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A Case with Avascular Bone Necrosis Developing as a Complication of COVID-19 Treatment

COVID-19 tedavisi Komplikasyonu Olarak Avasküler Kemik Nekrozu Gelişen Olgu

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Abstract

As our knowledge and experience of COVID-19 increases, our treatment approaches may change. For patients with respiratory failure due to COVID-19 disease, the disease table can be better controlled with systemic glucocorticoids, and mortality rates and hospitalization periods can also be reduced. Steroid therapy can be applied for the long-term, especially in cases with organized pneumonia, and patients can be discharged from hospital with maintenance treatment. Complications have been noted in patients in the post-COVID period resulting from the use of glucocorticoids. While mostly bacterial and fungal lung infections are seen, another side-effect of glucocorticoids is their negative effect on bone metabolism. We present here a case in which avascular bone necrosis developed as a result of long-term steroid use for the treatment of COVID-19.

Key words: Covid-19, steroid therapy, avascular bone necrosis.

Özet

COVID-19 hastalığı ile ilgili bilgilerimiz ve deneyimlerimiz arttıkça tedavi yaklaşımlarımız da değişebilmektedir. COVID-19 hastalığına bağlı olarak solunum yetmezliği gelişmiş olan hastalarda sistemik glukokortikoidler ile hastalık tablosu daha iyi kontrol altına alınabilmekte ve mortalite oranları ile hastane yatış süreleri de azalmaktadır. Özellikle organize pnömoni gelişmiş olgularda steroid tedavisi uzun süreli olabilmekte ve hastalar idame tedavisi ile taburcu olabilmektedirler. Bununla beraber, hastalarda glukokortikoid kullanımına bağlı olarak postcovid dönemde komplikasyonlar da görebilmekteyiz. Daha çok bakteriyel ve mantara bağlı akciğer enfeksiyonları görülürken, glukokortikoidlerin diğer bir yan etkisi de kemik metabolizması üzerine olan olumsuz etkileridir. Burada, COVID-19 nedeni ile uzun süreli steroid kullanımı sonucu avasküler kemik nekrozu gelişen olguyu sunduk.

Anahtar Sözcükler: *Covid-19, steroid tedavisi, avasküler kemik nekrozu.*

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The world has been struggling since December 2019 with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), being a new-type coronavirus identified in pneumonia cases first in Wuhan (1).

The vast majority of infected people (81%) do not develop symptoms or the disease is overcome with mild symptoms. Although the World Health Organization (WHO) and national guidelines have put forward some clinical classifications, such as mild, moderate, severe, ARDS and shock, for symptomatic patients, they do have made no clear recommendation regarding the treatment to be applied in the different phases of the disease (2).

At the beginning of the pandemic, WHO did not recommend the routine use of corticosteroids for viral pneumonia, and concerns were expressed that these would not have any survival benefit and may even lead to such issues as avascular necrosis, diabetes, psychosis and reduced viral clearance (3). It has been shown, however, that the use of corticosteroids has positive effects on critically ill patients in terms of hospitalization periods and mortality, with the complications in these patients being due to invasive mechanical ventilation rather than the side effects of corticosteroids (4).

In the RECOVERY treatment study it was reported that a significant reduction in 28-day mortality and hospitalization period was achieved with dexamethasone treatment at a dose of 6mg/day for 10 days. In patients not receiving oxygen therapy, however, no positive effect on either mortality or the hospitalization period was detected, and it was not recommended due to the possible side effects (5).

Avascular necrosis of the femoral head (ANFH) is the name given to osteonecrosis that develops in the femoral head as a result of the development of atherosclerosis or ischemia in the femoral head for different reasons. In this article, we present a case of avascular necrosis of the femoral head as a complication of COVID-19 treatment.

CASE

A 44-year-old female patient with congenital torticollis who is employed as a nurse was placed on Favipiravir for 5 days after testing positive in a COVID-19 PCR test by the filiation team, taken after her daughter recorded a positive COVID-19-PCR test. In post-treatment, the patient complained of shortness of breath and fever, and an image compatible with bilateral COVID-19 infection was observed on a Thorax Computed Tomography (CT) (Figure 1a). The patient was subsequently admitted to the pandemic clinic on November 25, 2020.

The results of laboratory tests were CRP: 72.6mg/l (0-5), D-dimer: 0.89mg/l (0-0.55), and hemogram, ferritin and fibrinogen levels within normal limits. The patient was hypoxic and so was placed on dexamethasone 6 mg/day (oral), levofloxacin 750 mg iv/day, enoxaparin sodium sc 1x1 iv and oxygen therapy. The favipiravir treatment was complemented to 10 days.

