Title: A case report on steroid-induced avascular necrosis treated with autologous adult live-cultured osteoblasts (AALCO) in COVID-19 patients

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Abstract

In the absence of a targeted antiviral agent effective against COVID-19, corticosteroids show improvements in hyperinflammation and acute respiratory distress syndrome (ARDS) associated with COVID-19. However, various adverse effects of corticosteroids have been reported, like delayed viral clearance, secondary infections, avascular necrosis and suppression of the hypothalamic-pituitary-adrenal axis. In this case report, we report clinical outcomes in two patients with symptomatic avascular necrosis (AVN) of the femoral head after being treated with corticosteroids for COVID-19. We implanted autologous adult live-cultured osteoblasts (AALCO), sourced from mesenchymal stem cells via bone marrow aspiration, for treating AVN in both patients. The MRI examination suggested steroid-induced AVN of the hip with Ficat-Arlet stage IIB in these patients. A prednisone (corticosteroid) was used during COVID-19 treatment for a mean treatment duration of 14.5 days. The AALCO implantation showed good clinical outcomes in treating steroid-induced AVN of the hip with Ficat-Arlet stage IIB in both patients with COVID-19.

Keywords: Femoral head avascular necrosis, autologous adult live-cultured osteoblasts, corticosteroids, cell therapy

Introduction

The current pandemic of COVID-19 has affected approximately 225 million people globally as of 14 September 2021.(1) Reported evidence indicates that COVID-19 is associated with potential short-term and long-term adverse events affecting various body systems.(2) In the absence of a targeted antiviral agent effective against COVID-19, a wide array of pharmacological agents in the management of the COVID-19 are used. In this regard, corticosteroids have shown benefits in overcoming both hyperinflammation and ARDS associated with COVID-19.(3) However, there have been inconsistent findings owing to limited sample sizes and varying dosing strategies, due to which the results remained inconclusive. Over the course of 18 months of this pandemic, a number of adverse effects of corticosteroids have been reported, such as delayed viral clearance, secondary infections, and suppression of the hypothalamic-pituitary-adrenal axis.(4)

There is a long-standing history of association between corticosteroids and risk for avascular necrosis.(5) Given the highly prevalent use of corticosteroids in patients with COVID-19, the incidence of avascular necrosis (AVN) is also expected to rise.(6, 7) There is not enough concurrence as to at what dose and duration of steroids develop AVN. According to literature, the cumulative dose of around 2000 mg prednisone or other drugs of its equivalent is required to develop AVN (8), it was also reported that 700 mg is the minimum dose required to develop AVN.(9) However, the minimum dose may range from 290 mg-3300 mg in different patient population.(7) The prognosis of untreated avascular necrosis remains poor and, if not diagnosed and treated on time, can result in subchondral bone collapse, due to which the joint will lose its function.

The objective of AVN treatment is to slow the rate of disease progression, relieve the pain, avert joint collapse and restore the function of the joint.(7) Although various treatments are available for managing AVN, no standardized protocol exists for its management post-COVID-19.(10) Cell-based therapies like implantation of autologous adult live-cultured osteoblasts (AALCO) have shown benefits in patients with avascular necrosis in general.(11) Here, we report two cases of symptomatic AVN of the femoral head after being treated with corticosteroid for COVID-19. We implanted autologous adult live-cultured osteoblasts

(AALCO) sourced from mesenchymal stem cells via bone marrow aspiration to treat AVN in both patients.

Case presentation

Case 1

A 49-year-old male interventional cardiologist was diagnosed with COVID-19 in September 2020, for which the patient was admitted to intensive care at hospital because of dropping oxygen saturation. During his hospitalization, the patient was administered a high dose of intravenous methylprednisolone for 14 days and intravenous remdesivir for the treatment. Sixty days after the COVID-19 diagnosis, the patient developed pain in the bilateral region of the hip and was unable to perform his daily activities due to intense pain. The patient came to our hospital (Sri Sri Holistic Hospital, Hyderabad, India) with a complaint of pain in the hip region.

The patient had no history of hip pain before COVID-19. Preoperative visual analog scale score (VAS) was 8 for the right hip and 6 for the left hip. The MRI evaluation of the hip done after 90 days of COVID-19 diagnosis showed bilateral hip AVN with Ficat-Arlet stage IIB *(figure 1).*

