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Femur head necrosis as a post-acute sequela of Covid-19 (SARS-CoV-2 infection)

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Abstract

Introduction While the COVID-19 pandemic may still be ongoing, we have simultaneously entered into the post-acute phase of COVID-19, which comes with its own challenges. This case series reports 11 patients of COVID-19 treated with corticosteroids who subsequently developed osteonecrosis of the femoral head (ONFH). **Methods** All consecutive patients diagnosed on MRI with ONFH from August 2020 to May 2021 and were retrospectively COVID-19 positive were included. The treatment administered for COVID-19 was retrieved and evaluated. The patients were managed for femoral head necrosis, and results were reported. **Results** Overall, 11 patients developed ONFH in a total of 16 hips. The severity of femoral head necrosis depended on the dose of corticosteroid administered during COVID-19. A high dose for a longer duration resulted in a higher ONFH stage (FICAT & Arlet). Hips in the lower grade were treated conservatively, and in the higher grade were treated surgically. The follow-up scores of patients demonstrated steady improvement. **Conclusions** High suspicion of femoral head necrosis has to be considered in patients treated with corticosteroids for COVID-19 as it can aid in early detection and early intervention to preserve the native femoral head.

Keywords: femur head necrosis, post-acute COVID-19 syndrome, case series, COVID-19

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INTRODUCTION

Since its emergence in December 2019 in Wuhan China [1], COVID-19 has become a watershed point in the health-care sector. Moreover, it will continue to play a cardinal role in the immediate future and beyond, as we deal with the post-COVID syndrome [2], also termed as long-COVID [3, 4]. In terms of orthopaedic consideration, the experience with SARS-COV-1 infection (SARS), with which COVID-19 is closely related, has been already known. The data on COVID-19 are still limited, but epidemiological data available from cases of SARS refer muscle pain, osteoporosis and avascular necrosis to its typical long-term effects [5].

The basis for these effects is to be clearly determined, but available literature first points to the disease process itself, including systemic inflammation [5], and second, to the therapeutic regimen which consists of corticosteroid and antiviral therapy. The role of antiviral agents in the development of osteonecrosis in SARS was reported in the literature [6, 7]. However, whether this fact is related to COVID-19 or not should be studied. Corticosteroids have been one of the mainstay therapies for COVID-19, and their role in increasing the risk of osteonecrosis of the femoral head has been generally known [8]. Moreover, the treatment of osteonecrosis of the femoral head (ONFH) as a post-acute COVID-19 sequela is still not described in detail. However, in terms of osteonecrosis secondary to SARS, the available literature advocates early detection and conservative treatment. In this case series of 11 patients, we share our experience in diagnosing and managing these patients who were COVID-19 positive and were treated for the same and developed ONFH in the follow-up period.

MATERIAL AND METHODS

Registration In accordance with the 1964 Helsinki declaration, the study was registered with CTRI, a primary registry in the WHO registry network. Prior authorization was taken from the institutional review board. Data was collected through the medical records department of the institution.

Participants Eleven patients (9 males, 2 females) with ages ranging from 27 to 56 were included. Data variables of the patients who were diagnosed with ONFH on MRI imaging, as well as positive for COVID-19 nucleic acid testing during the present pandemic, were enrolled. The inclusion criteria were patients diagnosed with ONFH and were previously positive for COVID-19 infection. The patients with any history of hip discomfort or any other hip pathology before the start of the COVID-19 pandemic were excluded. According to ICH-GCP guidelines, an informed consent was taken, an individual participant ID was allocated, and the patient's information was de-identified.

Study design This case series has been reported in line with PROCESS Guidelines [9, 10]. It is a single-centre retrospective observational study. The variables of consecutive patients, whose osteonecrotic changes in the femoral head were detected by MRI, were retrospectively identified. These candidates were determined for previous COVID-19 positive status.

Setting and time frame The setting for the study was the department of orthopaedics in a tertiary-care hospital situated in a tier-1 city located in India. The patients were diagnosed with ONFH with the use of MRI in a time frame of August 2020 to May 2021.

