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Case Series

Impact of COVID-19 infection in the occurrence of avascular necrosis of head of femur: a case series in a tertiary care hospital in Central Gujarat

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ABSTRACT

Avascular necrosis (AVN) is a degenerative bone condition characterized by the death of bone tissue due to reduced blood supply. Recent studies suggest an increased incidence of AVN in post-COVID-19. This may be linked to the virus-induced hypercoagulable state and corticosteroid treatment. However, there is a dearth of evidence to substantiate this association. Therefore, this case series aims to elucidate the potential relationship between COVID-19 infection and AVN. This case series included 11 male patients (ages 25-49) diagnosed with AVN following COVID-19 infection between January 2022 and August 2023. The results indicated a higher incidence of AVN in younger males (mean age: 35 years, range: 25-49), highlighting potential age- and gender-related risks of AVN among the post-COVID-19. Despite excluding patients with pre-COVID steroid use, AVN occurred in those with steroid exposure during COVID-19 treatment and even in home-isolated cases without steroid use. Additionally, the study reported a higher side of the normal range of D-dimer and CRP levels, suggesting hypercoagulability and inflammation may have accelerated AVN progression, with concurrent alcohol and tobacco use potentially increasing risk.

Keywords: Avascular necrosis, COVID-19, Hypercoagulability, Steroids

INTRODUCTION

Coronavirus disease (COVID-19), caused by the highly transmissible SARS-CoV-2 virus, has had a profound impact on global health. Since its emergence, the virus has continued to mutate, producing unpredictable effects on various organ systems.[1] It has been associated with both short-term and long-term complications, including opportunistic fungal infections, cardiovascular, neurological, and rheumatological disorders.[2-5] Emerging evidence has also suggested a surge of AVN, a degenerative bone condition characterized by an interruption of the subchondral blood supply leading to the death of cellular components of the bone.[1,6] A recent article published in 2022 stated that 10-15 cases of Vascular necrosis post-COVID are recorded each month.[7]

The pathophysiology of COVID-19 involves immune-mediated endothelial damage, primarily through the virus's interaction with angiotensin-converting enzyme 2 (ACE2) receptors. This mechanism triggers the coagulation cascade, resulting in a hypercoagulable state. The combination of hyperinflammation and hypercoagulability leads to widespread vascular damage,

compromising blood flow to various organs.[8] The main pathophysiological mechanism of AVN is a decrease in perfusion to the vessels of the bone resulting in bone cell death. [9]This hypercoagulable state caused by COVID-19 could therefore act as a potential trigger for AVN.

In addition to the direct effects of the virus, the widespread use of corticosteroids for COVID-19 may also play a role in the increased incidence of AVN. Corticosteroids, such as dexamethasone and hydrocortisone, were widely used to manage severe cases of COVID-19 by mitigating the hyperinflammatory response associated with organ dysfunction. The world health organization recommends 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every eight hours for seven to ten days in hospitalized patients with severe COVID-19. However, corticosteroid therapy is not indicated for patients with mild or moderate disease. Nevertheless, the fear of COVID-19 led to widespread misuse and self-medication with corticosteroids, raising concerns about their potential contribution to AVN development.[10]

Given the hypercoagulable state induced by COVID-19 and the extensive use of corticosteroids in its management, there may be an emerging association between the virus, its treatment, and the increased occurrence of AVN. Recent studies have demonstrated a potential link between excessive corticosteroid use and an increase in the incidence of AVN. However, the relationship between post-COVID-19 hypercoagulability and the development of AVN remains poorly understood. Our study aims to contribute valuable evidence to this emerging link, helping to clarify the underlying mechanisms and build a foundation for future research in this area.

CASE SERIES

All registered AVN cases with their contact details from January 2022 to August 2023 with a history of COVID-19 infection status. The study included COVID-19 infection positive patients and diagnosed with AVN through MRI after COVID-19 infection. Patients who were on long-term steroid therapy before COVID-19 infection, any injury or fracture to the affected joint, and patients with medical conditions like pancreatitis, systemic lupus erythematosus, Sickle cell anemia, decompression sickness, certain types of cancer like leukemia or known case of hypercoagulability state were excluded from the study.[9] In total, 11 participants met the eligibility requirements and provided consent, leading to their inclusion in the study.

