Osteonecrosis of the femoral head after COVID-19: a case series

O.A. Khamidov, Z.Kh. Ravshanov
Samarkand state medical institute, Samarkand, Uzbekistan

Corresponding author: Zafar Kh. Ravshanov, radiologyuz@gmail.com

Abstract

It is known that COVID-19 has an adverse effect on various organs and systems of the human body. In the available literature, there are isolated reports regarding the development of osteonecrosis after suffering COVID-19. These papers discuss the role of commonly used corticosteroids in the treatment of COVID-19 in the development of osteonecrosis. Our article presents clinical observations of four patients with bilateral osteonecrosis of the femoral heads during treatment with COVID-19. The doses of prednisolone in three patients were 4500 mg, 735 mg and 525 mg. One patient did not receive corticosteroids. Our data showed that osteonecrosis in COVID-19 survivors developed at a shorter time compared to osteonecrosis in patients without coronavirus infection. Two out of four patients had a positive family history (myocardial infarction, hypertension, thrombosis). It is possible that hereditary vascular factors played a role in the genesis of osteonecrosis of the femoral head. Further evidence is needed to understand the development of osteonecrosis after COVID-19. Probably, the development of the disease is synergistically affected by many factors, including steroid and ischemic.

Key words: COVID-19, coronavirus infection, corticosteroids, aseptic necrosis, osteonecrosis


Introduction. A novel coronavirus infection is the cause of a pandemic that began in December 2019, and on January 30, 2020, WHO declared the outbreak of a novel coronavirus infection a public health emergency of international concern. On February 11, 2020, the International Committee on Taxonomy of Viruses named the new coronavirus SARS-CoV-2, and the WHO named the disease COVID-19. Due to the rapid spread of the infection around the world and high mortality, on March 11, 2020, WHO announced the start of the COVID-19 pandemic. SARS-CoV-2 has significantly surpassed SARS-CoV and MERS-CoV in terms of the number of infected and epidemic zones: cases of a new coronavirus infection have now been recorded in 220 countries of the world. As of September 10, 2021, 223,022,538 cases of COVID-19 were registered in the world, including 4,602,882 deaths. The performed studies demonstrate that COVID-19 has an adverse effect on various body systems and can lead to such conditions as pulmonary thromboembolism, cardiomyopathy, Guillain–Barre syndrome, pulmonary fibrosis, dysfunction of the nervous system, etc.. The effects of COVID-19 can persist for weeks or even months. In 2020, in order to describe the protracted course of the consequences of COVID-19, the term “long COVID” was proposed, that is, long-term COVID, the duration of which exceeds 12 weeks. Symptoms of prolonged COVID-19 may include fatigue, feeling short of breath, depression and anxiety, chest, joint and muscle pain, and lack of concentration, which is referred to by the term “brain fog”. According to Russian clinical guidelines for the treatment of COVID-19 from 2021, therapy is divided into etiotropic, pathogenetic and symptomatic. Antiviral drugs are used as etiotropic therapy. Pathogenetic therapy is prescribed mainly for hospitalized patients and includes immunosuppressants for the treatment of “cytokine storm” (blockers of cytokines and their receptors). In the acute phase of COVID-19, 80 days after the onset of the disease, the patient noted the appearance of severe pain in the region of both hip joints (VAS 8 points) and lower back, and therefore experienced significant difficulty in walking. It should be noted that corticosteroids are used as a life-saving agent. It is well known that long-term and/or high-dose use of corticosteroids in clinical practice is a factor predisposing to the development of osteonecrosis (steroid-induced necrosis), including the femoral head. At the same time, it is known that in the genesis of the so-called idiopathic osteonecrosis of the femoral head, coagulopathy and vascular factors play a role, which are elements of the pathogenesis of thrombotic complications in severe forms of COVID-19. In this article, we present 4 clinical cases of patients with bilateral osteonecrosis of the femoral heads, diagnosed after a coronavirus infection, in which the genesis of osteonecrosis...
Clinical observation 1. A 42-year-old man (patient 1) without a burdened somatic and family history suffered a severe form of COVID-19 with 80% lung damage. He was hospitalized for 27 days. The patient was prescribed anticoagulants (enoxaparin 1.6 ml per day for the entire period of treatment), the antiviral drug favipiravir (3500 mg — 1 day, then 1500 mg — 6 days), tocilizumab (450 mg once). Prior to hospitalization, the patient received 18 mg of dexamethasone for 6 days. During inpatient treatment, dexamethasone therapy was continued at a dosage of 20 mg daily, followed by a decrease to 4 mg by the time of discharge. In total, during the illness, the patient received 600 mg of dexamethasone. After discharge from the hospital in order to prevent thrombosis, the patient received 20 mg of rivaroxaban per day for 1 month.