Pre-intervention consideration The included patients were confirmed COVID-19 positive with nucleic acid testing in a time frame from April 2020 to September 2020. All 11 patients had moderate to severe COVID-19 symptoms [11]. One of the patients had ICU admission, and the other 10 were NON-ICU admissions during COVID-19 management. Data variables of all laboratory investigations done during admissions were included and assessed. All the changes in the range of values were estimated. CT scan severity scores ranged from 14 to 20, with 4 patients showing values of 18 and more.

The details of treatment received for COVID-19 were evaluated in detail. During COVID-19 hospitalization, all the patients had treatment administered according to WHO/ICMR (World Health Organization/Indian Council of Medical Research) guidelines [12], including corticosteroids and antivirals. All the patients received an average of 1855.55 mg of methylprednisolone for an average of 22 days. Three patients received a total dose of more than 2000 mg of methylprednisolone, with one patient receiving the high

Est total dose of 2400 mg. The minimum total dose was 1600 mg. The average daily dose was 80 mg/day. These patients also received an antiviral treatment for an average of 14 days. Favipiravir was administered in an average dose of 26,000 mg per candidate. Four patients also received Remedesivir for the first five days of the treatment with an average total dose of 600 mg.

Interventions MRI scans of selected candidates were classified for ONFH according to FICAT and Arlet classification [13]. Out of a total of 16 hips, 5 were bilateral (Fig. 1). Two hips were classified as stage IV (Fig. 2). Five hips were in stage III, 8 hips were in stage II (Fig. 3 and 4), and one hip in stage I.

The dose and duration of corticosteroid treatment showed a direct link between the severity of osteonecrosis and staging. Patients who had a cumulative dose of more than 1800 mg, given over a time period of 22 days or more, showed stage III and higher. Apart from this, no other variable could be linked to the severity of staging. The average period from starting the corticosteroid therapy to the diagnosis on MRI was 7 months.

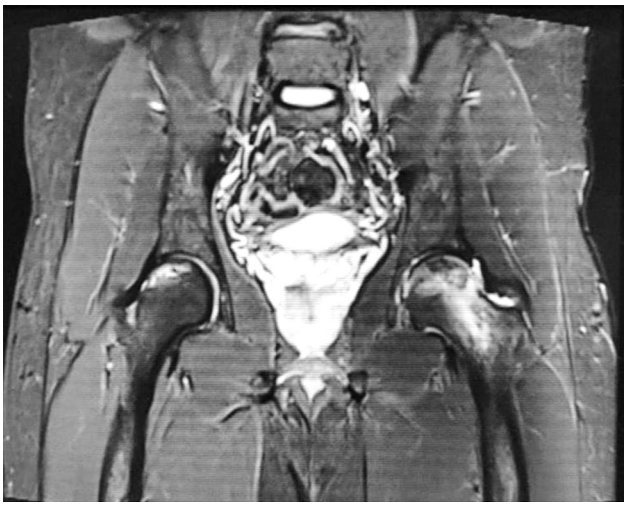

Fig. 1 Coronal section of T2 weighted MRI image showing Stage III osteonecrosis of left hip and Stage II osteonecrosis of the right hip

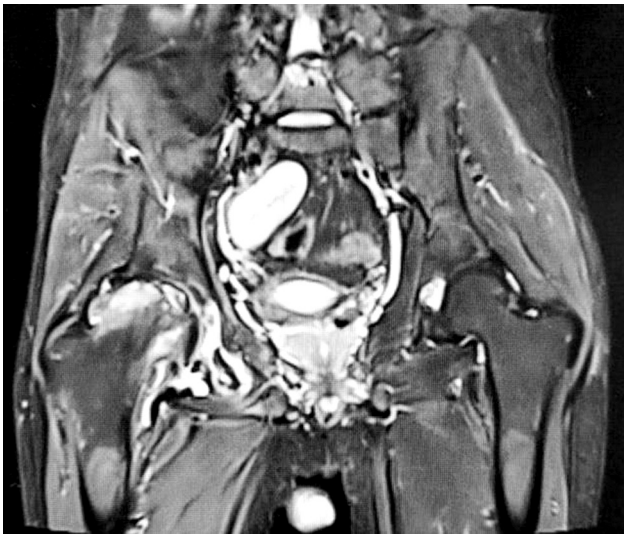

Fig. 2 Coronal section of T2 weighted MRI image showing Stage IV osteonecrosis of the right hip

