Just as the virus can mutate, so can coronavirus disease 2019-related bone necrosis!

Hany Hamed, Hesham M. Gawish

Department of Orthopedic Surgery and Traumatology, Kafr El Sheikh University, Kafr El Sheikh, Egypt

Correspondence to Hany Hamed, MD, Department of Orthopedic Surgery and Traumatology, Kafr El Sheikh University, Kafr El Sheikh 33511, Egypt
Tel: +20 122 015 7706;
e-mail: hany_hamed_wn@yahoo.com

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Background
The pandemic of COVID-19 virus had led to another pandemic of avascular necrosis.
Aim
To evaluate the altered clinical and radiological presentation of COVID-19-related AVN of the hip.
Methods
This study included 42 patients with AVN of the head of the femur who were presented to the outpatient clinic of Kafr El Sheikh University Hospital. Patients were classified into three main groups. The first group included patients who had COVID infection and received steroid therapy for their pulmonary manifestations. The second group included patients who had COVID infection without receiving steroid therapy. The final group included patients who had AVN of the hip after receiving COVID vaccination without taking any steroid therapy.
Results
The study included 42 patients who had AVN related to COVID-19 infection. Patients who had COVID-19 infection were more susceptible to AVN development at (a) lower threshold dose of steroid (900 g) and (b) earlier onset of presentation (less than a month).
Conclusions
To conclude, there is a silent epidemic of cases presenting daily in our clinics with COVID-19-related AVN.

Keywords:
CORONA-19, avascular necrosis, total hip replacement

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Introduction

The severe acute respiratory syndrome (SARS) coronavirus-2 [coronavirus disease 2019 (COVID-19)] pandemic has led to immense research to better understand the disease and its complications. Still many questions remain without a clear answer. A plethora of research articles have been published that have focused on the long-term complications of the disease, including the musculoskeletal complications [1].

Although many patients are recovering from COVID-19, it is important to keep in mind that there may be possible complications after convalescence, including unfavorable nonpulmonary affections. One of these complications is avascular necrosis (AVN), which may lead to negative outcomes and bone collapse if missed. AVN in the last few years was frequently seen in COVID-19 infection. It should be kept in mind that the threat of AVN still remains with patients recovered from COVID-19 infection [2].

To date, dexamethasone was the first drug found to be of great help in saving lives of COVID-19-infected patients. According to the RECOVERY clinical trial, which was one of the biggest studies about COVID-19 treatments, this medication decreased risk of death in hospitalized patients with severe COVID-19 who were on ventilator or receive oxygen by 20% [3].

Apart from steroids, the effects of the virus itself on the human body is another issue. AVN may also happen owing to microvascular thrombosis. Thrombi development could be a result of endothelial cell damage. AVN may occur distal to the site of arterial obstruction. It is known that SARS-CoV-2 enters host cells via angiotensin-converting enzyme 2 protein, which is expressed by endothelial cells as well as lungs and leads to vascular lesions via coagulopathy and

inflammatory syndrome. Endothelial activation and changes in endothelial cells were reported in severe COVID-19 infection cases [4,5].

Currently, in the absence of large data of patient follow-up, early diagnosis of AVN is important, because the consequent bone collapse may be prevented. Thus, it is recommended that large joint pain after COVID-19 should be taken seriously, in order to not miss AVN. The combination of hypercoagulability, leukocyte aggregation, and vasculitis can impair blood flow in the blood vessels of the bone and contribute to the development of bone necrosis in those patients [6].

However, we noticed that the COVID-19-related AVN showed different presentations and course of usual AVN encountered in our daily practice. This study was done to evaluate the altered clinical and radiological presentation of COVID-19-related AVN of the hip.

Patients and methods

This study included 42 patients with AVN of the head of the femur who were presented to the outpatient clinic of Kafr El Sheikh University Hospital between May 2021 and February 2022. A total of 37 patients had previous COVID infection and were admitted to Kafr El Sheikh University Hospital Chest Department during COVID-19 pandemic. The other five patients did not have COVID infection and just had COVID vaccine (Oxford–AstraZeneca COVID-19 vaccine). All of them were referred to our outpatient clinic with hip pain and limping that started after the course of the disease or after the vaccination. History taking along with complete clinical and radiological examination was done. All of them was found to have AVN of the femoral head.

This was a prospective therapeutic case series study that was approved by the Committee of Medical Ethics and the institutional review boards of Kafr El Sheikh University Hospitals. Written informed consents were obtained from all the patients before participation.

Inclusion criteria were PCR indicating positive COVID-19-infected patients with hip pain after healing of the respiratory manifestations or patients with hip pain after COVID-19 vaccine.

Exclusion criteria were prior injury to the affected joint, prior treatment with steroids for other reason than COVID infection, and severe chronic debilitating illness. Patients with prior hip pain before COVID-19 treatment, previous surgery in the involved hip, chronic steroid intake, and patients with hypercoagulable states were also excluded from the study.

Patients were classified into three main groups. The first group included patients who had COVID infection and received steroid therapy for their pulmonary manifestations. They were diagnosed as COVID-19 positive with RT-PCR and/or computed tomography (CT) of the chest. The second group included patients who had COVID infection without receiving steroid therapy. The final group included patients who had AVN of the hip after receiving COVID vaccination without taking any steroid therapy. Patients were evaluated clinically and radiologically for their osteonecrosis.

Methylprednisolone was the most commonly used steroid, and other steroid forms like dexamethasone and prednisolone were also used. For uniform reporting, we calculated the methylprednisolone equivalent dose by the conversion factor of 0.8 for prednisolone and 5.3 for dexamethasone [7].

Methods of evaluation

Clinical evaluation

Data regarding patients' age, sex, BMI, duration between COVID-19 infection and initial hip symptoms, and duration of hip pain were collected. The criterion for classifying the severity of COVID-19 infection was defined according to a four-point scale: mild, moderate, severe, and critical [8].

Hip function was assessed using the Harris hip score (HSS) [9]. Patient's level of pain before and after treatment was evaluated using visual analog scale (VAS) [10].

Laboratory parameters included in the study were erythrocyte sedimentation rate, C-reactive protein, and white blood cell count.

Radiological evaluation

All the patients who presented with acute hip pain to our outpatient clinic were screened with plain radiographs and then with MRI examination. AVN was diagnosed using MRI and interpreted by a senior musculoskeletal radiologist. The diagnosis of AVN was made by a single density "bandlike" lesion with a low rim of signal intensity that surrounds necrosis in T1 images and by a "double line sign" consisting of an external low signal intensity rim and a high signal intensity internal rim on the T2 image [7].

All patients had CT scans of the affected hip, and all were diagnosed with AVN.

AVN was classified according to Ficat [11], Steinberg [12], and ARCO (Association Research Circulation Osseous classification) [13] classification systems.

The China-Japan Friendship Hospital (CJFH) classification was also used to localize the lesion within the head. This Japanese investigation committee (JIC) classification was formerly usually used to categorize the location of the necrotic lesion at the weight-bearing zone. In stage A, lesions occupy the medial one-third or less of the weight-bearing portion. In stage B, lesions occupy the medial two-thirds or less of the weight-bearing portion. In stage C, lesions occupy more than the medial two-thirds of the weight-bearing portion. This stage has two subcategories: in stage C1, lesions do not extend laterally, and in stage C2, lesions extend laterally to the acetabular edge [14]. However, the CJFH classification is based on the locations of necrotic foci in the three pillars of the femoral head. Type M necrosis involves the medial pillar, type C involves the medial and central pillars, type L1 involves all three pillars with partial preservation of the lateral pillar, Type L2 involves the entire lateral pillar and part of the central pillar, and Type L3 involves all three pillars, including the cortical bone and marrow. We used the CJFH classification in this study [15].

The necrotic angle severity was calculated in midcoronal and midsagittal image in MRI and graded by the modified Kerboul angle into grade 1 (<200°), grade 2 (200°–249°), grade 3 (250°–299°), and grade 4 (>300°) [16].

The bone marrow edema involving only over the weight-bearing necrotic zone in the femoral head was graded as grade 1, edema extending into the femoral neck region was graded as 2, edema involving beyond neck region was graded 3, and edema involving acetabulum and periarticular soft tissue with effusion was graded as 4 [7].

Gross and histopathology examination

Cases that needed total hip replacement as a treatment of AVN of the hip were subjected to gross and histopathological evaluation of the excised head by the pathology department of our university.

Statistical analysis

Statistical analysis was done using SPSS program, version 25. (IBM SPSS Statistics for Windows, Version 25.0.; IBM Corp., Armonk, New York, USA). Data were found to be not normally distributed using Shapiro test. Nonparametric tests were used to evaluate results. *P* value was set at less than 0.05.

Results

The study included 42 patients who had AVN related to COVID-19 infection. Patients were classified into three groups. The first group (28 patients) had COVID-19 infection and received steroids in their treatment protocol. The second group (nine patients) had COVID-19 infection but did not receive steroids. The third group (five patients) did not have COVID infection but they just received the vaccine.

Group A included 28 patients. Their mean age was 32.7 ± 7.06 years. A total of 12 cases were males, whereas 16 were females. Their mean BMI was 28.2 ± 2.25 kg/m^2. Overall, 16 cases had moderate COVID infection, whereas 12 cases had severe infection. The average duration of the disease was 23 days. Hip pain developed after an average of 5 months (3–7 ± 1.3) from infection. The average dose of steroid received was 938.57 ± 282.31 g (560–1800). Most of the cases (38 cases) had bilateral affection but had pain more on one side. Seven cases had knee condyle AVN. Nine cases improved symptomatically only with medical treatment, 12 cases underwent core decompression, four cases received total hip replacement, and three cases refused any further treatment. Patients were followed up for an average of 5 months (Table 1).