Upon a deterioration in respiratory distress and progression observed in a CT on the 5th day, the patient was transferred to the intensive care unit (ICU) and placed on high flow oxygen therapy in the prone position, and three doses of immune plasma were given. After 5 days, upon the stabilization of the vital indicators, the patient was returned to the pandemic service. Upon increased need for nasal oxygen and no regression was observed in radiology imaging dose of the dexamethasone was adjusted as 2x 8 mg iv (Figure 1b). The dexamethasone dose was reduced daily in accordance with the patent's clinical condition. On the 35th day of the treatment, when the patient's need for oxygen had ceased and radiological improvement was observed (Figure 2), 2 mg of dexamethasone and enoxaparin sodium treatment were recommended, and the patient was discharged.

The patient was examined 10 days later in the outpatient clinic, when her respiratory complaints were found to have regressed significantly, but knee joint and hip pain had developed, and so the patient was checked by the Physical Therapy and Orthopaedics clinic. A Magnetic Resonance Image (MRI) taken 2 months after discharge, avascular necrosis was detected in the bilateral femoral head, adjacent to the acetabular joint (Figure 3a, b). Further examinations of the patient performed by all relevant clinics revealed no cause of avascular bone necrosis other than the glucocorticoids treatment. The heparin treatment of the patient was continued for 2 more months after discharge, and acetylsalicylic acid 100 mg was recommended. Hyperbaric oxygen therapy was planned for the patient for the treatment of avascular necrosis in the Orthopaedics clinic.

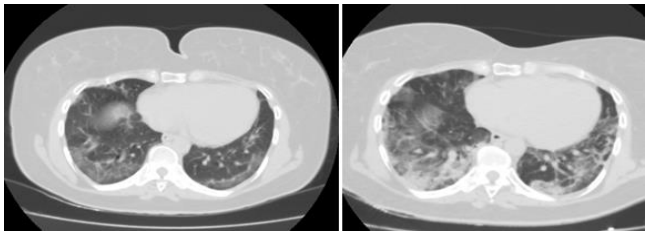

Figure 1: *In the initial chest computed tomography examination of the patient* ***(a)****, peripherally distributed ground-glass opacities were identified, and were more prominent in the lower lobes. A chest computed tomography 3 weeks later* ***(b)*** *revealed significant progression in infiltrations*

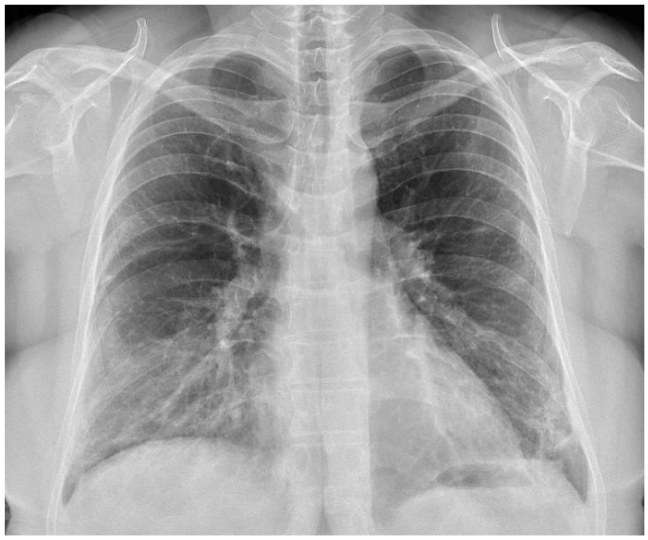

Figure 2: *Chest X-ray findings of the patient in which the bilaterally consolidated areas seem to have regressed*

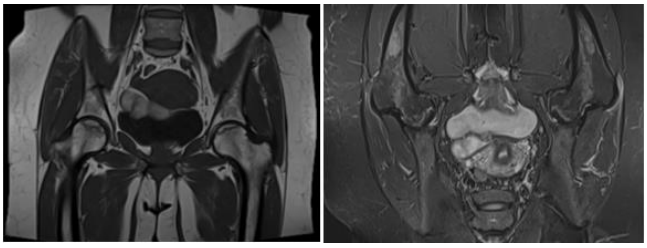

Figure 3: *Hip magnetic resonance imaging (MRI), T1-weighted* ***(a)*** *and fat-suppressed T2-weighted* ***(b)*** *coronal images reveal crescentic subchondral signal changes within both femoral heads, compatible with avascular necrosis*

DISCUSSION

Glucocorticoids are drugs that have immunosuppressive and anti-inflammatory effects in appropriate therapeutic doses, although there are many side effects encountered during glucocorticoid use (6). While osteoporosis is a recognized and common side effect affecting bone metabolism, avascular necrosis is a less frequent side effect (7,8).