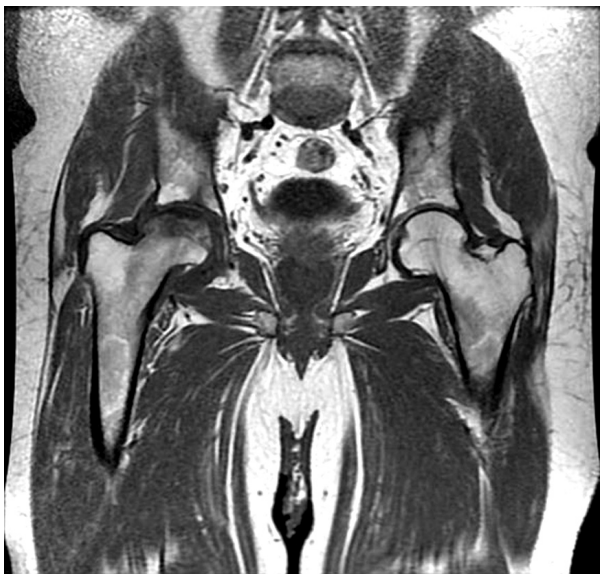

Fig. 3 Coronal Section of T1 weighted MRI image showing Stage II osteonecrosis of the right hip

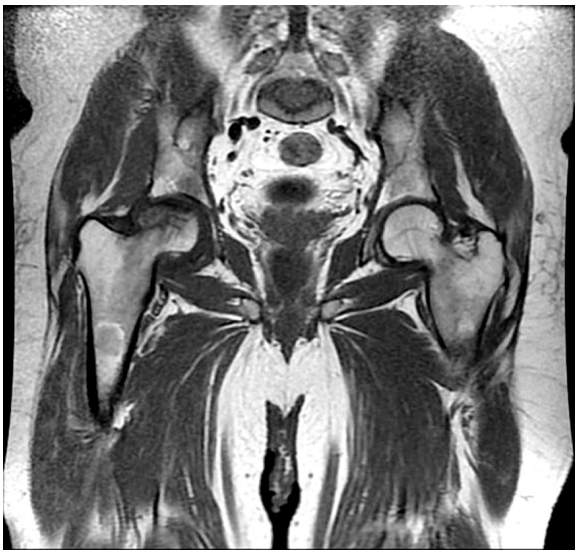

Fig. 4 Coronal Section of T1 weighted MRI image showing Stage II osteonecrosis of the right hip

Management modalities were both non-operative and operative. The literature from the SARS pandemic provides evidence that osteonecrotic lesions potentially stabilize and reduce in size over time [8, 14]. This contradicts osteonecrosis due to corticosteroids in other diseases (rheumatoid arthritis, nephrotic syndrome, etc.). Generally, osteonecrosis of the hip is a continuous and impairing disease which often leads to total hip arthroplasty (THA) [15]. With knowledge of non-operative intervention in the SARS pandemic, similar conservative management was given in 13 hips. Two FICAT stage IV hips underwent THA. Decompression was done for one stage III hip. The remaining hips were stage III or lower and were treated conservatively with bisphosphonate therapy (alendronate, 70 mg weekly) and zolendronic acid (5 mg, annually) and were advised protected weight-bearing and regular follow-ups.

Follow-up Monthly follow-ups recorded in the database revealed that by completion of the study, there was a longest follow-up of 10 months in a patient receiving bisphosphonate therapy. The average follow-up in this group was 7 months. The Harris Hip score (HSS) and Visual Analog Scale (VAS) for this group, on-average, showed 62 and 7 points at diagnosis and 76 and 3 points at 7 months of average follow-up, respectively. The shortest follow-up of bisphosphonate was of 2 months and was not included. The patient who underwent core decompression improved from 56 and 6 to 76 and 2 points at 7 months of follow-up, respectively. The last follow-up in two patients who were managed with THA was 8 months. The average HSS and VAS scores improved from 43 and 8 points to 90 and one, respectively.