Group B included nine cases. Their mean age was 38.4 ± 4.76 years. Five cases were men and four were females. Their mean BMI was 27.11 ± 1.36 kg/m^2. Two cases had moderate COVID affection, whereas most of cases (seven cases) had severe infection. The average duration of infection was 17 days. Hip pain was developed after an average of 5 months from infection. Patients were followed up for 4.6 months. Most of the cases had bilateral affection. Three patients improved symptomatically on medical treatment, five cases had core decompression, and only one case had total hip replacement (Table 1).

Group C included only five cases. Their mean age was 23.8 ± 4.2 years. All cases were males. Their mean BMI was 26.2 ± 0.08 kg/m^2. All had moderate affection. Hip pain developed after about 5 months from vaccination. All cases received AstraZeneca vaccine. After vaccination, they all had symptoms like, fever, reaction, swelling, and redness at the injection site. Four of them had bilateral AVN. They were followed up for an average of 5 months. Four cases received core decompression, and only one case received total hip replacement (Table 1).

All cases received the same protocol of management once proved AVN. They all had miacalcic injection 50 mg EOD, naftidrofuryl 200 (praxilan) twice daily, alendronate 70 mg once per week, and nonsteroidal for 15 days. If no improvement, core decompression was planned. If failure to improve after 2 months, total hip replacement was anticipated.

Table 1 Patients' demographic data

	Group A: COVID+steroid (*N*=28)	Group B: COVID without steroids (*N*=9)	Group C: AVN after COVID vaccine (*N*=5)	Test of significance
Age (years)	32.7±7.06	38.4±4.76	23.8±4.2	*H*=11.9 *P*=0.003*
Sex				χ^2=5.6 *P*=0.06
Male	12	5	5	
Female	16	4	0	
BMI (kg/m2)	28.2±2.25	27.11±1.36	26.2±0.08	H = 5.82 *P*=0.54
COVID grade				χ^2=45.77 *P*=0.000*
Mild	0	0	0	
Moderate	16	2	5	
Severe	12	7	0	
Critical	0	0	0	
Duration of infection (days)	23.6±7.4	17.66±4.3	No infection	*U*=18.0 *P*=0.000*
Steroid therapy	938.57±282.31	0	0	
dose (g)	(560–1800)			
Duration from infection to hip pain (months)	4.85±1.14	5.22±0.97	5±1.41	*H*=0.717 *P*=0.699
Affection				χ^2=4.48 *P*=0.61
Right	2	0	0	
Left	6	0	1	
Right>left	10	5	2	
Left>right	10	4	2	
Other joint affection (knee)	7 cases	7 cases	5 cases	χ^2=14.5 *P*=0.001*
Management				χ^2=4.54 *P*=0.60
Medical Rx	9	3	0	
Core decomp	12	5	4	
Arthroplasty	4	1	1	
No Rx	3	0	0	
Follow up (months)	5.1±0.91	4.6±0.89	5.2±0.44	
Vaccine received				χ^2=24.59 *P*=0.000*
AstraZeneca	1	4	5	
Johnson	16	3	0	
Sinopharm	10	2	0	
Pfizer	1	0	0	

χ^2, χ^2 test; AVN, avascular necrosis; COVID, coronavirus disease; *H*, Kruskal–Wallis test; *U*, Mann–Whitney test; *Z*, Wilcoxon signed-rank test.
**P* value less than 0.05.

Table 2 Clinical outcomes of the three cohorts

	Group A: COVID+steroid (*N*=28)	Group B: COVID without steroids (*N*=9)	Group C: AVN after COVID vaccine (*N*=5)	Test of significance
VAS first presentation	8.03±0.79	8.11±0.78	7.6±0.98	*H*=1.49 *P*=0.474
VAS at end of FU	4.39±1.4	4.56±1.42	3.2±1.03	*H*=3.23 *P*=0.199
Difference VAS	*Z*=4.64	*Z*=2.71	*Z*=2.03	
	P=0.000*	*P*=0.007*	*P*=0.42	
HHS first presentation	37.78±7.8	36.88±7.76	34.6±7.5	*H*=0.82 *P*=0.662
HHS at end of FU	74.71±10.0	70.44±7.1	73.4±9.3	*H*=1.23 *P*=0.54
Difference HSS	*Z*=4.62	*Z*=2.67	*Z*=2.03	
	P=0.000*	*P*=0.007*	*P*=0.43	

χ^2, χ^2 test; AVN, avascular necrosis; COVID, coronavirus disease; *H*, Kruskal–Wallis test, HSS, Harris hip score.

Patients who had COVID-19 infection were more susceptible to AVN development at (a) lower threshold dose of steroid (900 g) and (b) earlier onset of presentation (less than a month), as shown in Table 1.

Regarding clinical outcomes, most patients of groups A and B had better follow-up scores for VAS and HSS. This was not the scenario for group C. This difference may be owing to most cases of groups A and B underwent total hip replacement in comparison with group C, which had only one case that underwent total hip replacement (Table 2). We observed that only cases with total hip replacement had improved VAS and HSS scores. Core decompression was associated with worst prognosis with severe clinical and radiological deterioration

Table 3 Avascular necrosis grading, sizing, localization, and classification

	Group A: COVID+steroid (*N*=28)	Group B: COVID without steroids (*N*=9)	Group C: AVN after COVID vaccine (*N*=5)	Test of significance
Ficat classification				χ^2=1.99 *P*=0.92
I	0	0	0	
IIa	2	0	0	
IIb	12	3	2	
III	10	5	2	
IV	4	1	1	
Steinberg classification				χ^2=9.94 *P*=0.26
I	0	0	0	
II	2	0	0	
III	12	3	2	
IV	10	5	2	
V	0	0	1	
VI	4	1	0	
ARCO classification				χ^2=0.72 *P*=0.94
I	0	0	0	
II	1	0	0	
III	23	8	4	
IV	4	1	1	
CJFH				χ^2=39.2 *P*=0.000*
M	0	5	2	
C	0	4	2	
L1	4	0	0	
L2	17	0	0	
L3	7	0	1	
KFS classification				χ^2=22.54 *P*=0.000*
AI	5	9	4	
PS	14	0	0	
Pan	9	0	1	
Kerboul grading				χ^2=26.92 *P*=0.000*
<200	0	3	1	
200–249	4	6	3	
250–299	17	0	0	
>300	7	0	1	
BME grading				χ^2=5.86 *P*=0.209
Grade I	4	1	0	
Grade II	16	3	1	
Grade III	4	3	3	
Grade IV	4	2	1	

χ^2, χ^2 test; AVN, avascular necrosis; CJFH, China-Japan Friendship Hospital; COVID, coronavirus disease; *H*, Kruskal–Wallis test.
**p* value = 0.05

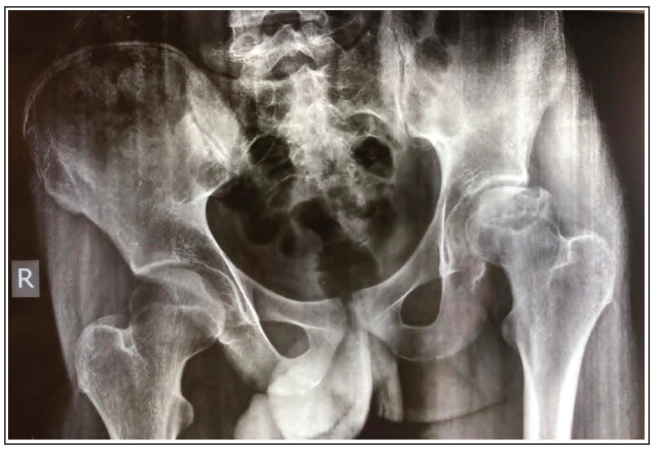
even after appropriate period of nonweight bearing. The mean final VAS score in cases with core decompression was 7.1 ± 0.9 points in comparison with a score of 2.4 ± 0.3 points in cases with total hip replacement (P<0.002). The same was observed with HSS score for core decompression cases (34.7 ± 4.5) in comparison with total hip cases (85.3 ± 2.3), with P value less than 0.05.

Regarding radiological observations, there was no statistically significant difference among the three cohorts concerning the osteonecrosis grading, either Ficat, Steinberg, or ARCO (Table 3).

The radiological appearance of COVID-19-associated osteonecrosis is somewhat different than the usual appearance of ordinary steroid-induced AVN. In the plain radiographs, a dense sclerotic rim of bone necrosis with an osteolytic large cystic lesion was observed just inferior to sclerotic area. In some cases, there was obvious pelvic obliquity due to severe joint irritation with subsequent adduction deformity (Fig. 1).

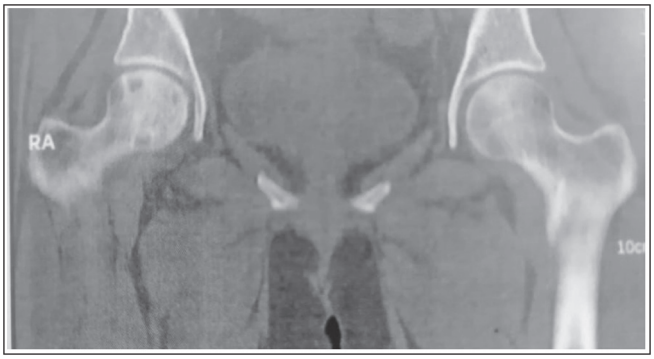
Regarding CT scans, diffuse sclerotic area of left head of the femur with multiple cyst formation was observed resembling "polling ball." This signifies both epiphyseal and metaphyseal circulatory occlusion (Figs 2 and 3).

