steroid (glucocorticoid)-induced osteonecrosis has been commonly reported within the femoral head. It is hypothesized to be caused via abnormal lipid metabolism, decreased osteogenic potential of bone marrow mesenchymal stem cells, intravascular thrombosis, increased osteocytic and osteoblastic apoptosis; and polymorphisms of the CYP3A4, MMP8, TNF α and MDR1 genes. Osteonecrosis of the jaw (ONJ) induced by steroid use is rare. We could find only

three cases in the published literature despite extensive search.^{4,5,6} All of the published case reports had two common features- history of long term usage of steroids and a recent tooth extraction.

Case report

The second wave of COVID-19 pandemic in India has seen an indiscriminate use of short-term high dose steroid therapy in infected patients. In the aftermath, we have observed an unusual increase in the number of cases of ONJ invariably associated with a history of short-term usage of a high dose of corticosteroids. Four such cases were identified within a span of four months following the subsidence of second wave of the pandemic. All the patients were males within an age range of 28-65 years (median: 48.5 years). They all admitted to being treated with oral/intravenous steroids for a period of approximately 2 weeks. Prior to the COVID illness, these patients had been healthy and denied receiving steroids for any other condition previously.

Within a few days of recovery from Covid-19 infection, these patients presented with pain, facial swelling and sudden mobility in the teeth (Table 1). Radiographs of three of the patients depicted ill-defined osteolytic lesion in the maxilla with maxillary sinus involvement (Figure 1A, B). In the fourth patient (case 4), moth-eaten appearance was found in the mandibular ramus and angle region (Figure 1C, D). All the lesions were unilateral.

Incisional biopsies were done for all the cases to rule out any invasive fungal or other microbial disease and exclude other entities that can present in a similar manner like metastasis, plasmacytoma of bone and Langerhans cell histiocytosis (Table 2). On gross examination, the specimens showed necrotic fragments of bone. Histopathological examination revealed fragments of irregular bony trabeculae with empty lacunae accompanied by surrounding necrotic bone marrow (Figure 2A, B). Special stains like Periodic acid Schiff and Grocott-Gomori's methenamine silver revealed no fungal organisms. Ziehl Neelsen staining showed no mycobacterium thus ruling out any microbial involvement. In three of the patients, further surgical interventions (curettage with extraction of involved teeth) were undertaken (Supplementary figure S1) following which they received broad spectrum antibiotics. Satisfactory healing was seen in these cases.

In one patient (case 1), endoscopic debridement of maxillary sinus was attempted, and KOH (potassium hydroxide) mount showed presence of hyaline aseptate hyphae. However, histopathology, special staining and culture were negative for fungal organisms. Thus, possibilities of steroid induced ONJ and/or mucormycosis were considered. Due to the suspicion of mucor in the KOH mount, an antifungal therapy with amphotericin B was promptly initiated, however the patient succumbed to the disease due to the treatment associated intractable nephrotoxicity and subsequent complications.

Discussion

In view of the rapid progression, associated morbidity and mortality, the clinical overlap with conditions forming the differential diagnoses and commonality of the susceptible patient group, it is advisable for head and neck/oral and maxillofacial pathologists to be vigilant about encountering ONJ and the need to initiate dialogue with the clinician in this regard. Few authors have already raised red flags regarding the potential emergence of avascular necrosis in the femoral head of patients recovering from COVID 19 with Agarwala et al reporting it as a part of 'long COVID-19'.^{7, 8} Daltro et al reported a possible association between osteonecrosis and the use of glucocorticoids to treat COVID-19 infection.

Clinically, steroid induced ONJ may be confused with medication-related osteonecrosis of the jaw (MRONJ), osteoradionecrosis and bacterial/fungal osteomyelitis (table 2). The need to differentiate it from mucormycosis and other fungal lesions is imperative, so that antifungal therapy can be initiated promptly in indicated cases. This was also essential because a wave of sinonasal mucormycosis was sweeping the country in the aftermath of the second pandemic. Histopathological features and special stains can be helpful in distinguishing these entities.⁹