80 days after the onset of the disease (positive PCR test for COVID-19), the patient noted the appearance of severe pain in the region of both hip joints (VAS 8 points), the lower back, and therefore experienced significant difficulty in walking. It should be noted that such symptoms were noted by the patient for the first time in his life. 120 days after the onset of COVID-19, according to MRI, bilateral necrosis of the ARCO IIC stage femoral heads on both sides was diagnosed (Figure 1). 140 days after the onset of COVID-19 disease, bilateral decompression of necrosis foci was performed with the introduction of bone marrow concentrate (BMC) and drug therapy with statins, taking into account the alleged steroid-induced necrosis, bisphosphonates, and anticoagulants. 3 months after the operation, the patient noted an improvement in motor activity, a decrease in pain syndrome (from 8 to 4 points according to VAS), unfortunately, no significant improvement was found according to MRI data.

Clinical observation 2. In a 32-year-old man (patient 2), without an aggravated somatic and family history, the disease manifested from an increase in temperature to 38°C for 7 days, he independently took antipyretic drugs (paracetamol). Due to the deterioration of his condition, he consulted a doctor and was hospitalized, where COVID infection was confirmed and 40% of lung damage was detected. During inpatient treatment (8 days), the patient received anticoagulants (enoxaparin 1.2 ml for the entire period of inpatient treatment), an antiviral drug (triazaverin 750 mg per day for 5 days), tocilizumab (450 mg once) and dexamethasone, the total dose of which was 100 mg. After discharge from the hospital for 1 month, the patient received 15 mg of rivaroxaban per day.

75 days after the onset of the disease, the patient complained of severe pain in the hip and knee joints, pain in both hips and lower back (VAS 8 points). Due to pain, he was forced to use crutches when walking. The patient turned to a neurologist, a diagnosis of intervertebral hernia in the lumbar spine was established, conservative treatment was recommended (NSAIDs, muscle relaxants, intravenous infusions with dexamethasone 4 mg in combination with novocaine 0.5% 50 ml three times, vitamin therapy, physiotherapy) for 4 weeks. Against the background of the therapy, an improvement in the condition was noted initially (a decrease in VAS to 4 points), the patient refused to use crutches and switched to a cane. During a second examination by a neurologist, a pathology of the hip joints was suspected, which was confirmed by MRI: bilateral necrosis of the femoral heads of the ARCO IIC stage. (Figure 2.) In connection with the revealed necrosis of the heads of the femoral bones, the patient turned to an orthopedist. Taking into account the revealed aseptic necrosis of the femoral heads in the precollaptoid stage (ARCO IIC), drug therapy (anticoagulants and bisphosphonates) was prescribed, an operation was proposed — decompression of necrosis foci, which the patient categorically refused.

Clinical observations 3 and 4. We present observations...
3 and 4 together, since these patients: a 32-year-old woman (patient 3) and a 30-year-old woman (patient 4) are sisters who had COVID-19 in the same period, after which both were diagnosed with bilateral aseptic necrosis of the femoral heads. An important circumstance, in our opinion, is a burdened family history common to the sisters. The father of the patients at the age of 49 suffered a myocardial infarction, currently suffering from heart failure and hypertension stage III; the elder sister, at the age of 41, suffered from acute phlebothrombosis of the lower extremities; the mother of patients from an early age (37 years) suffers from hypertension.

Both patients almost simultaneously suffered moderate COVID. Patient 3 was hospitalized for 6 days with 25% lung involvement. Inpatient treatment included an antiviral drug (favipiravir 2450 mg — 1 day, then 1200 mg for 5 days), anticoagulants (enoxaparin 0.6 ml for 6 days) and dexamethasone in a total dose of 80 mg. After discharge from the hospital for 1 month, the patient received 15 mg of rivaroxaban per day.

Patient 4, with a similar percentage of lung involvement, was on outpatient treatment that did not include corticosteroids. Patient 4 received favipiravir 1 day — 2450 mg, then 1200 mg — 6 days, as well as rivaroxaban 10 mg for 30 days from the onset of the disease.

Patient 3, 120 days after the onset of the disease, developed pain in the hip joint and was diagnosed with bilateral necrosis of the femoral heads on the left ARCO IIIC stage, on the right ARCO IIB. In Figure A, the arrow shows the crescent sign, indicating a subchondral bone fracture.

4 weeks after the diagnosis of bilateral aseptic necrosis due to the presence of a subchondral fracture of the left femoral head (ARCO IIIC stage), patient 3 underwent total left hip arthroplasty.

Patient 4, 180 days after the COVID-19 disease, began to notice low back pain, an MRI of the lumbosacral spine and hip joints was performed. Bilateral necrosis of the femoral heads was revealed: on the right side ARCO IIB degree, on the left side ARCO IIA degree (Figure 4).

Patient 4 is under dynamic observation, at this stage conservative treatment is being carried out (anticoagulants and bisphosphonates), decompression of necrosis foci is planned.