Figure 1



Plain radiograph of a 19-year-old male patient with COVID-related AVN. The left hip is seen with dense sclerotic rim of bone necrosis with an osteolytic large cyst just inferior to sclerotic area. There was obvious pelvic obliquity due to severe joint irritation with subsequent adduction deformity. AVN, avascular necrosis; COVID, coronavirus disease.

Figure 2



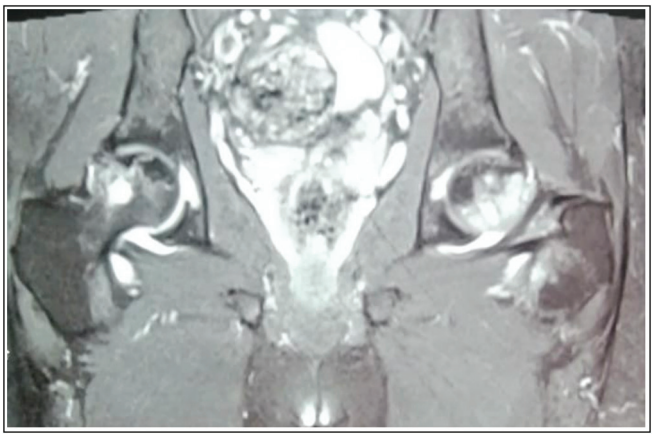
CT scan of left hip showing diffuse sclerotic area of left head of the femur with multiple cyst formation "polling ball sign." This signifies both epiphyseal and metaphyseal circulatory occlusion. CT, computed tomography.

Regarding MRI, three distinctive zones were identified in MRI. First is the necrotic cap. The second is multiple cysts arranged in belt fashion. The third is the bone marrow edema zone that extends beyond the neck region (Figs 4–7).

MRI pattern of COVID-19-related AVN is more diffuse the usual steroid-induced AVN. Lesions are more diffuse than and a little bit inferior and anterior than what we usually tend to see in AVN cases. The crescent is not usually in the superior part of the head. There are bigger semilunar areas with more central and inferior lesions (Fig. 8).

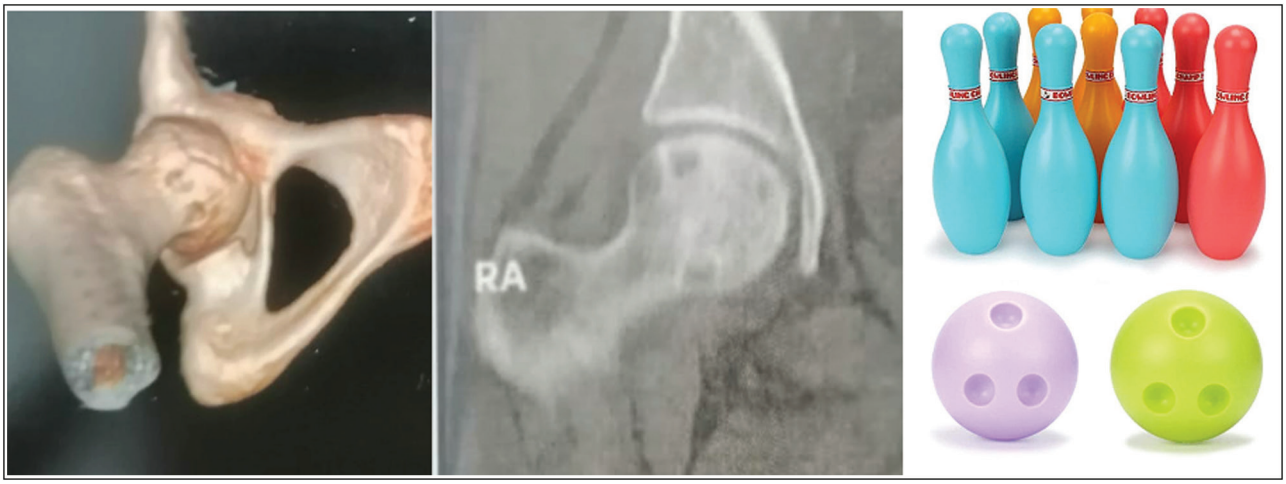
In the lateral view of the radiograph and in the axial views of the MRI scan, the lesion was always seen very anterior. In most non-COVID AVN, the lesion is mostly posterior. This point is of an important surgical value intraoperatively

Figure 4



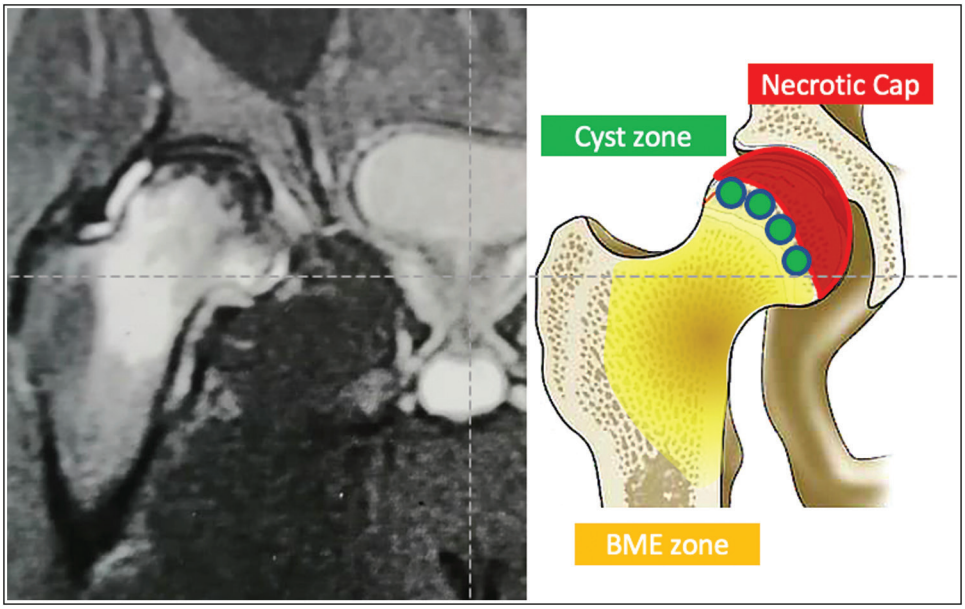
MRI T2 FS image showing zone of necrosis followed by zone of cyst formation and then zone of bone marrow edema extending through whole neck region till trochanteric area.

Figure 3



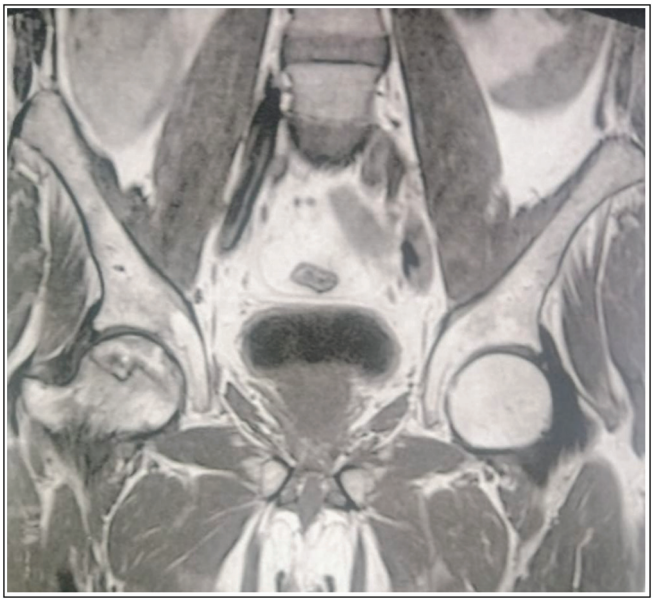
In the coronal CT scan films, the head appeared full of cysts as a polling ball. CT, computed tomography.

Figure 5



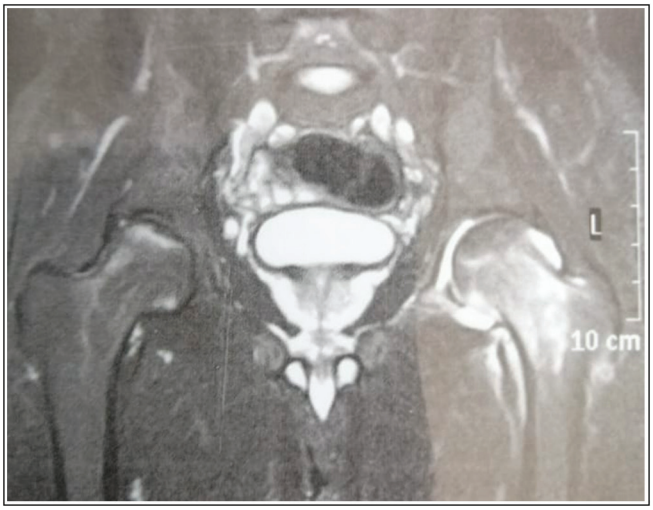
Three classical zones can be seen in MRI: the first is the necrotic cap, the second is multiple cysts arranged in belt fashion, and the third is the bone marrow edema zone that extends beyond the neck region.