Previously, Nisi et al has reported jaw osteonecrosis, post extraction of left mandibular premolar in a 50-year-old male patient with history of 2-year intake of prednisone (7.5 mg/day) for psoriatic arthropathy.⁵ Surgical debridement was done with a 30-day follow-up showing recovery. Wong et al has also reported mandibular osteonecrosis at the site of non-healing extraction socket (left premolar) in a 30-year-old female with history of 9 year steroidal intake for systemic lupus erythematosus.⁴ Conservative management with antibiotics and chairside chlorhexidine mouthrinse was initially attempted followed by sequestrectomy and ultrasound

therapy. Interestingly, the patient developed bilateral femoral head osteonecrosis within the two-year follow-up period for which she was managed with oral bisphosphonates. Silva et al has reported mandibular osteonecrosis caused by 18-month use of corticosteroids for mycosis fungoides in a 78-year-old female at the extraction site of left second molar. The patient passed away before the treatment could be instituted.⁶

There are significant differences in the current cases and the cases reported previously primarily in terms of gender, affected jaw, involved side, history of extraction, duration of steroid intake and medical history. All our cases developed in males, whereas majority of the previous case reports are in females. Only one (n=4) of current case had a history of extraction whereas all the previously reported cases had history of recent extraction. Curiously, all the previous jaw osteonecrosis developed on the left side whereas our cases predominantly affected the right side. Most importantly, prolonged steroidal intake has been reported in the previous case reports for varied autoimmune disorders, though only one of them mentions the drug and the dosage. All the current cases had a short history of intensive steroid therapy following diagnosis of COVID-19.

Osteonecrosis of the femoral head (ONFH) as a post COVID-19 sequelae has been reported by several authors. Agarwala et al reports a mean dose of 758mg of prednisone used in such cases following which they presented with avascular osteonecrosis after a mean of 58 days.⁸ In a recent case series, Dhanasekararaja et al reports an average cumulative dose of methylprednisolone of 811mg, an average duration of steroid intake of 2.8 weeks and mean time of 39.3 days for the onset of symptoms.¹⁰ This is in agreement with the results of a meta-analysis conducted on high-dose corticosteroid use and risk of hip osteonecrosis which reported that patients on >20 mg per day had a higher risk of developing osteonecrosis.¹¹ Our cases received an average cumulative dose of 561.7 mg (average daily dose of approximately 44 mg) over a mean period of 12.7 days. A mean interval of 12 days was observed between conclusion of steroid therapy and oral symptoms. We believe that steroid therapy, along with COVID-19 induced impairment in microcirculation may have complementary role in producing these complications of avascular necrosis in susceptible regions of the body.¹²

Published literature has included steroid as a risk factor for MRONJ,¹³ however, the present authors believe that the steroid induced osteonecrosis (avascular necrosis) of the jaw in post COVID period is a distinct entity. In view of the rarity of its occurrence, unequivocal recognition

of its pathognomonic features and additional insights would require further reports of such lesions.

Author contribution

Conception- D.M and A.S; Data collection- V.N, A.S.B. and A.R; Supervisory Guidance: A.R, A.S.B. and D.M; Initial manuscript draft formulation- A.S, V.N and D.M; Finalization of manuscript- A.S, D.M, V.N, A.S.B. and A.R.

Supplementary Material

Supplementary figure S1- Gross examination (case 3) showed multiple extracted teeth with necrotic bone.

Conflict of Interest

The authors state that there are no conflicts of interest regarding the publication of this article.

