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

Anubhuti Sood, MDS,a Vivek Nayar, MDS,a Ajoy Roychoudhury, MDS,b Ashu Seith Bhalla, MD,c and Deepika Mishra, MDSa

The COVID-19 pandemic continues to evolve and spread with new variants of SARS-CoV-2 across the globe, as well as bring to clinical attention several post-COVID conditions. We report a post-COVID condition observed 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. Present authors believe that the post-COVID steroid-induced avascular necrosis of the jaws 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 require 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.

The COVID-19 pandemic continues to evolve and spread with the episodic appearance of new variants, creating panic and alarm around the globe. The associated morbidity and mortality with the infection is continuously challenging the understanding of this disease among health care workers. In addition, several novel post-COVID conditions have been reported in the literature due to the multiorgan damage induced by SARS-CoV-2. Such damage further impedes the recovery and affects the quality of life of the patients for a prolonged period following recovery from COVID.1 Herein, we report a post-COVID condition increasingly observed at our tertiary care center: spontaneous de novo development of osteonecrosis (avascular necrosis) in the jaws in patients who have recently recovered 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, intraosseus vascular compression or occlusion, and so on.2,3

Steroid (glucocorticoid)-induced osteonecrosis has been commonly reported within the femoral head. It is hypothesized to be caused by 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, tumor necrosis factor alpha (TNFα), and MDR1 genes. Osteonecrosis of the jaws (ONJ) induced by steroid use is rare. We could find only 3 cases in the published literature despite extensive search.4,5,6 All of the published case reports had 2 common features: history of long-term usage of steroids and a recent tooth extraction.

MATERIALS AND METHODS

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 4 months following the subsidence of second wave of the pandemic. All the patients were men 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. Before 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 3 of the patients depicted ill-defined osteolytic lesion in the maxilla with maxillary sinus involvement (Figure 1A, B). In the fourth patient (case

| Table I. Clinical details and management of all the cases |
|-----------------|-----------------|-----------------|-----------------|
| **Case 1**      | **Case 2**      | **Case 3**      | **Case 4**      |
| **Age (y)/ Sex**| **52/Male**     | **28/Male**     | **65/Male**     |
| **Chief complaint** | Pain in the right maxillary region for 15 d | Mobile teeth, multiple draining sinuses and pus discharge in left maxillary region for 2 mo | Pain and mobile teeth with pus discharge in right maxillary region for 2 mo | Pain in the right side of face for 2 mo |
| **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 d 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 d 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 d after COVID-19 management. Patient underwent extraction of right mandibular first, second, and third molar, and afterward, 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 hyperglycemia during COVID-19 therapy. Glycated hemoglobin (HbA1C) at the time of presentation was 6.0%. | Nothing significant |
| **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 200 mg, tab Ivermectin 12 mg. | Corticosteroid therapy with antipyretic, anti-inflammatory, antibiotics, and cough syrup, Pirfenidone 400 mg and anti-fibrotic therapy for fibrotic changes in lungs. | Corticosteroid therapy with antipyretic, anti-inflammatory, antibiotics and cough syrup. Tab Ivermectin 12 mg. |
| **Steroid dose and duration** | As the patient succumbed to disease, no data were available. Dexamethasone 4 mg iv BD for 2 wk (cumulative dose 700 mg in prednisone-equivalent). | Prednisolone 16 mg BD oral for 12 d (cumulative dose 385 mg in prednisone-equivalent). | Dexamethasone 4 mg iv BD for 12 d (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; **CT**, computed tomography; **PNS**, paranasal sinus; **OPG**, orthopantomogram; **MRI**, magnetic resonance imaging, **CBCT**, cone beam computed tomography; **Inj**, injection; **Tab**, tablet; **IV**, intravenous
4), moth-eaten appearance was found in the mandibular ramus and angle region (Figure 1C, D). All the lesions were unilateral.

Incisonal 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 II). During gross examination, the specimens showed necrotic fragments of bone. Histopathologic 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 necrotic bone is a finding common to these entities.