Figure 6



MRI T1 image of both hips showing left hip COVID-related AVN with large crescent area of bone infarction extending below the fovea. AVN, avascular necrosis; COVID, coronavirus disease.

Figure 7



MRI T2 image showing left COVID-related AVN with evident joint effusion and bone marrow edema extending below the necrotic area in a diffuse fashion till the lesser trochanteric "pan trochanteric bone marrow edema." AVN, avascular necrosis; COVID, coronavirus disease.

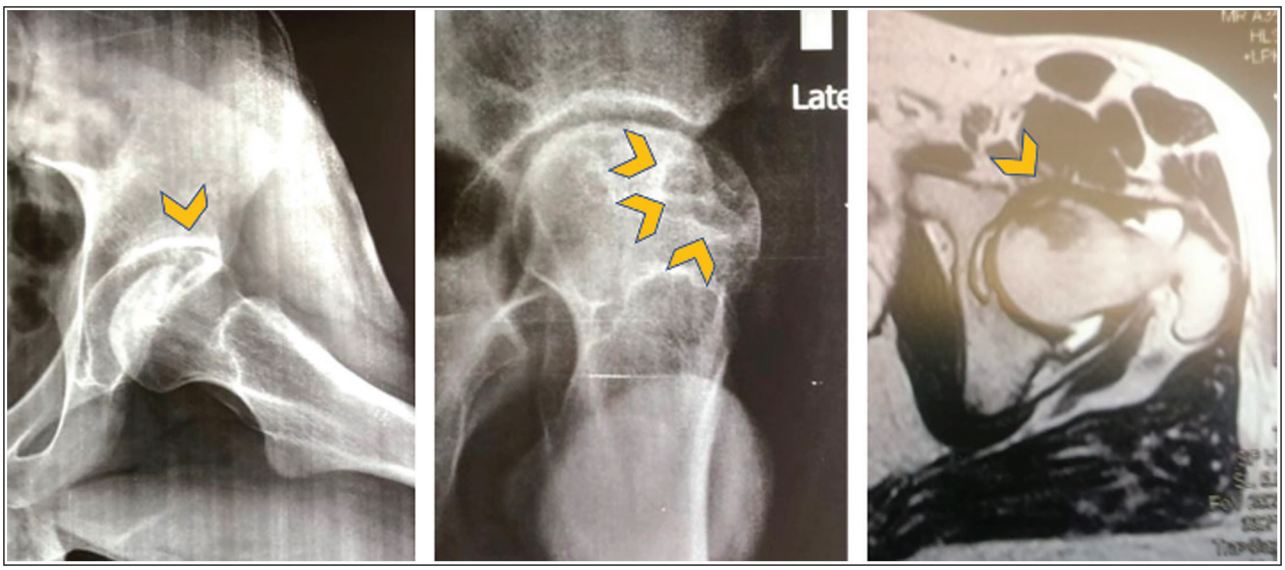
while performing a surgical core decompression for those cases. The reamer should go far anterior to violate the sclerotic rim of anterior lesion (Fig. 9).

Multiple subchondral cysts and hemorrhagic areas are seen than usual AVN, denoting more severe coagulopathic pathology. This was observed in most cases with nonhip osteonecrosis, especially at knee joint. This was rarely seen with steroid-induced AVN (Fig. 10).

Regarding bone marrow edema associated with cases of AVN after COVID-19, cases were classified into four groups as previously mentioned (Fig. 11 and Table 3). The four types were observed in all the three groups, with no statistically significant difference between their distributions. Most of cases of steroid-induced AVN do not usually show these aggressive forms of BME.

The necrotic area was calculated using the Kerboul angle. The necrotic angle severity was calculated in midcoronal and midsagittal images in MRI and graded by modified Kerboul angle into grade 1 (<200°), grade 2 (200°–249°), grade 3 (250°–299°), and grade 4 (>300°).

Figure 8



An evident anterior affection in the most cases of the COVID-19-associated AVN. AVN, avascular necrosis; COVID, coronavirus disease.

Higher angles were seen in cases of group A (P<0.001, Table 3, Fig. 12).

The CJFH classification is based on the locations of necrotic foci in the three pillars of the femoral head. In our study, most cases of group A were L2 and L3, denoting more severe affection. However, most cases of groups B and C were types M and C, denoting more medial and central affection (Fig. 13, Table 3).

Based on these observations, we developed a simpler classification for COVID-related AVN. Our classification is based mainly on anatomical arterial supply of the femoral head. Some cases had isolated anterioinferior affection owing to coagulopathy of anterior retinacular artery, a branch of lateral circumflex femoral artery. Another group of cases had more anteriosuperior or dome affection owing to isolated injury to superior retinacular artery, which is a branch of medial circumflex femoral artery. Another group of cases had affection in two or three arteries, leading to pan head necrosis (Table 4, Fig. 14).

There was a major striking difference in the MRI between dome-free and dome-affected types. In the dome-free type, the lesion is more vertical and extends below the axis of the neck. However, in the dome-affected type, the lesion is usually horizontal and rarely crosses the neck axis (Fig. 15).

Regarding the gross pathological evaluation of the extracted femoral heads during total hip replacements, bigger semilunar areas of bone infarction with larger hemorrhagic areas were seen. Lesions are more central, inferior, and anterior. Larger areas of infarction are seen infrafoveal. Large cystic lesions are also present, which is not reported with steroid-induced AVN (Figs 16–18).

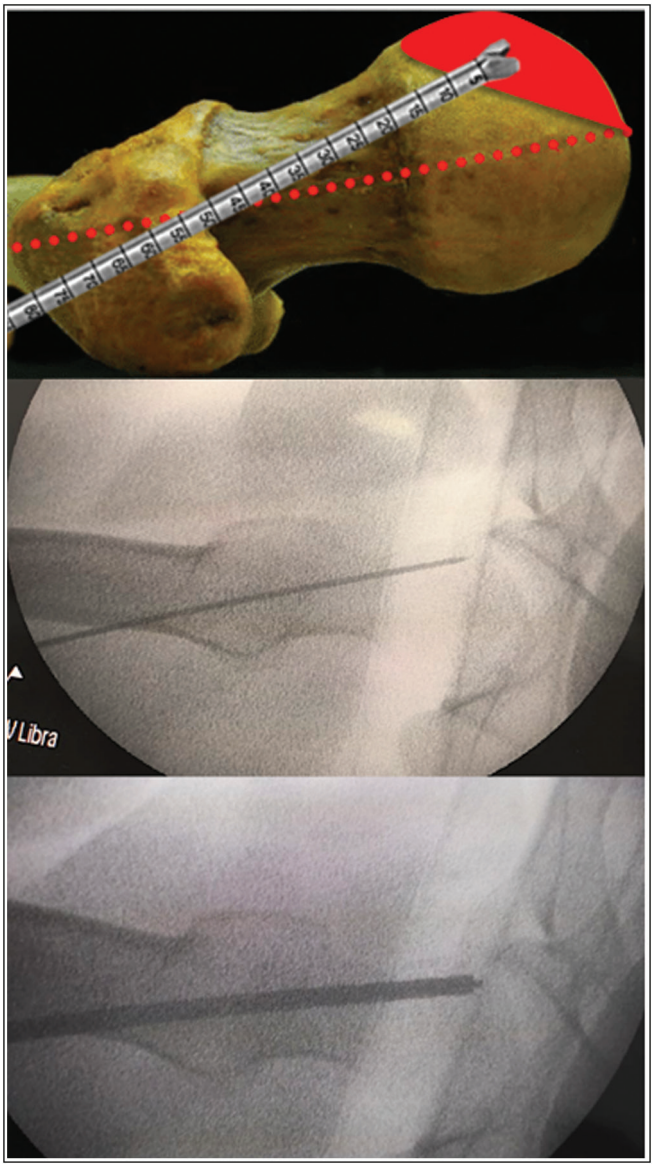
Regarding the histopathological evaluation, examination of bone sections with hematoxylin and eosin stain by Leica ICC50 HD microscope, Leica application suite EZ program, was done in our pathology department. Avascular bone necrosis of femoral head exhibited massive areas of bone necrosis admixed with fibrin and numerous blood clots. A large number of empty lacunae, some dilated, were seen in bone trabecula. Bone trabecula's color is darker than normal. Poorly vascularized fibrous marrow with widened bone marrow spaces is seen. There is calcified marrow in adjacent nondiseased areas (Figs 19–24).

Discussion

The severe morbidity and potential mortality in the SARS-CoV-2-induced COVID-19-infected patients can be largely attributed to the augmented immune response characterized as a cytokine storm [17]. Law *et al.* [18] noted that the use of high doses of corticosteroids increased the risk of the appearance of AVN of the joint and hip.

Corticosteroids have been employed to suppress these aggravated immune responses in severely ill patients. Excessive use of glucocorticoids has been shown to increase the plasma levels of von Willebrand factor (vWF), which is essential for the aggregation and adhesion of platelets; thus, its loss due to the

Figure 9



The reamer should go far anterior to violate the sclerotic rim of anterior lesions.

glucocorticoid-induced endothelial damage also increases the risk of thrombosis and AVN [18].