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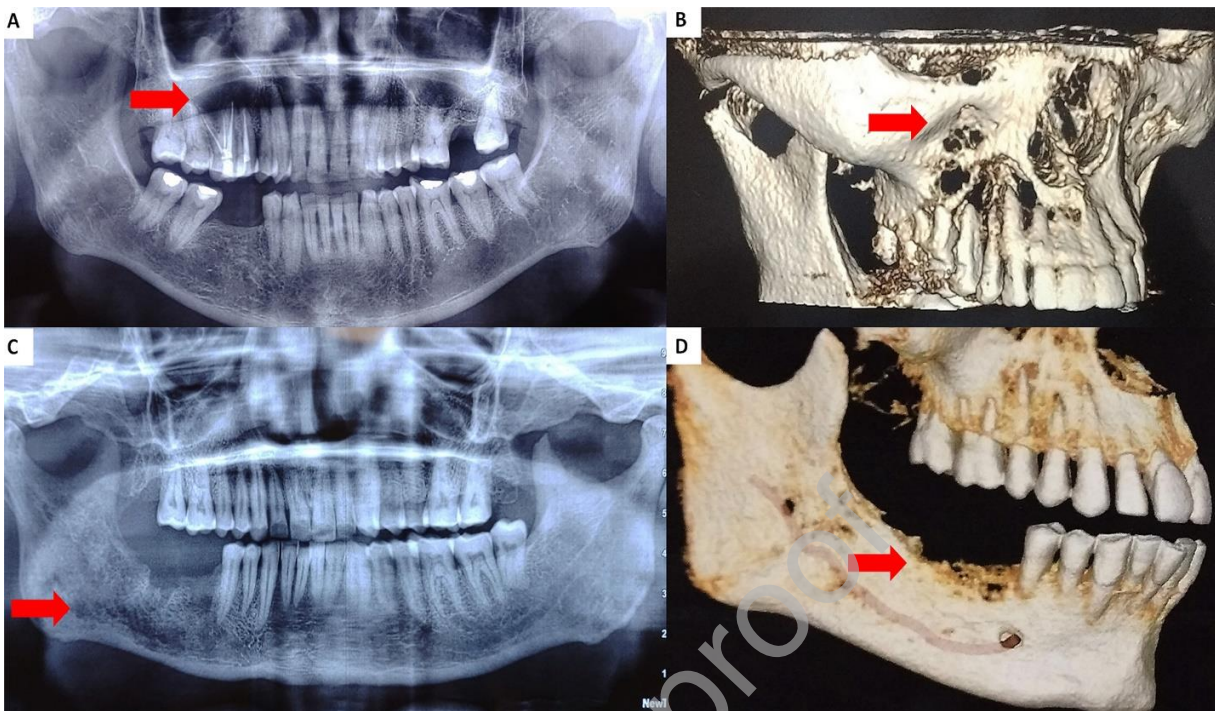


Figure 1. A, B – Radiographs (Case 3) showing osteolytic lesion in the right maxillary posterior region causing break in the medial wall, floor of right maxillary sinus and thinning of nasal floor. C, D – Radiographs (case 4) showed mixed radiolucent- radiopaque osteolytic lesion in the right body-angle-ramus of mandible with ragged and irregular margin giving it a moth-eaten appearance.

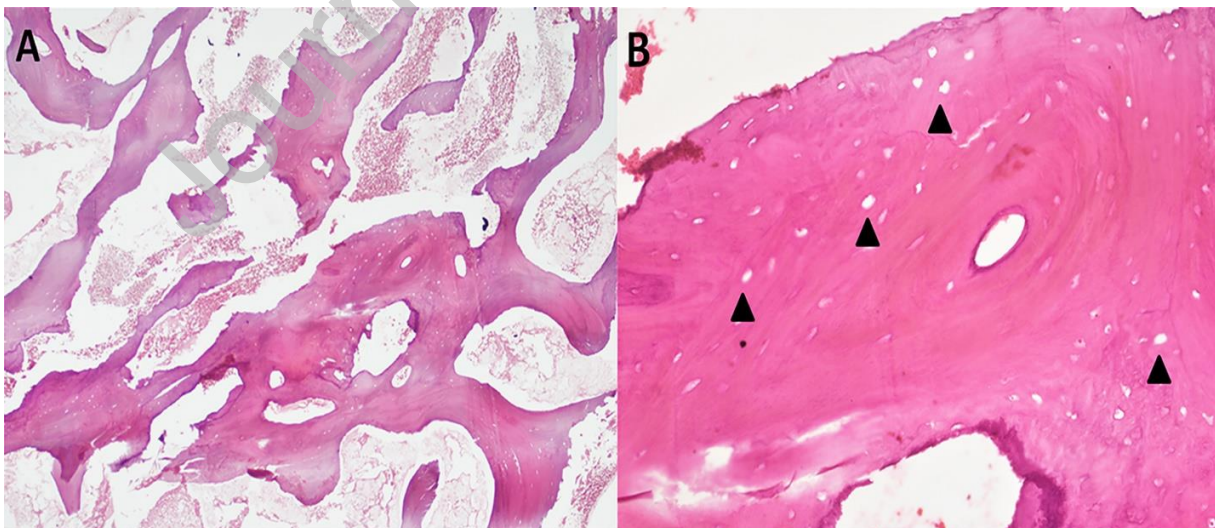


Figure 2. A, B Histopathology revealed irregular shaped fragments of bony trabeculae with empty lacunae (arrowheads).

Table 1: Clinical details and management of all the cases.