Case 1

A 42-year-old male patient weighing 85 kg presented to the orthopedic OPD on 19th June 2022 with the chief complaints of left hip pain radiating to the left side of the groin area for the past 10 days. The patient complained of difficulty in walking. The patient had a history of COVID-19 infection and was hospitalized from 5/8/2020 to 17/8/2020. The infection was diagnosed with chest imaging, which showed ground glass opacities in both the lung fields with a CORAD-5 Score indicating very high infection in the lungs, and subsequently confirmed by a positive RT-PCR test. His D-DIMER and CRP levels during the COVID-19 infection were 467 ng/ml (normal) and 8.3mg/L(elevated) respectively. The patient was treated with high-dose steroids, antibacterial, antivirals, and anticoagulants. The patient has no addictions or habits. The patient has no significant family history and no other chronic illness. The patient is concurrently on tablet ecosporin and ayurvedic medicine. On physical examination, the patient had pain on the external hip rotation. On further radiological testing, the patient was diagnosed with stage 2 AVN on 29th June 2022. The patient was prescribed non-steroidal anti-inflammatory drugs (NSAIDs), ibridonic acid, and vitamin D3. He was asked for regular follow-up.

Case 2

A 28-year-old male patient weighing 82.7 kgs presented to the orthopedic OPD on 18th August 2023 with the chief complaints of bilateral hip pain radiating to both the thighs and buttocks area since 2-3 weeks. He also complained of bilateral shoulder pain on impingement. The patient complained of difficulty in walking, squatting his legs, and sitting cross-legged. The patient had a history of COVID-19 infection with subsequent post-viral pneumonia diagnosed on 12th June 2021. A positive RT-PCR test confirmed the infection. The HR-CT score was 22 tested on 24th May 2021. The D-DIMER levels were 918 ng/ml (elevated) on 26th May 2021, 250 ng/ml (normal) on 29th May 2021 and 490 ng/ml (normal) on 4th June 2021. He was hospitalized and admitted to ICU care for COVID-19 infection. The patient also had a history of oxygen support for the infection. The infection and pneumonia were treated with steroids, anticoagulants, antifibrotic drugs, and antiviral drugs. Further, the patient was also prescribed statins, beta blockers, calcium channel blockers, and ivabradine for relief of symptomatic chest pain. The patient has no addictions or habits. The patient has no significant family history and no other chronic illness. Radiographic evidence showed bilateral AVN of the hip and shoulder. The patient was diagnosed with stage 2 bilateral hip AVN. The patient was prescribed NSAIDS, ibridonic acid, vitamin D3, and calcium and was asked for regular follow-up.

Case 3

A 47-year-old male patient weighing 55 kg presented to the orthopedic OPD with the chief complaints of right hip pain radiating to the right thigh, right buttock, and right-sided groin area for the past 6 months. The patient complained of difficulty in walking, squatting his legs, and sitting cross-legged. The patient has a habit of tobacco consumption. The patient had a history of

COVID-19 infection. He resorted to home isolation to manage the infection. The patient has no other significant family history and no other chronic illness. The X-ray showed no significant features of osteonecrosis. The MRI indicated right and left-sided grade 2 AVN. The patient was treated with NSAIDs, ibridonic acid, vitamin D3, and calcium and was asked for regular follow-up.

