

Osteonecrosis-An Emerging Challenge of Post COVID-19 Sequelae

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ABSTRACT

Our case report aims to present a rare interesting case on osteonecrosis associated with COVID-19 infection. We retrospectively evaluated this case after the patient underwent surgical management. In our patient, AVN was found to be developed secondary to COVID-19 infection. Infection with coronavirus confers a hypercoagulable state leading to various systemic complications. So, we suggest proper studies should be done to understand the physiopathology of COVID-19 to prevent complications and to improve supportive care during treatment.

Keywords: COVID-19, hypercoagulable state, osteonecrosis, systemic complications.

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I. INTRODUCTION

Osteonecrosis also known as avascular necrosis, ischemic bone necrosis, or aseptic necrosis develops when the blood supply to a segment of bone is disrupted. It can be secondary to various reasons, broadly divided into traumatic and non-traumatic. Any fracture following trauma can compromise the blood supply to the involved bone leading to bone death. Of all non-traumatic causes, long-term high-dose steroid use is the most commonly observed non-traumatic cause followed by alcoholism.

Epidemiological data on osteonecrosis is limited and not clear. In the US, approximately, 15000 new cases are reported each year [1]. In India data on the prevalence and incidence of ON are not available.

Severe COVID-19 may manifest as a cytokinin storm, progressing into life-threatening complications such as ARDS, DIC, and shock. Steroids are found to be lifesaving in preventing such events. However, recent studies have reported that the sudden rise in ON cases may be due to the large-scale use of steroids in severe COVID-19 cases. Apart from steroid use, ON is found to be a rare MSK manifestation of COVID-19 [2].

The mechanism behind the development of ON seems to

be multifactorial. The dilemma in determining the etiopathogenesis can lead to treatment impairment as ON develops after both steroid therapy and severe covid-19. So, it is important to understand etiopathogenesis and its risk factors as a consequence of COVID-19 and its treatment.

Despite the need, Reports on COVID-19 associated ON with or without steroid therapy are limited. So, we aim to present this case to aid the healthcare workers in better treating the patients.

II. CASE DESCRIPTION

A 31-year-old male patient was diagnosed with COVID-19 on January 2022 for which he was treated with IV methylprednisolone (600 mg) followed by an oral dose (8 mg). 65 days after COVID-19 infection he developed pain in both hip joints (right > left), and morning stiffness in both hips. The patient was evaluated by physical examination, X-ray, and MRI which showed bilateral avascular necrosis stage 2 as shown in Fig.1. After appropriate tests, the patient was managed by core decompression of both the femoral head and BMAC. The patient underwent procoagulant workup details of which are given below.

TABLE I: PROCOAGULANT WORKUP

Test	Observed value	Reference value
Anticardiolipin IgM	Negative	-
Anticardiolipin IgG	Negative	-
Homocysteine	19.58	<15µmol/L
Factor V Leiden	95	85-122%
Protein C	60	75-130%
Protein S	108	70-120%

III. DISCUSSION

Osteonecrosis is most commonly associated with steroids. About 10-30% of ON cases are found to be associated with steroid therapy. Steroids have various side effects which depend on the dose, duration, and the individual patient. The mechanism behind steroid-induced ON is not clear. Proposed theories include:

- 1) Steroid-induced fat mobilization leads to enhancement of fat emboli formation resulting in occlusion of minor blood vessels [3].
- 2) Another theory is that the number and size of adipocytes in bone marrow increases, resulting in elevated intraosseous pressure which blocks venous outflow.
- 3) Steroids can cause changes in venous endothelial cells, elevating stasis and intraosseous pressure predisposing to necrosis [4].

COVID-19 appears to be an independent risk factor for ON. It is now emerging as a rare musculoskeletal complication of COVID-19. Various factors like hypercoagulability, leukocyte aggregation, and endothelial dysfunction may lead to the development of ON.