RESULTS

We had a total of 11 patients with 16 affected hips. The average age of patients was 44 years. One patient was comorbid with hypertension. Patients received, on average, a total dose of 1855.55 mg of corticosteroid for an average of 22 days. The average time span for the diagnosis of osteonecrosis from the administration of corticosteroid was 7 months. A high dose was linked to the severity of the disease. The outcome of conservative management was promising. The follow-up HSS and VAS scores of the hips with lower severity and managed conservatively were favorable. There was continuous improvement in patient's quality of life over time. The adherence of patients to treatment was good and was well-tolerated. No complications and adverse effects were reported. No additional challenges were faced in the cases of surgical treatment. The procedures were performed as in regular non-Covid patients with osteonecrosis of the hip.

Table 1

Showing patient data

	Age	Average dose of methylprednisolone (mg)	ONFH stage according to FICAT & Arlet	HHS before treatment	VAS before treatment	Treatment for ONFH	VAS after treatment	HHS after treatment
Case 1	27	1800	Stage 1	67	5	Conservative	1	83
Case 2	56	1600	Stage 2	65	6	Conservative	2	81
Case 3	40	1600	Stage 2 (left hip)	64	7	Conservative	3	79
			Stage 2(right hip)	63	7	Conservative	3	77
Case 4	54	2400	Stage 4	41	8	THA	1	92
Case 5	55	2210	Stage 3 (left hip)	56	7	Decompression	2	76
			Stage 2(right hip)	61	6	Conservative	2	78
Case 6	48	1600	Stage 2	64	7	Conservative	2	80
Case 7	38	1800	Stage 3 (left hip)	58	9	Conservative	4	71
			Stage 2(right hip)	60	8	Conservative	3	74
Case 8	44	2100	Stage 4 (left hip)	45	8	THA	1	88
			Stage 3(right hip)	58	8	Conservative	4	69
Case 9	42	1800	Stage 3 (left hip)	61	7	Conservative	3	73
			Stage 3(right hip)	57	7	Conservative	5	72
Case 10	51	1700	Stage 2	66	7	Conservative	3	76
Case 11	49	1800	Stage 2	62	8	Conservative	4	75

DISCUSSION

With large gaps in our knowledge of post-acute COVID-19 sequelae yet to be filled, we would like to report our encounter and experience with this retrospective case series. The long-term effects of COVID-19, to some extent, turned out to be as predicted by our experience following the SARS pandemic. The opportunistic fungal-infection which created havoc in post-COVID-19 patients was already previously demonstrated in patients with SARS [16]. The literature concerning bone manifestations in the form of osteonecrosis following SARS is also extensive. Despite various theories of the pathogenesis behind manifestations of COVID-19, the relationship between steroid therapy and the development of osteonecrosis remains the strongest [17]. Some literature indicates systemic inflammation leading to the development of hypercoagulable and hyperfibrinolytic states which results in bone ischemia and necrosis [18]. There is also some evidence suggesting the development of osteonecrosis due to antiviral treatment in the SARS pandemic [6, 7]. However, the antiviral agents primarily used in SARS and COVID-19 are different. Ritonavir and lopinavir were used in SARS and, remdesivir and favipiravir are being used in Covid-19 [19]. Nevertheless, there is no evidence suggesting the same for COVID-19.