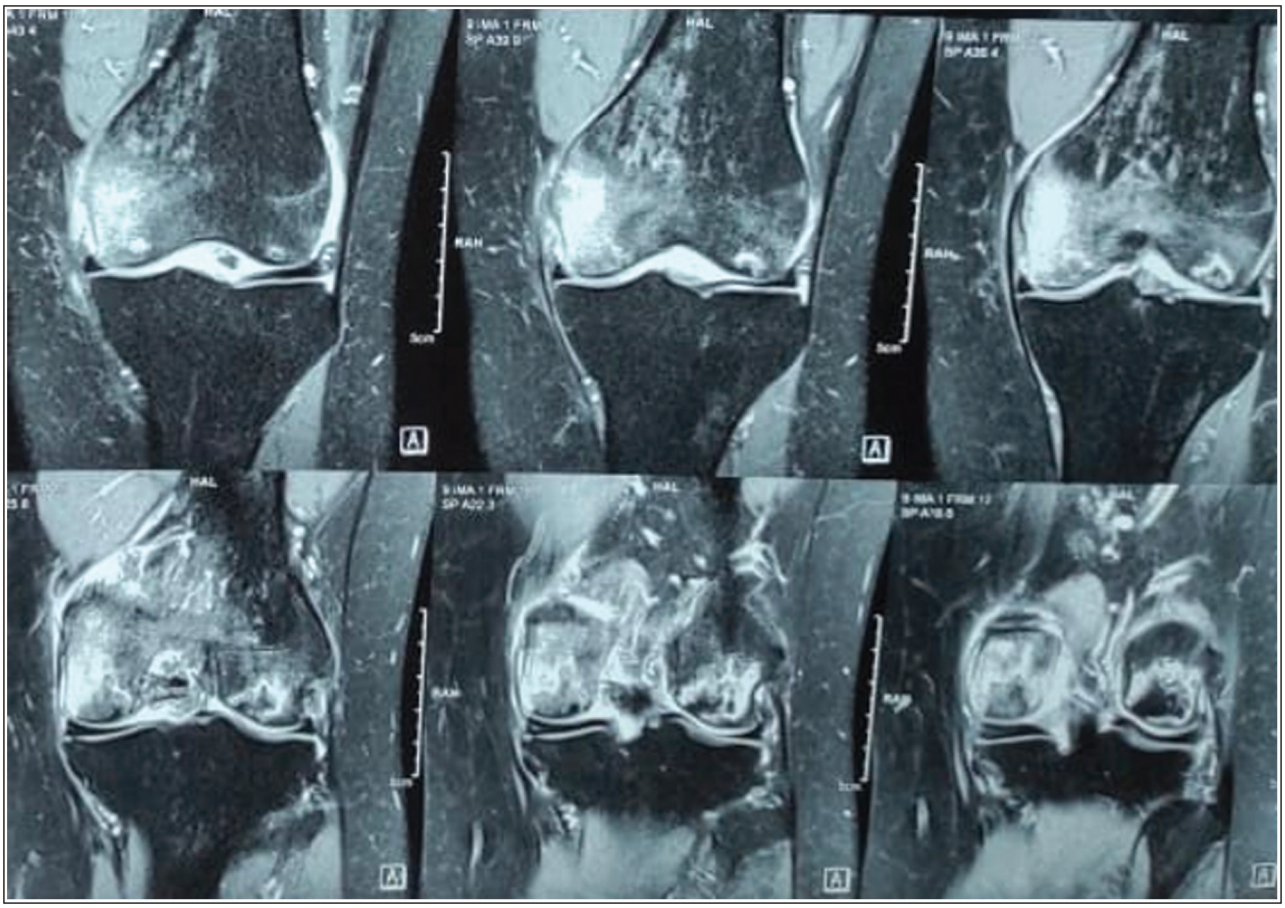
The SARS-CoV-2 infection in itself can induce endothelial dysfunction producing excess thrombin and fibrinolysis shutdown, resulting in a state of hypercoagulability. Thus, all recovered COVID-19-infected patients should be screened for suspected AVN with MRI before any surgical intervention [19].

COVID-19 infection causes an obvious hypercoagulable state, increasing the risk for both arterial and venous thrombosis. A high incidence of thrombotic complications has been documented in the literature. There have been a number of reports for arterial thrombosis. The pathogenesis of this prothrombotic state is currently incompletely understood. A myriad of factors may play a role, and different mechanisms have been proposed. Consequently, this phenomenon has been termed "COVID-associated coagulopathy" [20]. The severe morbidity and potential mortality in the COVID-19-infected patients can be largely attributed to the augmented immune response characterized as a "cytokine storm" [21].

In one large study of 3335 hospitalized patients with COVID-19, thrombotic events occurred in 16% of patients. Arterial events included ischemic stroke (1.6%), systemic thromboembolism (1.0%), and myocardial infarction (8.9%) [22]. Marked increases of endothelial activation and injury markers including vWF, angiopoietin 2, P-selectin, and thrombomodulin have been noted, where vWF and thrombomodulin correlate with mortality [23]. Hyperactivation of the complement system has been seen in COVID-19, with increased circulating markers correlating with severe disease. Activation of complement may be direct from COVID-19 or as a sequela of endotheliopathy, which, in turn, activates the complement system [24]. Laboratory analysis has been consistent with a hypercoagulable state in COVID-19. Increased D-dimer, fibrinogen, factor VIII, and vWF and decreased antithrombin have been noted in the critically ill [25]. Although critical illness is known to cause a hypercoagulable state, COVID-19 appears to cause a profoundly proinflammatory state, escalating prothrombotic factors. These factors have been confirmed to cause thromboembolism despite appropriate thromboembolic prophylaxis [26].

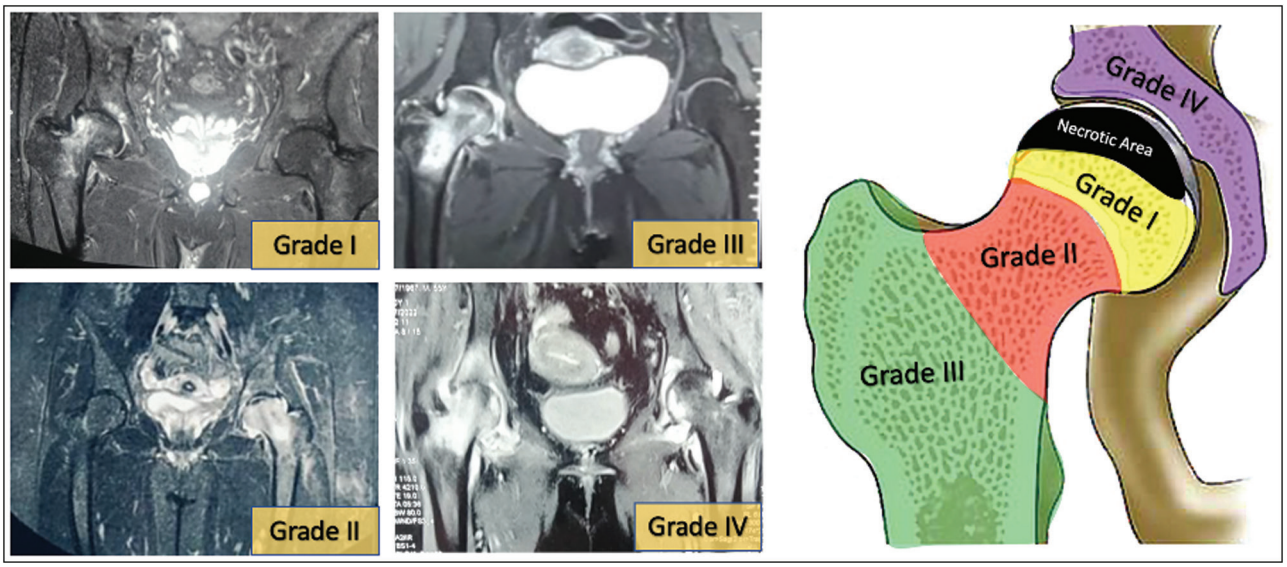
In our study, 42 patients had AVN related to COVID-19 infection. Patients were classified into three groups. The first group (28 patients) had COVID-19 infection and received steroids in their treatment protocol. The second group (nine patients) had COVID-19 infection but did not receive steroids. The third group (five patients) did not have COVID-19 infection but they just received the vaccine. Regarding the first group, we observed a very aggressive course of the disease than usual reported with steroid-induced AVN. Cases had developed AVN with a small dose of steroid less than 1000 mg with rapidly deteriorating course and severe hip pain. Overall, 14% of the cases received total hip replacement as a solution for their pain. The second group developed AVN without steroid therapy. One case only received total hip replacement. The third group had AVN after vaccination with AstraZeneca vaccine. One cases also received a total hip replacement. Moreover, we observed that cases that sustained core decompression, they did not improve radiologically, but pain and function were partially improved, which was the same scenario with medical treatment. Therefore, we do not recommend core decompression as a solution for COVID-19-related

Figure 10



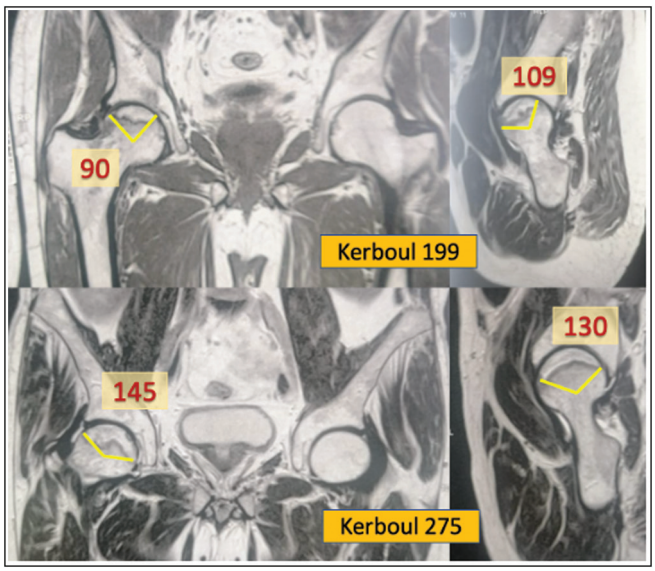
Osteonecrosis of knee femoral condyles.