It is postulated that ON due to steroid therapy usually develops after 6 months to 1 year after steroid therapy whereas in our case patient developed osteonecrosis after 2 months. Consistent with recent reports, we found that the time interval between steroid therapy and ON onset was shorter in patients with covid 19 than in those without COVID-19. A study done by [5] also suggests that COVID-19 hastens the progression of ON.

In our study, the cumulative steroid dose taken by our patient was 700 mg. A review of literature showed reports of osteonecrosis of the knee with cumulative doses ranging from 1000 mg-6000 mg (approximately) of prednisolone. The mean steroid dose appears to differ from study to study. As the dose and duration of steroid therapy may play a significant role in the development of ON, it is important to establish dose limits. More studies should be done to determine the reliable dose and duration of steroid therapy [6].

As both COVID-19 and ON are associated with coagulation, it is important to examine the coagulation profile in high-risk patients. In our patient, post-operative procoagulant workup showed mild elevation in homocysteine levels, deficiency in protein C levels, and the presence of lupus anticoagulant. Hence, he was suspected to have antiphospholipid syndrome [7]. Antiphospholipid syndrome (APS) is an acquired autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. Characteristic laboratory abnormalities in APS include persistently elevated levels of antibodies directed against membrane anionic phospholipids (e.g.:

anticardiolipin antibody), their associated plasma proteins, or evidence of a circulating anticoagulant [8].

Lupus anticoagulant is an antiphospholipid antibody. Phospholipids are involved in facilitating the coagulation cascade. Antiphospholipid antibodies (APLAs) are autoantibodies against phospholipids or plasma proteins bound to phospholipids. The most common subgroups involved in disease states are anticardiolipin antibodies, lupus anticoagulant antibodies, and anti-β2-glycoprotein I antibodies. Antiphospholipid antibodies promote clotting in arteries and veins (i.e., thrombophilia) by activation of endothelial cells, via oxidant-mediated injury to endothelium, and by modulating the regulatory function of coagulation proteins [9].

Protein C deficiency can be inherited or acquired. Vitamin K is necessary for protein c synthesis. Protein C is activated by thrombin. The binding of thrombin to endothelial thrombomodulin and endothelial protein C receptor (EPCR) makes PC more active. In other words, when thrombin binds to thrombomodulin (TM) on the endothelial surface, it is inactivated by activated protein c (its ability to convert fibrinogen to fibrin is lost leading to anticoagulation effect). Vitamin K deficiency may be caused by the fact that antibiotics given to prevent bacterial pneumonia in severe COVID-19 patients kill bacteria that synthesize vitamin K in the intestines.

Homocysteine is a sulphur-containing amino acid that functions as a key intermediate in methionine metabolism. Endothelial dysfunction is caused by high levels of homocysteine due to impaired bioavailability of endothelium-derived nitric oxide (NO) which is a potent vasodilator. This has been linked to high concentrations of endothelial asymmetric dimethylarginine (ADMA) an endogenous inhibitor of NO synthase. ADMA interferes with the synthetization of Nitric Oxide from L-Arginine. Elevated levels of homocysteine have been shown to affect bone health and increase the risk of fracture. Additionally, higher levels of HC have been linked to structural changes in bone characterized by an increase in trabecular separation and a decrease in thickness. Folic acid, pyridoxine (vitamin B6), and cobalamin (vitamin B12) play a major role in homocysteine metabolism. Deficiency in these vitamins may lead to an increase in homocysteine levels [10]. Vitamins B6, B12, and Folic acid supplements can be given to lower homocysteine levels as in our case.

There are numerous treatment options available, however, no standard therapeutic management protocols exist. So, we propose proper studies should be conducted to provide better treatment.

IV. CONCLUSION

The purpose of our case report is to evaluate the impact of COVID-19 and its management in the development of osteonecrosis. Our case represents that COVID-19 and steroid therapy has a significant impact on the development of osteonecrosis. However, it lacked a clear explanation on how they are linked to osteonecrosis. Also, we propose thromboembolic prophylaxis is essential in post covid patients who had steroids to prevent potential systemic complications.



Fig. 1. Anteroposterior radiograph of the patient confirming bilateral avascular necrosis of the femoral head.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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