The available literature gives substantial agreement between steroid usage and the occurrence of osteonecrosis. Nakamura et al showed how steroids played a vital role in developing ONFH in patients with systemic lupus erythematosus [20]. Shibatani et al showed similar results in renal transplant recipient patients [21]. In SARS, it was shown that the patients receiving more than 3000 mg of corticosteroids for an average duration of 25 days who are younger than 50 years of age should be suspected as candidates for progression to avascular necrosis [22]. Geo et al studied 539 SARS patients. Almost 40 % prevalence of osteonecrosis was attributed to a total dose of approximately 2000–3000 mg of corticosteroids over approximately 25 days with more affinity in younger individuals [23]. Sing et al in their 17-year follow-up study show a clear link between short course-high dose corticosteroid therapy and association with no other major disease except avascular necrosis [24]. Zhang et al even called for a risk stratification system for patients at risk [25]. In our case series we were similarly able to link the severity of MRI staging with the total collective dose taken by the patients. One of the candidates in our study was a 49-year old male who received a cumulative dosage of 2400 mg for 25 days. The patient developed hip symptoms after 5 months and came to our OPD after 6 months and was diagnosed with stage IV on MRI. Understanding of SARS has shown that the development of osteonecrosis may take as few as one to two months post-treatment and can go up to one year or several years [26]. Similar trend of osteonecrosis of the femoral head, after months succeeding infection, was also observed in SARS patients [27]. Kubo et al demonstrated a time period as short as 3 weeks for the occurrence of osteonecrosis following high-dose corticosteroid therapy [28]. Therefore, the immediate follow-up after COVID-19 also becomes important and should not be disregarded, and frequent follow-ups at an orthopaedic department may be advised [29, 30]. With this background known to us, there was no hesitance in recommending urgent MRI for any hip discomfort in the patients.

Predominantly the treatment for osteonecrosis seems to be unambiguous, with THA being the resultant [15]. On the contrary, the data on ONFH secondary to SARS primarily seems to come out of China, where the infection was most numerous as reported, and the literature appears to advocate a conservative trial initially as the osteonecrosis subsequently due to steroid treatment in SARS patients seems to stabilize and potentially reduce over time [8, 11, 22]. This is different to what is seen in steroids therapy for other conditions [31, 32]. The evidence claims regression after 1 to 3 years of follow-up in majority of cases. These findings raise essential questions whether the viruses of this family give some added pathogenesis that makes bone more sensitive to corticosteroid-induced ONFH and then also plays a role in stabilization and regression of these lesions. Similarly, Liu et al, in their 12-year follow-up of 66 hip joints, advocate conservative treatment [33]. The treatment included giving alendronate drug orally 70 mg weekly for 12 consecutive years, which resulted in significant and progressive improvement in VAS and HHS scores. According to them, the ground for such an intervention is that the average age of these patients is young, and the native femur head should be preserved as long as possible. The patients in our case series were also young with an average age of 44 years and had lately gone through the stress of COVID-19 and were readily willing to take up conservative treatment. Conservative treatment was administered in hips in stage III or lower except for one stage III hip that received core decompression as an intervention. The rest of the 2 hips in the higher stage were given surgical intervention (THA). The patient who received decompression of femoral head had bilateral ONFH. But only one side was decompressed, which was stage III, the other hip was stage II, and after the surgery the patient was kept on bisphosphonate therapy. The follow-up scores in both conservative and surgical interventions were encouraging.

This experience implies that suspicion of ONFH should be aroused in patients who were treated with corticosteroids for COVID-19 infection. This is one of the first case series suggesting such a linkage, and we assume a screening protocol may be advised for patients with any hip discomfort and a history of COVID-19 infection. Thereby, we are also setting a direction

for more studies in this regard. At-risk patients from appropriate databases need to be identified and followed upon as this is the right time to evaluate post-acute COVID-19 sequelae. However, the report does not come without its limitation and weakness, the number of participants is small. The case series being low on the evidence pyramid, further follow-up study on a large group of participants is required.

CONCLUSION

Our experience leads to the inference that there is high clinical suspicion of ONFH in patients treated with corticosteroids after being diagnosed with COVID-19. While intervening in these patients, evidence from the SARS pandemic should be kept in mind as the experience with COVID-19 cases is still limited. Hence we are also setting a base for further studies in this direction.

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Checklist reference *This case series has been reported in line with the PROCESS Guideline 20209 mentioned in the EQUATOR Network.*