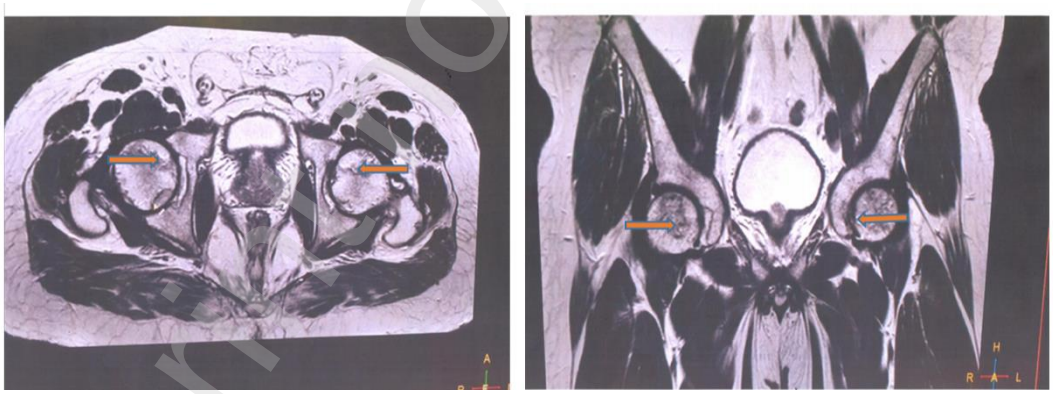

Figure 1: MRI and anteroposterior radiograph of the 49-year-old male patient confirming avascular necrosis of the femoral head of the bilateral hip (Ficat-Arlet-stage IIB).

Case 2

A 27-year-old female was diagnosed with COVID-19 in September 2020, for which the patient was admitted only for two days at a hospital (Nair Hospital, Mumbai, India). During the course of her treatment, the patient was administered prednisolone for 15 days (three times a day) and intravenous remdesivir injection for 3 days. Ninety days after the COVID-19 diagnosis, the patient developed pain in the bilateral region of the hip. The patient is a shopkeeper by occupation, and she had intense pain while walking and sleeping.

The patient visited our hospital complaining of intense pain in the hip region, and prior to COVID-19, the patient had no history of pain in the hip. The preoperative visual analog scale score (VAS) was 3 for the right hip and 6 for the left hip. Radiograph and MRI of hip done after seven months since COVID-19 diagnosis showed bilateral hip AVN with Ficat-Arlet stage IIB *(figure 2)*.

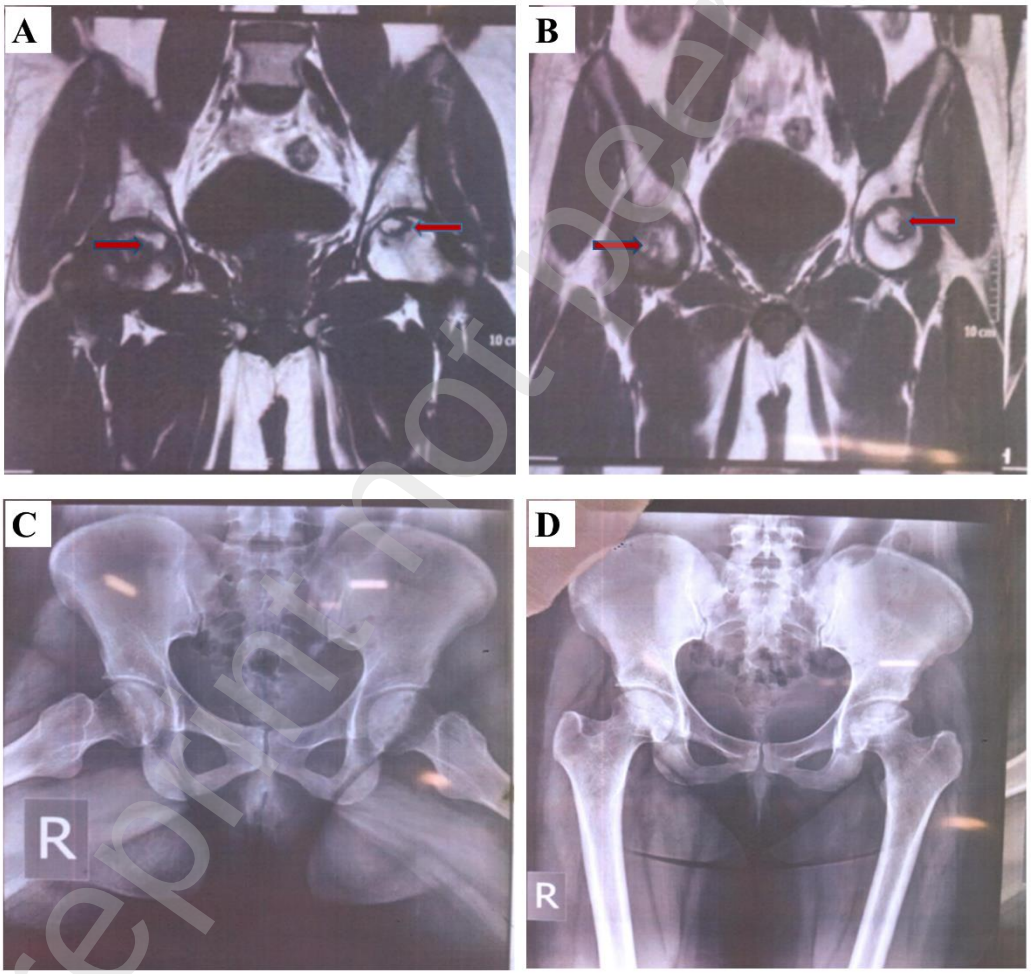

Figure 2: MRI (A and B) and anteroposterior radiograph (C and D) of the 27-year-old female patient confirming avascular necrosis of the femoral head of the bilateral hip (Ficat-Arlet-stage IIB).