Case 4

A 30-year-old male patient weighing 80 kg presented to the orthopedic OPD in January 2022 with the chief complaints of bilateral hip pain radiating to both the knees, thighs, buttocks, and groin area. The patient complained of pain on rest and pain on weight bearing. The patient also limped while walking. On physical examination, the patient had pain on the internal rotation of the right hip. He had a history of COVID-19 in April 2021. The patient was treated with steroids for the COVID-19 infection, but he had no records of how much medication he was prescribed. Hospital records were not obtainable. Radiographic evidence showed lesions on the lateral, medial, and central pillars of both left and right hip. The right-side hip also showed subchondral fracture and collapse. The patient was diagnosed with grade 2 left and grade 2 right side AVN. The patient was admitted and operated on for bilateral hip core decompression, curettage, and bone implantation. Further, he was treated with antibiotics, paracetamol, NSAIDs, antacids and antiemetics. The patient was discharged after 4 days of operation and asked for follow-up.

Case 5

A 32-year-old male patient weighing 71 kg presented to the orthopedic OPD on 5th January 2022 with the chief complaints of right and left hip pain for the past 1 month. The pain radiated to both the thighs, knee, buttocks, and groin area. The patient complained of the patient on rest and pain on weight bearing. He had difficulty walking, squatting his legs, and sitting cross-legged. The patient has a habit of alcohol consumption. The patient also had a history of COVID-19 Infection. The infection was diagnosed through a positive RT-PCR test and managed through only home isolation. The patient has no other significant family history and no other chronic illness. On physical examination, the patient had a limited range of motion with pain on external, internal rotation, extension and flexion of both right and left hips. The X-ray showed features of osteonecrosis. The MRI indicated stage 3 right-sided and stage 2 left-sided AVN with lesions on the lateral, medial, and central pillars of both left and right hip. Both hips also showed a subchondral fracture and collapse with damage to the articular cartilage. The patient was operated on for total hip joint replacement surgery. The patient was discharged within a few days and asked for follow-up.

Case 6

A 38-year-old male patient weighing 94 kg presented to the orthopedic OPD with the chief complaints of left-sided hip pain radiating to the left thigh, left buttock, and groin area for the past 5 months. The patient had difficulty walking and sitting cross-legged. The patient also complained of pain on weight bearing. The patient has a habit of tobacco consumption. The patient also had a history of COVID-19 infection. The infection was managed through only home isolation. The patient has no other significant family history and no other chronic illness. On physical examination, the patient complained of slight pain on internal rotation and flexion of the left side hip. Radiographic evidence suggested stage 2 AVN of the left side hip. The patient was prescribed NSAIDs, ibridonic acid, and calcium. He was asked for regular follow-up.

Case 7

A 49-year-old male patient weighing 93 kg presented to the orthopedic OPD with the chief complaints of left-sided hip pain radiating to the left side knee, left side buttock, and left side groin area since the last 2 years. The patient complained of difficulty in walking and squatting. The patient had a history of COVID-19 Infection confirmed with a positive RT-PCR test. He was hospitalized from 12th May 2021 to 24th May 2021. The infection was diagnosed through HR-CT of the lungs which indicated atypical viral pneumonitis with a CORAD-5 Score indicating very high suspicion of COVID-19 infection. The D-DIMER Levels were 284.8 ng/ml (normal) on 12th May 2021 and 230 ng/ml (normal) on 21st May 2021 after adequate treatment. The CRP level on 12th May 2021 was 27 mg/L (elevated) and the SGPT level was also high. The infection was treated with antifibrotic drugs, steroids, antibacterial drugs, antitussives, and aspirin. The patient has no addictions or habits. The patient has no significant family history and no other chronic illness. On physical examination, pain on the internal rotation of the left side hip was noticed. On radiological examination, the MRI indicated stage 1 right-sided and stage 2 left-sided AVN. The patient was prescribed NSAIDS, ibridonic acid, calcium and antacid. He was asked for regular follow-up.

