Avascular necrosis as sequelae of ‘long COVID-19’: A prospective study

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Abstract
COVID-19, caused by SARS-CoV-2, is affecting many people worldwide. Huge numbers of people are being killed due to the virus. Although many patients are recovering from COVID-19, there may be possible complications after convalescence, including unfavorable non-pulmonary effects. One of these complications is avascular necrosis (AVN), which may lead to negative outcomes and bone collapse if missed. AVN was seen frequently in SARS and may also be common in COVID-19 infection. It should be kept in mind that the threat of AVN remains with patients recovered from COVID-19 infection, like SARS. The recent outbreak of coronavirus disease 2019 (COVID-19) has become a global pandemic. Corticosteroids have been widely used in the treatment of severe acute respiratory syndrome (SARS), and the pathological findings seen in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are very similar to those observed in severe acute respiratory syndrome-related coronavirus (SARS-CoV) infection. However, the long-term use of corticosteroids (especially at high doses) is associated with potentially serious adverse events, particularly steroid-induced avascular necrosis of the femoral head. In today's global outbreak, whether corticosteroid therapy should be used, the dosage and duration of treatment, and ways for the prevention, early detection, and timely intervention of steroid-induced avascular necrosis are some important issues that need to be addressed. This review aims to provide a reference for health care providers in COVID-19 endemic countries and regions.

Keywords: Covid-19, avascular necrosis, coronavirus, Remdesivir

Introduction
A novel coronavirus named ‘COVID-19’ by the WHO is the cause of the current pandemic that began in December 2019 in Wuhan city, Hubei province, China. By 28 January 2021, more than 100200107 individuals had been infected with COVID-19, of which 2158761 were fatal [1]. Emerging evidence suggests that COVID-19 adversely affects different human body systems as a part of ‘long COVID-19’, such as Guillain-Barré syndrome, lung fibrosis, pulmonary thromboembolism, cardiomyopathy, sensory dysfunction, and stroke [2]. The second wave of Covid-19 in India saw more and more cases of complications in recovered coronavirus patients, such as mucormycosis, blood clots, new-onset diabetes, chronic fatigue among others. The latest is avascular necrosis or osteonecrosis. Long COVID-19 is a term used to describe the long-term effects of COVID-19 infection that continue for weeks or months after the patient has recovered from COVID-19 [3]. National Institute for Health and Care Excellence defines 'long COVID- 19' as lasting for more than 12 weeks. Symptoms of long COVID-19 can include fatigue, breathlessness, anxiety and depression, palpitations, chest pains, joint or muscle pain and not being able to think straight or focus ('brain fog') [3]. Since the outbreak, many agents that could have efficacy against COVID-19 have been used including various antivirals, angiotensin receptor blockers, chloroquine phosphate, and corticosteroids. The efficacy of angiotensin receptor blockers and chloroquine phosphate has not been well established [4, 5]. Corticosteroids are life-saving in the management of COVID-19, however, it is a predisposing factor for the development of avascular necrosis (AVN) [6]. Based on this premise, in view of the large-scale use of life-saving corticosteroids, there could be a resurgence in the number of AVN cases.

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An early diagnosis of AVN is important to arrest the disease’s progress and prevent subsequent femoral head collapse [7]. If diagnosed early in Ficat-Arlet stage I or II, 92%–97% of the patients do not require surgery and can be managed with bisphosphonate therapy. Hence, it is crucial to diagnose AVN early to decrease the morbidity and the requirement of surgery.

Here, we report three cases of symptomatic AVN of the femoral head after being treated for COVID-19. This is the first case report of AVN as sequelae of ‘long COVID-19’.

Case presentation

Case 1

A 40-year old male patient was diagnosed with COVID-19 on 10 March 2021, for which the patient was admitted to intensive care because of dropping saturation. During his hospitalization, the patient was administered intravenous methylprednisolone 80 mg per day for 9 days (totaling-720 mg of methylprednisolone equivalent to 900 mg prednisolone) and intravenous remdesivir and intravenous tocilizumab. The patient was discharged on oral prednisolone in tapering dose over 30 days (total-350 mg). The total steroid received by the patient was 1250 mg of prednisolone equivalent. 50 days after the COVID-19 diagnosis, the patient developed pain in the right groin. The patient had no history of hip pain before this. Radiograph and MRI of the hip done (67 days since COVID-19 diagnosis) showed bilateral hip AVN. (Ficat-Arlet stage II on both hips)

Case 2

A 38 years old male patient was diagnosed with COVID-19 on 20 March 2021, the patient was given oral dexamethasone in tapering dose over 10 days (total-60 mg equivalent to 400 mg of prednisolone), the patient developed pain in the left groin region. The patient had no history of hip pain in the past. Radiograph and MRI of the hip done showed left hip AVN. (Ficat-Arlet stage II)

Case 3

A 50-year old male patient was diagnosed with COVID-19 on 28 March 2021, for which intra- venous methylprednisolone (500 mg) was given equivalent to 625 mg prednisolone. Forty-five days post COVID-19 detection, the patient developed pain in the bilateral groin. The patient had no history of hip pain in the past. Radiographs and MRI were done 52 days post COVID-19 detection that showed bilateral hip AVN. (Ficat-Arlet stage II)