Table II. Differential diagnosis for post-COVID steroid induced avascular osteonecrosis of the jaw

| Diagnoses                        | Histologic Features                                                                 |
|----------------------------------|-------------------------------------------------------------------------------------|
| Mucormycosis                     | Presence of broad, ribbon-like aseptate fungal hyphae branching at an obtuse angle. |
| Mediation-related osteonecrosis of the jaw | Specific diagnostic guidelines by the American Association of Oral and Maxillofacial Surgeons include: |
| 1 History of treatment with antiresorptive or antiangiogenic agents |
| 2 Bone sequestrum in the oral and maxillofacial region for >8 wk |
| 3 No history of radiation therapy or metastasis to the jaws15 |
| Osteoradionecrosis               | History of radiotherapy                                                              |
| Osteomyelitis                    | History of trauma or extraction; presence of inflammation; presence of microbial organisms inside marrow spaces on histopathologic 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. |

Fig. 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) showing mixed radiolucent-radiopaque osteolytic lesion in the right body-angle-ramus of mandible with ragged and irregular margin giving it a moth-eaten appearance.
fungal organisms. Ziehl-Neelsen staining showed no mycobacterium, ruling out any microbial involvement. In 3 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.

Clinically, steroid-induced ONJ may be confused with medication-related ONJ, osteoradionecrosis, and bacterial/fungal osteomyelitis (Table II). It is crucial to differentiate it from mucormycosis and other fungal lesions, 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. Histopathologic features and special stains can be helpful in distinguishing these entities.10

Previously, Nisi et al.5 reported jaw osteonecrosis after extraction of left mandibular premolar in a 50-year-old male patient with history of 2-year intake of prednisone (7.5 mg/d) for psoriatic arthropathy. Surgical debridement was done with a 30-day follow-up showing recovery. Wong et al.4 has also reported mandibular osteonecrosis at the site of non-healing extraction socket (left premolar) in a 30-year-old female with a history of 9-year steroidal intake for systemic lupus erythematosus. 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 and was managed with oral bisphosphonates. Silva et al.6 has reported mandibular osteonecrosis caused by 18-month use of corticosteroids for mycosis fungoides in a 78-year-old woman at the extraction site of left second molar. The patient passed away before the treatment could be instituted.

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.

FIG. 2. (A, B) Histopathology revealed irregular shaped fragments of bony trabeculae with empty lacunae (arrowheads).
All our cases developed in men, whereas majority of the previous case reports are in women. Only 1 (n = 4) current case had a history of extraction, whereas all the previously reported cases had history of recent extraction. Curiously, all the previous cases of 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 1 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. reported a mean dose of 758 mg of prednisone used in such cases following which they presented with avascular osteonecrosis after a mean of 58 days. In a recent case series, Dhanasekararaja et al. reported an average cumulative dose of methylprednisolone of 811 mg, an average duration of steroid intake of 2.8 weeks, and mean time of 39.3 days for the onset of symptoms. This is in agreement with the results of a meta-analysis conducted on 39.3 days for the onset of symptoms. This is in agreement with the results of a meta-analysis conducted on high-dose corticosteroid use and risk of hip osteonecrosis. This analysis reported that patients on >20 mg/d had a higher risk of developing osteonecrosis. 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 (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.

Published literature has included steroid as a risk factor for MRONJ. However, the present authors believe that the steroid induced osteonecrosis (avascular necrosis) of the jaws in the 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.

DECLARATION OF INTEREST

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

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2022.08.014.