Figure 11



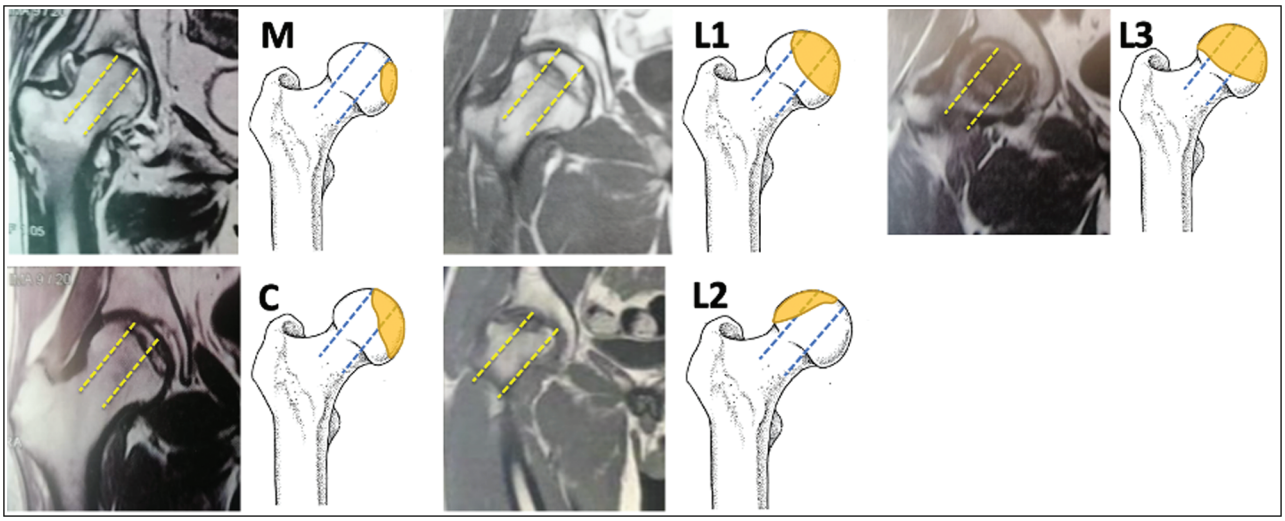
Bone marrow associated with COVID-related ONFH. The bone marrow edema involving only over the weight-bearing necrotic zone in the femoral head was graded as grade I, edema extending into the femoral neck region was graded as II, edema involving beyond neck region was graded III, and edema involving acetabulum and periarticular soft tissue with effusion was graded as IV. COVID, coronavirus disease.

Figure 12



Kerboul angle severity was calculated in midcoronal and midsagittal images in MRI.

Figure 13



The China-Japan Friendship Hospital (CJFH) classification seen in our cases.

Table 4 The proposed Kafr El Sheikh University pathogeographical classification system for coronavirus disease 2019-related avascular necrosis

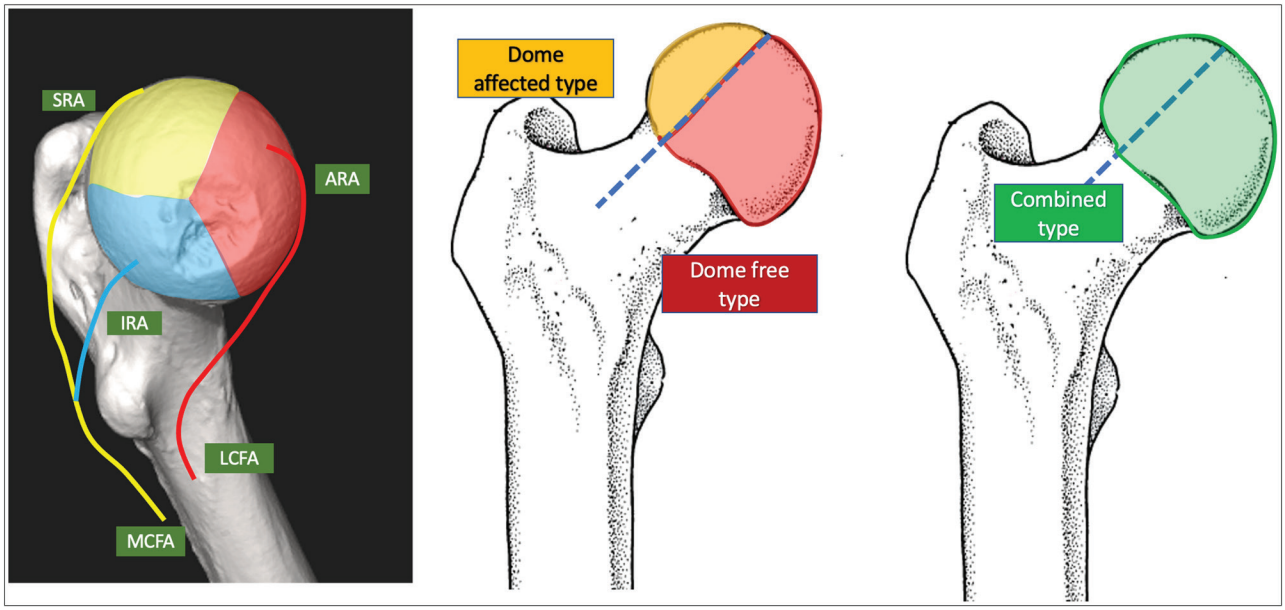
Type	Affection	Injury	Proposed treatment
I Dome free type	Central and medial	Affection of ARA alone	Medical with nonweight bearing
II Dome type	Superior (resemble steroid-induced AVN)	Affection of SRA alone	Core first if failed: THR
III Combined	Pan head necrosis	2 or 3 arterial affection	THR from the start

AVN, avascular necrosis; THR, total hip replacement.

AVN, especially those late presenting cases and those with severe pain and limitation of hip function owing to high-grade osteonecrosis.

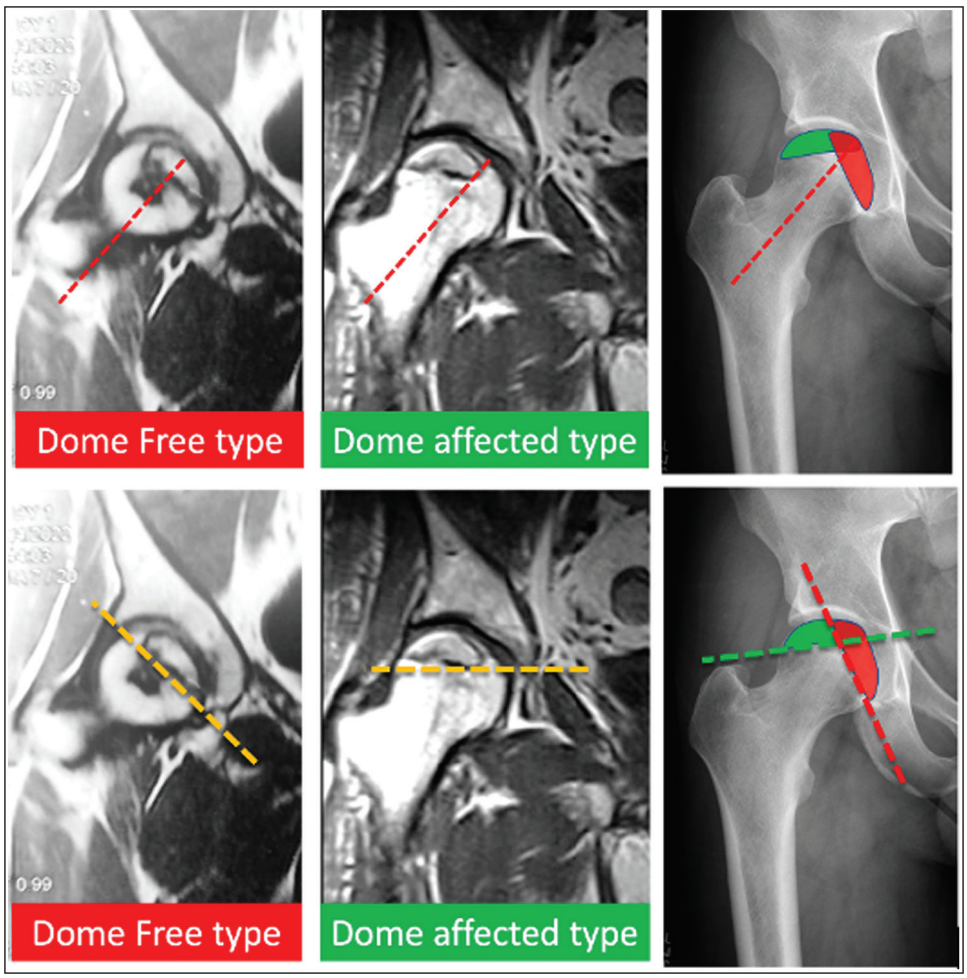
Mañón *et al.* [27] reported a 72-year-old man who presented to their department for surgical management of his infarcted maxilla, which developed as a sequela of infection with COVID-19. They concluded that infection with COVID-19 confers a hypercoagulable state in patients, leading to various thromboembolic complications even in the head and neck region.