Case 8

A 29-year-old male patient weighing 73 kg presented to the orthopedic OPD on 8th July 2022 with chief complaints of right-sided hip pain radiating to the groin and thigh. The patient complained of difficulty walking and sitting. The patient had a history of COVID-19 infection. The infection was confirmed by an RT-PCR test positive for COVID-19 infection on 2nd February 2022. The X-ray chest was normal. The CRP value was 52.4 mg/L (elevated) on 2nd February 2022 and 12.9 mg/L (elevated) on 5th February 2022. The infection was treated with steroids, antivirals, anticoagulants, and

antibacterials. The patient has no addictions or any habits. The patient has no significant family history and no other chronic illness. The MRI findings revealed AVN of the head of femur on the right side with minimal joint effusion (Stage 2 AVN on the right side). NSAIDs, Ibridonic acid, vitamin D3, and calcium were prescribed and asked for regular follow-up.

Case 9

A 25-year-old male patient weighing 96 kg presented to the orthopedic OPD on March 2023 with chief complaints of bilateral hip pain radiating to both the thighs, knees, buttocks, and groin area for the past 1 year. The patient complained of pain on rest and pain on weight bearing. The patient also complained of difficulty walking, squatting, and sitting cross-legged. The patient had a history of COVID-19 Infection in March 2022. The patient was hospitalized in a private hospital for treatment of the infection. The patient did not recall the medications given for the treatment of COVID-19 infections. Hospital records were unobtainable. The patient has no addictions or any habits. The patient has no significant family history and no other chronic illness. On physical examination, the patient had pain on the internal rotation of both hips. The X-ray showed features of bilateral osteonecrosis changes. The MRI findings revealed stage 3 bilateral hip AVN. The patient was prescribed aspirin, Ibridonic acid, NSAIDs, and antacids and asked for regular follow-up.

Case 10

A 26-year-old male patient weighing 86 kgs presented to the orthopedic OPD in June 2023 with the chief complaints of bilateral hip pain radiating to both the thighs, knees, buttocks, and groin area. The patient had difficulty walking, sitting cross-legged, and squatting. The patient had a history of COVID-19 Infection. He received treatment from a private hospital. He has no habits or addictions. He has no significant family history or any other chronic illness. Radiographic evidence indicated stage 2 bilateral AVN. The patient was prescribed NSAIDs, Ibridonic acid, vitamin D3, and calcium and was asked for regular follow-up.

Case 11

A 39-year-old male patient weighing 84 kgs presented to the orthopedic OPD in August 2023 with the chief complaints of bilateral hip pain radiating to both the thighs, knees, buttocks, and groin area. The patient had pain with weight bearing. The patient had difficulty in walking, sitting cross-legged, and squatting. The patient had a history of COVID-19 Infection on 25/4/2021. The infection was confirmed with a positive RT-PCR test. The chest imaging showed multiple areas of subpleural and peri broncho vascular ground glass opacities with smooth interstitial septal thickening in bilateral lung fields and a CT score of 7 out of 25 indicating mild COVID-19 infection. The D-DIMER level was 474.16 (normal) and the IL-6 level was 55.1 (elevated) on 25/4/2021. The patient was advised home isolation. He has no habits or addictions. He has no significant family history or any other chronic illness. Radiographic evidence indicated stage 2 left-side AVN and stage 2 right-side AVN. The patient was prescribed NSAIDs, ibridonic acid, vitamin D3, and calcium and was asked for regular follow-up.

DISCUSSION

This study systematically examines the chief complaints, lifestyle factors, and key diagnostic findings in AVN cases, while exploring potential links between early cytokine profiles, management strategies, and COVID-19 infection severity. AVN is the result of bone cell death caused by either traumatic or non-traumatic disruptions in the blood supply.[11] In our analysis of 11 cases, all involved males aged 25 to 50, with four cases (2, 8, 9, and 10) being diagnosed before the age of 30. These findings are not isolated but align with existing literature, which indicates that while AVN can affect individuals across all age groups, but more generally observed in those under 50 years, with men being disproportionately affected.[12] However, a concerning trend has emerged with a noticeable rise in AVN cases among younger individuals following COVID-19 infection.[13] This underscores the importance of early diagnosis and intervention in COVID-19 patients to prevent the progression of AVN and improve long-term outcomes.