REFERENCES

1. Centers for Disease Control and Prevention. COVID-19 and Your Health. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed January 21, 2022.
2. Chan K, Mok C. Glucocorticoid-induced avascular bone necrosis: Diagnosis and management. Open Orthop J. 2012;6:449-457.
3. Matthews AH, Davis DD, Fish MJ. Avascular Necrosis. Treasure Island, FL: StatPearls Publishing; 2022.
4. Wong LS, Tay KK, Chiang YL. Osteonecrosis of mandible: a rare complication of long-term steroid use. J Oral Maxillofac Surg Med Pathol. 2015;27:255-257.
5. Nisi M, La Ferla F, Graziani F, Gabriele M. Osteonecrosis of the jaws related to corticosteroids therapy: a case report. Ann Stomato
tol. 2014;5(suppl 2):29-30.
6. Silva AP, Patr
cjor N, Rajasekaran S. Aggressive presentation and rapid progression of osteonecrosis of the femoral head after COVID-19. Indian J Orthop. 2022;55:1-9.
7. Sood A, Nayyar V, Mishra D, Kakkar A, Priya H. Post-COVID mucormycosis: ascertainment of the pathological diagnostic approach. J Oral Maxillofac Pathol. 2021;25:219-222.
8. Dhanasekararaja P, Soundarrajan D, Kumar KS, Pushpa BT, Rajkumar N, Rajasekaran S. Aggressive presentation and rapid progression of osteonecrosis of the femoral head after COVID-19. Indian J Orthop. 2022;55:1-9.
9. Daltro G, Silva ICF, Daltro PB, Silva ICF, Botelho VL. SARS-CoV-2/ COVID-19 and its Implications in the development of osteonecrosis. J Regen Biol Med. 2020;2(4):1-19.
10. Sood A, Nayyar V, Mishra D, Kakkar A, Priya H. Post-COVID mucormycosis: ascertainment of the pathological diagnostic approach. J Oral Maxillofac Pathol. 2021;25:219-222.
11. Dhanasekararaja P, Soundarrajan D, Kumar KS, Pushpa BT, Rajkumar N, Rajasekaran S. Aggressive presentation and rapid progression of osteonecrosis of the femoral head after COVID-19. Indian J Orthop. 2022;25:1-9.
12. Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. High-dose corticosteroid use and risk of hip osteonecrosis: meta-analysis and systematic literature review. J Arthroplasty. 2015;30:1506-1512. e5.
13. Kanooart Edul VS, Caminos Egui
der R, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127:117-135.
14. Nicolau-Galitsis O, Schmidt M, Mendes RA, et al. American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72:1938-1956.

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REFERENCES

1. Centers for Disease Control and Prevention. COVID-19 and Your Health. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed January 21, 2022.
2. Chan K, Mok C. Glucocorticoid-induced avascular bone necrosis: Diagnosis and management. Open Orthop J. 2012;6:449-457.
3. Matthews AH, Davis DD, Fish MJ. Avascular Necrosis. Treasure Island, FL: StatPearls Publishing; 2022.
4. Wong LS, Tay KK, Chiang YL. Osteonecrosis of mandible: a rare complication of long-term steroid use. J Oral Maxillofac Surg Med Pathol. 2015;27:255-257.
5. Nisi M, La Ferla F, Graziani F, Gabriele M. Osteonecrosis of the jaws related to corticosteroids therapy: a case report. Ann Stoma
tol. 2014;5(suppl 2):29-30.
6. Silva AP, Patr
cjor N, Rajasekaran S. Aggressive presentation and rapid progression of osteonecrosis of the femoral head after COVID-19. Indian J Orthop. 2022;55:1-9.
7. Sood A, Nayyar V, Mishra D, Kakkar A, Priya H. Post-COVID mucormycosis: ascertainment of the pathological diagnostic approach. J Oral Maxillofac Pathol. 2021;25:219-222.
8. Dhanasekararaja P, Soundarrajan D, Kumar KS, Pushpa BT, Rajkumar N, Rajasekaran S. Aggressive presentation and rapid progression of osteonecrosis of the femoral head after COVID-19. Indian J Orthop. 2022;55:1-9.
9. Daltro G, Silva ICF, Daltro PB, Silva ICF, Botelho VL. SARS-CoV-2/ COVID-19 and its Implications in the development of osteonecrosis. J Regen Biol Med. 2020;2(4):1-19.
10. Sood A, Nayyar V, Mishra D, Kakkar A, Priya H. Post-COVID mucormycosis: ascertainment of the pathological diagnostic approach. J Oral Maxillofac Pathol. 2021;25:219-222.
11. Dhanasekararaja P, Soundarrajan D, Kumar KS, Pushpa BT, Rajkumar N, Rajasekaran S. Aggressive presentation and rapid progression of osteonecrosis of the femoral head after COVID-19. Indian J Orthop. 2022;25:1-9.
12. Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. High-dose corticosteroid use and risk of hip osteonecrosis: meta-analysis and systematic literature review. J Arthroplasty. 2015;30:1506-1512. e5.
13. Kanooart Edul VS, Caminos Egui
der R, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127:117-135.
14. Nicolau-Galitsis O, Schmidt M, Mendes RA, et al. American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72:1938-1956.