Figure 14



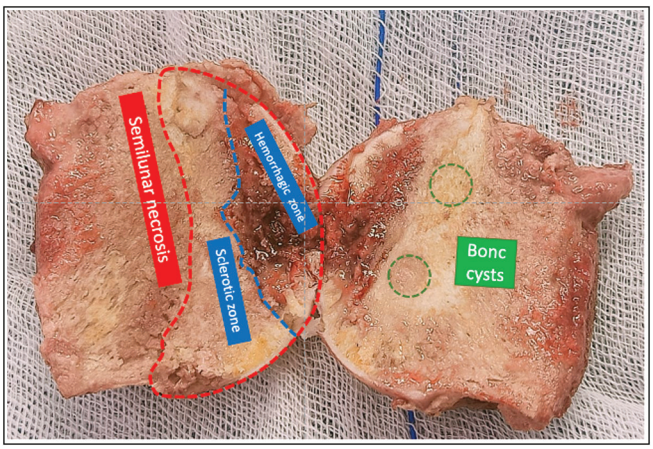
The most important finding of this study was clarifying the different pathological affection in COVID-19-related AVN. Some cases with AVN show isolated affection of SRA (dome affection) and in some cases ARA (dome free type). This clearly explains the isolated anteroinferior affection of some cases without dome affection which was not observed in most cases with steroid-induced AVN. AVN, avascular necrosis; COVID, coronavirus disease.

Figure 15



The difference between dome-free and dome-affected types.

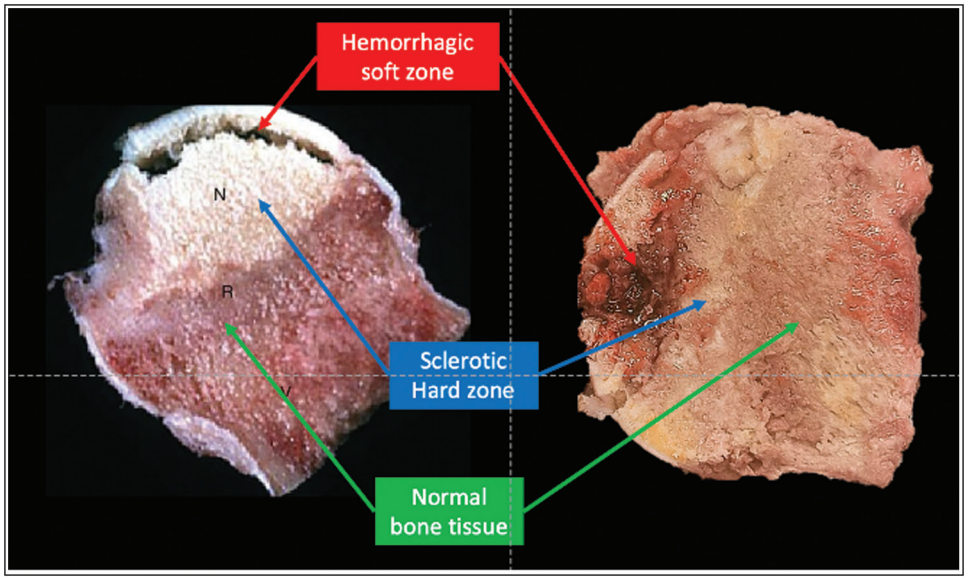
Figure 16



Bigger semilunar areas of bone infarction with larger hemorrhagic areas were seen along with cystic lesions.

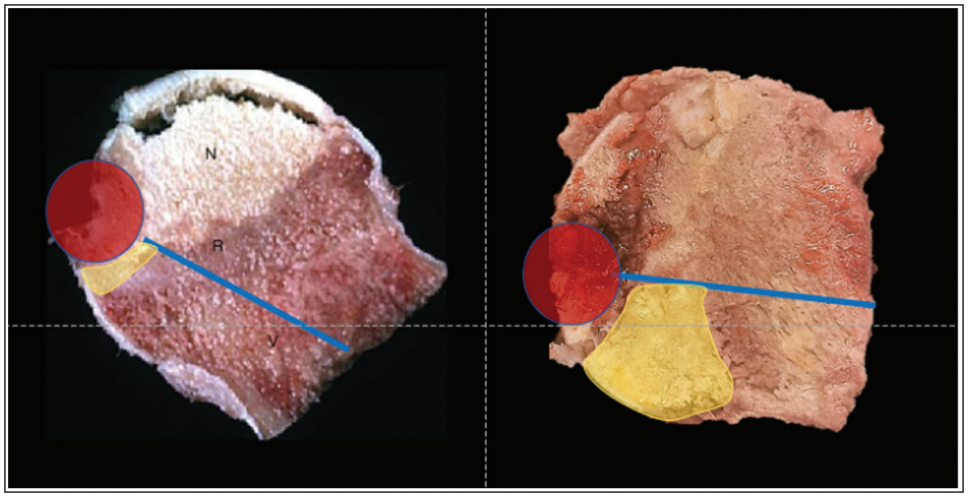
Dhanasekararaja *et al*. [7] reported an aggressive course of COVID-19-related AVN in 22 patients recovered from COVID-19 and presented with osteonecrosis of the femoral head (ONFH). All of them received corticosteroids. They classified patients into two types based on the type of presentation, namely, classic ONFH and rapidly destructive coxarthrosis. The mean time to diagnose of ONFH from the onset of hip symptoms was 39.3 days. The average duration of onset of hip symptoms after COVID 19 infection was 7.5 months. The average cumulative dose of methylprednisolone equivalent was 811 mg, and the average duration of steroid intake was 2.8 weeks. There was significant elevation in the inflammatory markers in rapidly destructive coxarthrosis group compared with classic ONFH (P<0.05). The HSS improved from 63.6±23.2 at presentation to 82.6±9.6 after treatment (P<0.05). Three patients had

Figure 17



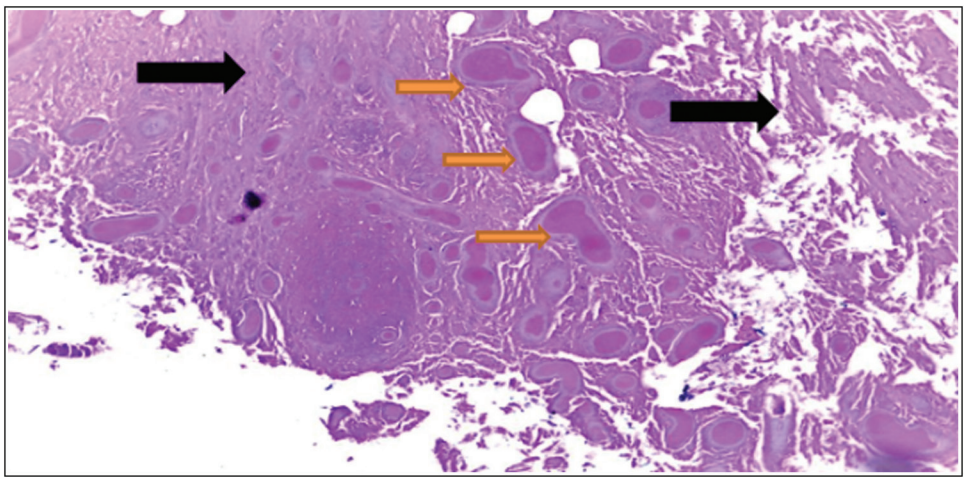
The difference between osteonecrosis in steroid-induced AVN (left) and COVID induced (right). AVN, avascular necrosis; COVID, coronavirus disease.

Figure 18



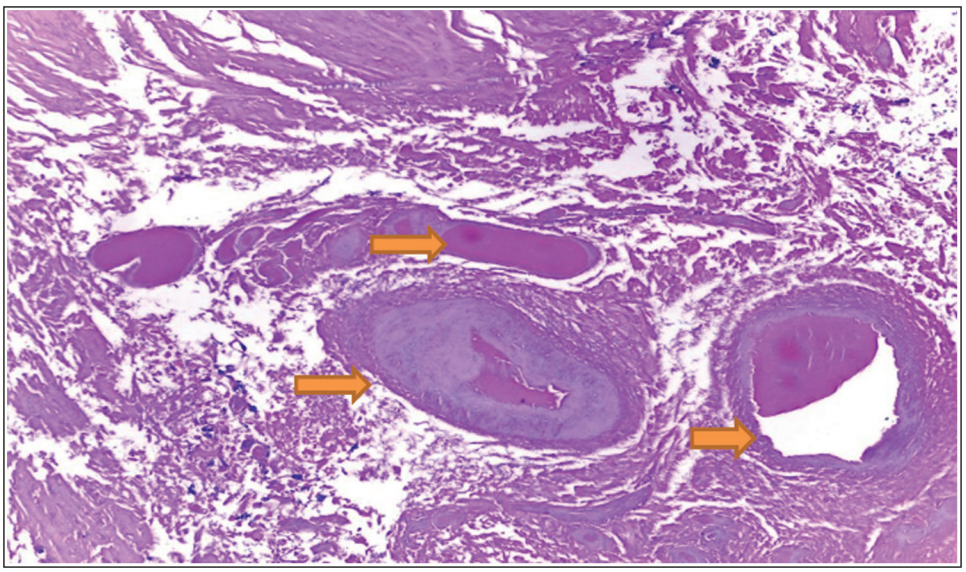
Larger areas of infarction are seen infrafoveal with COVID-related AVN (right side). AVN, avascular necrosis; COVID, coronavirus disease.