Case 4

A 45-year old male patient was diagnosed with COVID-19 on 03 April 2021, for which IV dexamethasone in tapering dose over 15 days was given, the patient developed pain in the left groin region. Fifty-two days post COVID-19, the patient developed pain in the right groin. The patient had no history of hip pain in the past. Radiographs and MRI were done 58 days post COVID-19 detection that showed right hip AVN. (Ficat-Arlet stage II)

Case 5

A 36-year old male patient was diagnosed with COVID-19 on 15 April 2021, for which intra- venous methylprednisolone (550mg) was given. Forty-five days post COVID-19 detection, the patient developed pain in the bilateral groin. The patient had no history of hip pain in the past. Radiographs and MRI were done 54 days post COVID-19 detection that showed bilateral hip AVN. (Ficat-Arlet stage II)

Outcome and follow-up

The mean dose of prednisolone equivalent steroid taken by the patient in our study was 758 mg (400 mg–1250 mg). The time duration for the development of AVN post-COVID-19 diagnosis in our patients was 62 days in the first case, 67 days in the second case, and 45 days in the third case, 58 days in the fourth case, and 54 days in the fifth case with a mean duration of 57 days (range 45–67 days). All five patients were started on oral alendronate 70 mg weekly dosages along with intravenous zoledronic acid 5 mg annually [8]. At the last mean follow-up of 70.7 days (30–84 days), none of the patients required surgery and were comfortable pain-wise. Mean Visual Analogue Score for pain reduced from 8 (6–9) to 2.7 (1–4) at the mean follow-up of 70.7 days.

Discussion

Doctors have observed a sudden rise in AVN cases during the Covid-19 second wave. “We used to have around five AVN patients in a week, but suddenly the number is growing. The commonality here was that they were all survivors of COVID-19. All these patients were receiving life-saving steroids.

Corticosteroid use is considered to be one of the most common causes for the development of AVN. The pathogenesis of steroid-induced AVN is not well established, but postulated mechanisms include fat emboli, fat hypertrophy, hypercoagulable condition, vascular endothelial dysfunction, and abnormality of the bone marrow stem cell [9]. There is a lack of consensus about the dosage and duration of steroids required to develop AVN. Some authors have reported that a cumulative dose of 2000 mg prednisone (or its equivalent) was required for AVN development [10]. Some studies have shown that 700 mg is the minimum dose required to develop AVN [11]. However, McKee et al. have shown that in their series of 15 patients who developed AVN, the mean steroid dose in prednisone equivalents was 850 mg with a range of 290 mg–3300 mg [12]. The mean dose of prednisolone equivalent steroid taken in our study was 758 mg (range 400–1250 mg).

Controversy exists about the time after the steroid administration to the development of AVN symptoms. In a case report of a 23-year-old male patient who developed shoulder AVN after receiving oral dexamethasone (equivalent to 700 mg of prednisolone), the authors have reported that the patient developed symptoms 2 years after the administration of steroids [11]. McKee et al, in their study, have reported a mean time of 16.6 months (range 6–33 months) from the administration of corticosteroids to the development of AVN [12]. Literature review shows that the interval between corticosteroid intake and development of symptomatic AVN is usually 6 months to 1 year [13, 14]. The mean time duration for the development of AVN post-COVID-19 diagnosis in our series was 58 days (range 45–67 days).

The treatment objective in AVN is to obtain pain relief, retard disease progression, prevent collapse and restore joint function. Multitude treatment options are available for managing AVN ranging from conservative, medical to surgical modalities, however, no standardized protocol exists. Various medical therapies tried in the past including iloprost, nifedipine, and hyperbaric oxygen therapy have not shown significant benefits [7]. Therefore, arthroplasty remains the
mainstay of treatment. Although it provides a good outcome when performed at a young age will necessitate at least one revision in the future. Successful use of bisphosphonates for the treatment of AVN in adults was first reported by Agarwala et al. [8] the authors have shown that bisphosphonates not only give good clinical outcomes but also retard the progression of the disease and the need for surgery. Subsequently, various authors have published the role of bisphosphonates in the management of AVN, and it is now considered to be one of the standard options of treatment of AVN.

In our study, AVN occurred with a low mean steroid dosage of 758 mg with a minimum dose of 400 mg compared with the literature which shows that a mean cumulative dose of 2000 mg steroid is required for the development of AVN. Further, the patient developed AVN very early with a mean range of 58 days after COVID-19 diagnosis compared with the literature which shows that it generally takes 6 months to 1 year to develop AVN post steroid exposure. Post COVID-19, there is a greater propensity to develop AVN, mainly if the patient has been on steroids. The literature suggests the mean dose of steroid in prednisone equivalents of 2000 mg is required to cause AVN, but we feel that due to the COVID-19 virus, the sensitivity to develop AVN is higher and to a smaller cumulative dose of steroids.

Steroids are life-saving and have to be administered. However, AVN, being picked up early, may decrease the patient’s morbidity by bisphosphonate combination therapy. The most sensitive and least invasive test to diagnose early AVN is an MRI of the hips. Hence, it is recommended that on early suspicion, early MRI should be advised.

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