Trauma is a known cause Of AVN however, non-traumatic factors like corticosteroid use significantly increase the risk. Zhao's research shows a 35-fold increase in femoral head AVN among corticosteroid users.[14] Our study excluded long-term steroid users before COVID-19, found that cases 3, 5, 6, and 11-who underwent home isolation and likely did not receive steroids unless self-medicated-still developed AVN. Case 5, had a history of alcohol use but no steroid treatment, and cases 3 and 6, with tobacco use, highlighting additional risk factors. The literature indicates a six-fold increase in AVN of femoral head risk among individuals with alcoholism, suggesting it may be a significant factor in post-COVID AVN development.[14]

A least-discussed pathophysiological factor in AVN is hypercoagulability. During the COVID-19 pandemic, increased thrombotic events were widely observed, which may contribute to AVN development.[15] D-Dimer levels, which indicate the presence of blood clots or clotting problems, were found to be at the higher end of the normal range in cases 1, 2, 7, and 11. This suggests that hypercoagulability during COVID-19 might have accelerated the progression of AVN in these patients. Additionally, elevated C-reactive protein (CRP), a marker of inflammation, was noted in cases 1, 7, and 8, further indicating an inflammatory response that could be contributing to AVN. Research indicates that

proinflammatory single nucleotide polymorphisms in genes such as IL-1β, IL-6, and IL-8 can exacerbate hypercoagulability in COVID-19 patients, elevating the risk of bone necrosis.[1] In Case 11, elevated IL-6 levels may have triggered hypercoagulability and subsequent AVN.

Hypercoagulability is not unique to COVID-19; it is also observed in diseases such as pancreatitis, Gaucher's disease, systemic lupus erythematosus, Sickle cell anemia, decompression sickness, certain types of cancer or known case of hypercoagulability.[9] Given these findings, it is crucial to investigate further how hypercoagulability contributes to AVN in both pandemic and non-pandemic contexts.

This study highlights various risk factors for AVN, with a particular focus on hypercoagulability. However, limitations include incomplete medical records for several cases and unattainable hospital records. The small sample size and regional focus also restrict the study's generalizability. Future research should involve a larger and diverse sample to explore the precise pathogenesis of AVN, especially with post-COVID hypercoagulability.

CONCLUSION

The findings suggest that besides steroid use, post-COVID hypercoagulability and alcohol and tobacco consumption may contribute significantly to the development of AVN. Future research with larger sample sizes and diverse geographical settings is recommended to strengthen these findings.

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ANNEXURE

Table 1: Characteristics of cases.

Age (in years)	Sex	Weight (in kg)	Addictions	AVN hip-side	Ficat and Arlet grading (Left and right)		Mode of COVID treatment	D-DIMER during COVID	CRP during COVID	Steroid therapy during COVID
42	M	85	-	Left	2	_	Hospital admission	467 ng/ml	8.3 mg/l	Yes
28	M	82.7	-	Bilateral	2	2	ICU admission	26/5/21-918 ng/ml 29/5/21-250 ng/ml 4/6/21-490 ng/ml	NA	Yes
47	M	55	Tobacco consumption	Bilateral	2	2	Home isolation	NA	NA	No
30	M	80	-	Bilateral	2	2	Hospital admission	NA	NA	Yes
32	M	71	Alcohol	Bilateral	2	3	Home isolation	NA	NA	No
38	M	94	Tobacco consumption	Left	2	-	Home isolation	NA	NA	No
49	M	93	-	Bilateral	2	1	Hospital admission	12/5/21- 284.8 ng/ml 21/5/21-230 ng/ml	27mg/l	Yes
29	M	73	-	Right	-	2	Hospital admission	NA	2/2/22-52.4 mg/l 5/2/22-12.9 mg/l	Yes
25	M	96	-	Bilateral	3	3	Hospital admission	NA	NA	NA
26	M	86	-	Bilateral	2	2	Hospital admission	NA	NA	NA
39	M	84	-	Bilateral	2	2	Home isolation	474.16 ng/ml	NA	No