ANFH is defined as the death or necrosis of regional bone tissue due to the loss of vascular support (9,10), and is divided into two groups, as primary (idiopathic) and secondary (traumatic-nontraumatic) based on the underlying aetiology (11). Secondary reasons include femoral neck fracture, hip dislocation, steroid and alcohol use, collagen tissue diseases, hypofibrinolytic and thrombophilia diseases, Caisson disease, transplantation and sickle cell anaemia (12).

Although corticosteroids were not recommended for treatment by WHO at the beginning of the pandemic, in subsequent studies the use of anti-inflammatory therapy in the hyperinflammation period in the clinical staging of COVID-19 was suggested to be effective (13).

In early September 2020, a WHO-mandated panel of experts published guidelines on the use of corticosteroids for the treatment of COVID-19. While this guideline was being prepared, two meta-analyses were reviewed, including eight randomized controlled trials, including the RECOVERY study that had been published by that time. As a result, while systemic (oral or intravenous 6 mg dexamethasone per day, or 50 mg hydrocortisone every 8 hours) corticosteroid therapy for 7–10 days in severe and critically ill COVID-19 patients was strongly recommended, as a conditional recommendation, corticosteroid therapy (14) was not advised for non-severe COVID-19 patients.

According to the guidelines published by the Ministry of Health of Republic of Turkey, 6mg/day dexamethasone or 0.5–1 mg/kg prednisolone, or an equivalent methylprednisolone, are recommended for 10 days in patients in need of oxygen therapy support due to respiratory distress. Despite this treatment, considering the risk conditions it has been stated that high-dose steroids ($\geqslant$ 250mg/day methyl prednisolone, 3 days) can be given to patients with an increased oxygen need or acute phase reactants within 24 hours. After the application of high-dose steroids, it was recommended that treatment continue with 6 mg/day dexamethasone or 0.5-1mg/day prednisolone, or an equivalent methylprednisolone (15).

Cases of avascular bone necrosis as a complication of treatment during past viral pandemics have been reported in literature. During the SARS pandemic in 2003, corticosteroids were found to improve a patient's condition in the early stages by lowering the fever, reducing lung inflammatory infiltration and improving oxygenation, although their long-term use (especially in high doses) was associated with potentially serious adverse incidents (16). In a follow-up study, 23.1% (18/78) of Chinese patients with SARS developed steroid-induced ANFH, due mainly to the use of high-dose glucocorticoids during SARS treatment (17).

In coronavirus literature, in a series of three cases by Agarwala SR et al., ANFH was reported in COVID-19 patients after a mean steroid (methylprednisolone) dosage of 758mg (min. 400mg, max. 200mg) and a mean 58 days after diagnosis (18).

In our patient, the need for intensive care emerged due to the onset of COVID-19 disease with a severe clinical manifestation, and the steroid dose was increased to 2 x 8 mg dexamethasone dose, the steroid dose was reduced and given for about 1 month. ANFH developed in our patient as a result of the long-term use of glucocorticoids.

In our clinical practice, infectious complications are mostly related to long-term glucocorticoid use in patients with COVID-19, while ANFH has been observed as a treatment complication in only one patient to date.

In conclusion, the long-term use of glucocorticoids is possible in patients with severe COVID-19 requiring inpatient treatment. In the post-discharge follow-up of these patients, it is very important to look for the possible adverse effects of glucocorticoids on bone metabolism to ensure the early diagnosis and treatment of any complications.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - İ.Y., B.S.K., E.Ç.E., F.E.U., C.Ç.; Planning and Design - R İ.Y., B.S.K., E.Ç.E., F.E.U., C.Ç.; Supervision - İ.Y., B.S.K., E.Ç.E., F.E.U., C.Ç.; Funding - İ.Y., F.E.U.; Materials - İ.Y., B.S.K., F.E.U.; Data Collection and/or Processing - İ.Y., B.S.K., E.Ç.E.; Analysis and/or Interpretation - İ.Y., E.Ç.E.; Literature Review - İ.Y., E.Ç.E.; Writing - İ.Y.; Critical Review - İ.Y., E.Ç.E.

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