Treatment and clinical outcomes

The average treatment duration of steroids for both patients was 14.5 days. The average time duration for the development of AVN post-COVID-19 diagnosis was 90 days. Both patients had undergone AALCO implantation on the recommendation of their consulting orthopedic surgeon after getting informed about complications of the disease and its therapeutic options.

AALCO implantation is a minimally invasive 2 step surgical procedure. Osteoblasts were obtained from the bone marrow aspirated from the posterior iliac crest of patient. Mesenchymal stem cells were isolated and differentiated into osteoblasts *ex-vivo*. Osteoblasts were then cultured for approximately 4 weeks under controlled laboratory conditions and multiplied up to 48 million osteoblasts (OSSGROW®, Regrow Biosciences Pvt. Ltd., India). Both patients were operated under general anesthesia. Under C-arm X ray, core decompression was performed and then osteoblasts were implanted using a Tisseel kit (Baxter, U.S.) at the site of avascular necrosis.(11)

After implantation, both the patients underwent appropriate rehabilitation therapy, which included 4 weeks of complete bed-rest post-implantation. After these four weeks, the patients performed passive lower limb exercises for the next two weeks. Accordingly, non-weight bearing, partial weight-bearing, and full weight-bearing exercises were suggested to the patients. No adverse events were reported by both patients immediately after OSSGROW® transplantation or during the follow-up

The visual analog scale (VAS) score was reduced from 8 to 2 for the right hip and 6 to 1 for the left hip in case 1 after a 6 months follow-up post-treatment. No significant reduction in the right hip VAS score was observed, but it was reduced from 6 to 4 after transplantation for the left hip for case 2 after 2 months post-treatment. The mean Harris Hip Score (HHS) was increased from 73 to 86 and 51 to 67 in case 1 and case 2, respectively.

Discussion

Here, we have presented two cases of steroid-induced AVN treated by the AALCO implantation technique. AALCO implantation showed good clinical outcomes in treating steroid-induced AVN of the hip with Ficat-Arlet stage IIB in both patients with COVID-19. In this case report, high dose prednisone was used during COVID-19 treatment for a mean treatment duration of 14.5 days for both patients.

A meta-analysis has shown that a mean cumulative dose of 2000 mg steroid was associated with AVN development.(8) We feel that due to the COVID-19 infection, the sensitivity to develop AVN is increased, and a smaller cumulative dose of steroids may also lead to AVN. Additionally, controversy exists regarding the development of AVN symptoms after administration of the first dose of steroid. Studies reported that the interval between corticosteroid intake and the development of symptomatic AVN is usually 6 months to 1 year.(12, 13) However, patients may become symptomatic and develop AVN at 58 days after COVID-19 diagnosis.(7) Patients in this report developed AVN after 90 days since the first dose of corticosteroid treatment; they were successfully treated with the AALCO implantation.

The conservative approach to manage AVN consists of bed rest and restricting weight-bearing by using crutches or canes. However, it is reported that to halt the progression of the disease, a conservative approach alone is not sufficient; in a prospective review, including 36 patients with hip AVN,(14) the rate of successful treatment outcome of surgical approach was 70% compared to 20% with a conservative approach in Ficat-Arlet stage I AVN. Where other conservative and medical treatments fails, hip arthroplasty is the last resort, but may require another revision surgery in the future when performed at a young age.(7) AALCO implantation is used to treat AVN in various studies and has shown promising results.(11, 15, 16) Palekar et al. reported that the treatment with AALCO halted the osteonecrosis progression, preserve the natural hip and improves functional activity, and prevented the need for hip replacement in 72 out of 101 hips.(11) The AALCO technique also showed low total hip arthroplasty conversion rate than the natural progression to osteoarthritis resulting from AVN of the femoral head.(15, 16) In this case report, we found a decrease in the VAS (pain) and an increase in the HHS (functional activity) after AALCO treatment in both patients with Ficat-Arlet stage IIB AVN following the steroid treatment for COVID-19.

Conclusion

Steroids have been a critical part of the therapeutic armamentarium in the management of COVID-19; however, they should be used prudently with a careful watch on its short-term and long-term complications. Avascular necrosis of the femoral head is one of the critical long-term complications of the COVID-19, the prognosis of which may be poor. AALCO implantation offers an effective treatment option in patients with avascular necrosis due to steroids following the COVID-19.

Conflict of interest: Nil

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