	Case 1	Case 2	Case 3	Case 4
Age (years)/ Gender	52/Male	28/Male	65/Male	49/Male
Chief complaint	Pain in the right maxillary region for 15 days	Mobile teeth, multiple draining sinuses and pus discharge in left maxillary region for 2 months	Pain and mobile teeth with pus discharge in right maxillary region for 2 months	Pain in the right side of face for 2 months
Dental status	Root stumps of right maxillary first and second premolar and carious right maxillary canine present	History of multiple mobile teeth which started within 10 days after discharge from the hospital for Covid-19. Later developed multiple draining sinuses and pus discharge in left maxillary region.	History of pain and swelling in jaws which started within 15 days of hospitalization for Covid-19. Patient underwent root canal treatment of right maxillary second premolar and first maxillary molar after which he presented to our center.	History of pain in the right side of face which started within 12 days after Covid-19 management. Patient underwent extraction of right mandibular first, second and third molar after which he presented to our center.
Radiographic features	CECT of head and contrast CT PNS with angiography showed opacification of right maxillary and ethmoidal sinuses, mucoperiosteal thickening of right ethmoid with hypertrophy of right inferior turbinate, and preseptal soft tissue on right side	OPG and MRI showed horizontal bone loss of alveolar bone with mucosal thickening causing complete opacification of maxillary sinus, rhinosinusitis with invasion into right posterior antral space	OPG and CBCT showed osteolytic lesion in right maxillary lesion with erosion in the floor and medial wall of right maxillary sinus and thinning of right nasal floor	OPG and CBCT showed mixed radiolucent-radiopaque osteolytic lesion in the right body, angle-ramus of mandible with ragged and irregular margin giving it a moth-eaten appearance
Medical history	Nothing significant	Nothing significant	Hypertensive and developed	Nothing significant

			hyperglycemia during Covid therapy. Glycated hemoglobin (HbA1C) at the time of presentation was 6.0 %.	
Covid management	Corticosteroid therapy. No data available on the other medications prescribed.	Corticosteroid therapy with antipyretic, anti-inflammatory, antibiotics, anti-emetic and cough syrup. Oxygen support, Inj Heparin 5000 IU, Inj Remdesivir 200mg, tab Ivermectin 12mg	Corticosteroid therapy with antipyretic, anti-inflammatory, antibiotics and cough syrup. Pirfenidone 400mg and anti-fibrotic therapy for fibrotic changes in lungs.	Corticosteroid therapy with antipyretic, anti-inflammatory, antibiotics and cough syrup. Tab Ivermectin 12mg.
Steroid dose and duration	As the patient succumbed to disease, no data was available.	Dexamethasone 4mg iv BD for 2 weeks (cumulative dose 700 mg in prednisone-equivalent)	Prednisolone 16mg BD oral for 12 days (cumulative dose 385 mg in prednisone-equivalent)	Dexamethasone 4mg iv BD for 12 days (cumulative dose 600 mg in prednisone-equivalent)
Treatment	Endoscopic debridement followed by antifungal and antibiotic therapy	Surgical curettage and extraction of mobile teeth followed by antibiotic therapy	Surgical curettage and extraction of mobile teeth followed by antibiotic therapy	Surgical curettage followed by antibiotic therapy

CECT- Contrast-enhanced computed tomography, MRI- Magnetic resonance imaging, Inj- Injection, mg- Milligram, MP- methylprednisolone, PNS- Paranasal sinus, Tab-Tablet, IU – International unit

Table 2. Differential diagnosis for post- COVID steroid induced avascular osteonecrosis of the jaw. Necrotic bone is a finding common to these entities.

Mucormycosis	Presence of broad ribbon like aseptate fungal hyphae branching at an obtuse angle.
Mediation-related osteonecrosis of the jaw	Specific diagnostic guidelines by American Association of Oral and Maxillofacial Surgeons include: <ol style="list-style-type: none"> 1. History of treatment with antiresorptive or antiangiogenic agents. 2. Bone sequestrum in the oral and maxillofacial region for more than eight weeks. 3. No history of radiation therapy or metastasis to the jaws.¹⁴
Osteoradionecrosis	History of radiotherapy
Osteomyelitis	History of trauma or extraction. Presence of inflammation. Presence of microbial organisms inside marrow spaces on histopathological examination
Metastasis to jaws	Diagnostic histology of primary tumor type (most common in men are carcinoma of lung, prostate, kidney, bone, adrenal)
Langerhans cell histiocytosis	Young age (children and infants). Diagnostic Langerhans cells morphology on histology and immunopositivity for CD1a, S100, langerin.
Plasmacytoma of bone	Histology shows infiltrate of plasma cells exhibiting anaplasia and light chain restriction on immunohistochemistry.