Figure 19



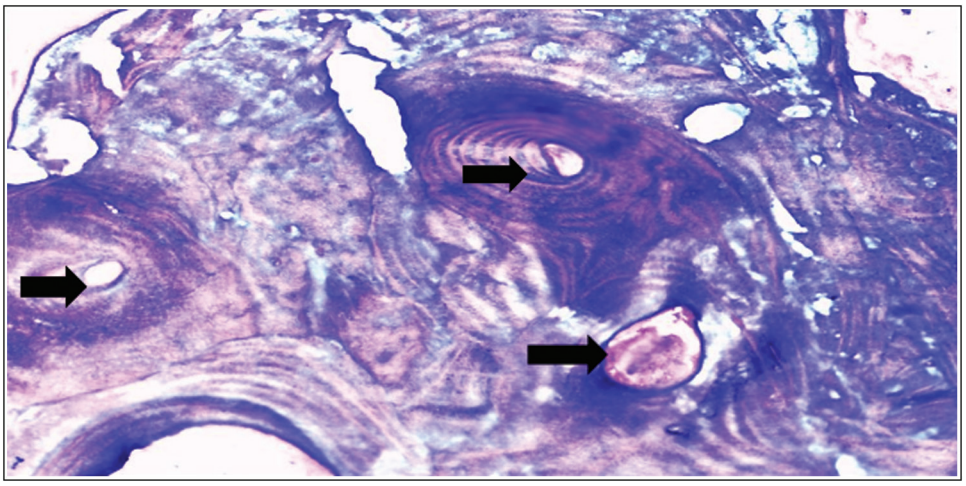
AVNFH exhibiting massive areas of bone necrosis admixed with fibrin (black arrow) and numerous blood clots (orange arrow) “hematoxylin and eosin ×100.” AVNFH, avascular bone necrosis of femoral head.

Figure 20



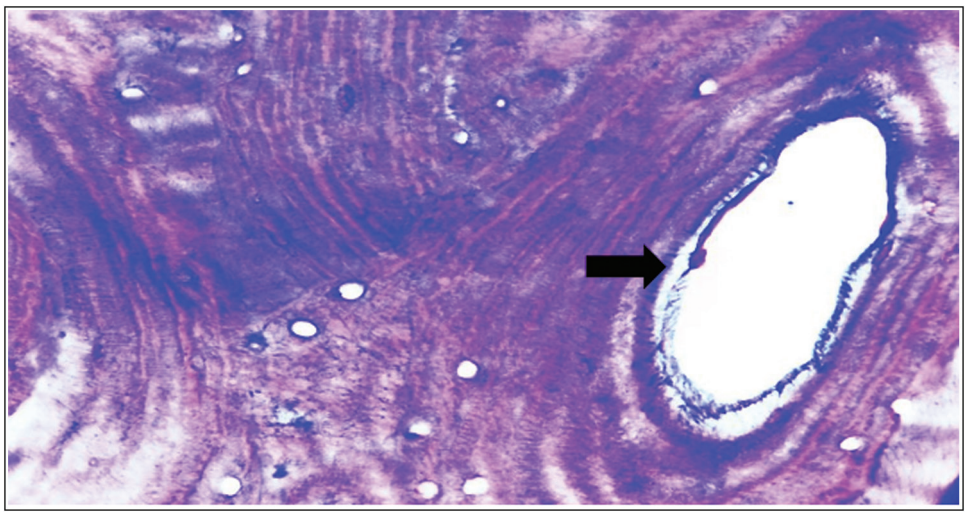
AVNFH showing numerous blood clots with variable sized (small & large) blood vessels (orange arrow) “hematoxylin and eosin ×100.” AVNFH, avascular bone necrosis of femoral head.

Figure 21



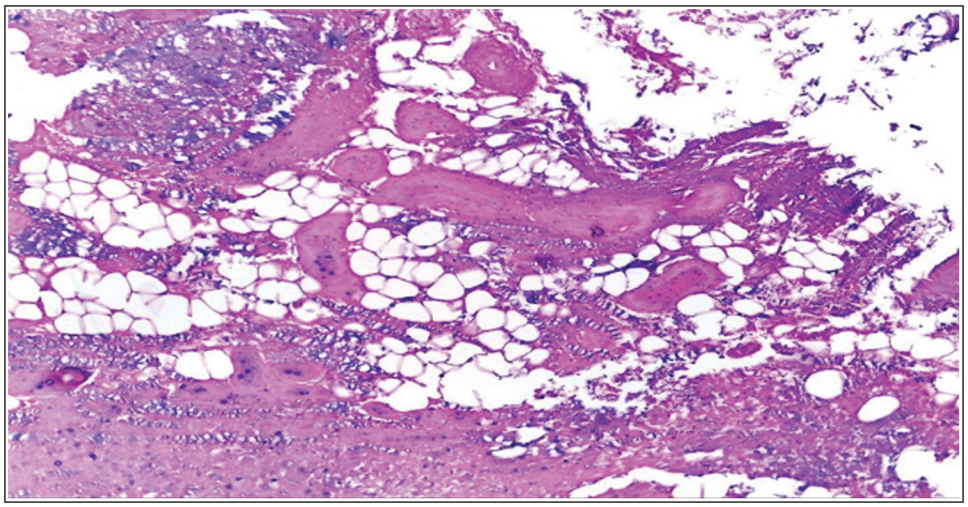
AVNFH showing dilated empty lacuna of bone trabecula (black arrow) “hematoxylin and eosin ×200.” AVNFH, avascular bone necrosis of femoral head.

Figure 22



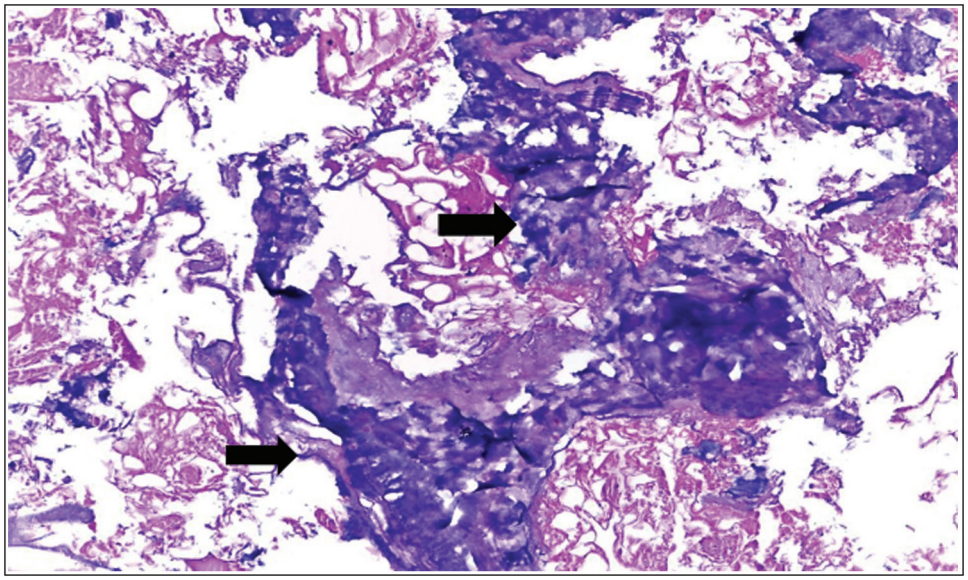
Higher magnification of previous figure of AVNFH showing dilated empty lacuna of bone trabecula (black arrow) “hematoxylin and eosin ×400.” AVNFH, avascular bone necrosis of femoral head.

Figure 23



AVNFH showing poorly vascularized dilated marrow spaces “hematoxylin and eosin ×100.” AVNFH, avascular bone necrosis of femoral head.

Figure 24



AVNFH showing calcification in adjacent marrow spaces (black arrow) “hematoxylin and eosin ×100.” AVNFH, avascular bone necrosis of femoral head.

features of rapid deteriorating coxarthrosis. Among the three patients with rapidly progressive coxarthrosis, two patients had rapid progression of ONFH and underwent total hip arthroplasty. The third patient is awaiting THA. They concluded that ONFH after COVID-19 can have a varied presentation. Although the most common presentation is likely classical ONFH, some patients can have an acute and aggressive presentation with rapid destruction. They have features like elevated serological markers and extensive periarticular bone and soft tissue edema.

Shetty [28] reported the double-trouble phenomenon, i.e., COVID-19 and the widespread use of corticosteroids may result in an osteonecrosis epidemic? In his review, he found that the "angiocentric" pathogenesis of SARS-CoV-2 and treatment with high-dose of steroids may increase the risk of ON in COVID-19-infected patients. Risk stratification based on steroid intake during COVID-19 treatment can help identify patients at moderate to high-risk for ON where early preventive and follow-up plans can be initiated.

Our study has some limitation. First, the cases were not randomized, and the study design was just a report of case series. Second, the small number of cases reported in this study is another limitation. Moreover, a short period of follow-up was reported in our series.

To conclude, there is a silent epidemic of cases presenting daily in our clinics with COVID-19-related AVN. Osteonecrosis can be developed after steroid therapy or without steroid therapy after COVID affection. Even the live-attenuated vaccines themselves can cause osteonecrosis. This course and presentation of osteonecrosis after COVID is more aggressive and rapidly deteriorating than the steroid-induced AVN even after core decompression and medical treatment. Cases are highly resistant to conservative protocols, and the only predictable accepted outcome was achieved with only total hip replacement.

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Conflicts of interest
There are no conflicts of interest.

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