Key summary data for 4 clinical cases are shown in Table 1.

Discussion. In modern conditions, studies of the impact of COVID-19 on the course of human chronic diseases and the development of de novo diseases are extremely relevant.

Over the past year (2021), 4 patients came to us with aseptic necrosis of the femoral heads after suffering COVID-19.

In this regard, we searched for similar clinical observations in large information resources (PubMed and ResearchGate) by entering a combination of the terms COVID, coronavirus, AVN, avascular necrosis, osteonecrosis into the search string. Two publications were found. The first publication dealt with the impact of coronavirus and its treatment on the course of previously developed steroid-induced osteonecrosis. The authors have not received convincing data on the negative impact of coronavirus on the progression of the stage of osteonecrosis.

The second publication is of the case report type and describes three clinical observations of patients with aseptic necrosis of the femoral heads that occurred after suffering COVID-19. In this paper, the authors suggest the formation of steroid-induced necrosis in all three patients, despite the relatively low doses of hormones that they received during the treatment of COVID-19.

The pathogenesis of steroid-induced aseptic necrosis is not fully understood, but it is believed that the mechanism of its development includes fat embolism, fat hypertrophy, hypercoagulation, endothelial dysfunction, etc.

There is no consensus on the minimum dose of hormones, as well as the duration of their administration, necessary for the development of aseptic necrosis. Some authors report that the minimum cumulative dose of prednisolone for the formation of aseptic necrosis is 2100 mg. Other researchers show that already 800 mg of prednisolone is a sufficient dose for the formation of osteonecrosis. M.
### Table 1.
Clinical characteristics of patients with necrosis of the femoral heads after COVID-19.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42 32 32 30</td>
</tr>
<tr>
<td>Confounded family history (MI, coronary artery disease, thrombosis, GB)</td>
<td>-   -  +  +</td>
</tr>
<tr>
<td>The course of COVID-19</td>
<td>heavy The average The average The average</td>
</tr>
<tr>
<td>Total dose of dexamethasone/prednisolone, mg</td>
<td>600/4500 112/735 80/525 -</td>
</tr>
<tr>
<td>The time period for the development of necrosis from the onset of COVID-19, days</td>
<td>80 75 120 180</td>
</tr>
<tr>
<td>Necrosis Severity (ARCO) Right/Left</td>
<td>ARCO IIC/ARCO IIC ARCO IIC/ARCO IIC ARCO IIB/ARCO IIC</td>
</tr>
</tbody>
</table>

McKee et al. demonstrated that in patients with steroid-induced necrosis (n=15), the disease manifested after taking prednisolone in a cumulative dose of 290 to 3300 mg with an average value of 850 mg. According to a meta-analysis conducted by M.A. Mont et al., prednisolone doses greater than 10,000 mg increase the risk of aseptic necrosis by a factor of two in organ transplant patients. In the present study, three of four patients received dexamethasone for the treatment of COVID-19 at a cumulative dose of 600 mg, 112 mg, and 80 mg, corresponding to 4500 mg, 735 mg, and 525 mg of prednisolone. Taking into account the above literature data, in these three patients, with varying degrees of probability, it is possible to assume a steroid genesis of aseptic necrosis.

The first clinical signs of aseptic necrosis in our patients appeared 80, 75, 120 and 180 days after the start of medical treatment for COVID-19, including corticosteroids, except for patient 4.

The available literature provides conflicting data regarding the time required for the formation of necrosis while taking corticosteroids. J. Anderton et al. reports a 23-year-old patient who developed aseptic necrosis of the head of the humerus 2 years after finishing a course of oral dexamethasone. McKee et al. reported a median time from corticosteroid treatment to aseptic necrosis of 16.6 months (range 6 to 33 months). In turn, a review of the literature on the pathogenesis of aseptic necrosis shows that, as a rule, the manifestation of osteonecrosis occurs in the period from 6 to 12 months after taking hormones. The authors of the only publication on post-COVID necrosis (S. Agarwala et al.) indicate the average time for the onset of necrosis after COVID-19 to be 58 days (from 45 to 67 days). Our data, as well as those of S. Agarwala et al., show that the time of development of aseptic necrosis after COVID-19 is significantly shorter than the time of development of osteonecrosis given in the literature after a course of hormone therapy in the pre-Covid era. This suggests that not only the use of corticosteroids, but also other factors associated with Covid and its treatment, may influence the accelerated development of osteonecrosis.

Patients 3 and 4, who are sisters, deserve a separate discussion. Patient 3 received a small cumulative dose of hormones (Table 1). Patient 4 did not receive corticosteroids. We assumed a different (non-steroidal) genesis of the development of aseptic necrosis of the femoral head, and therefore their family history was carefully studied, which turned out to be extremely burdened. The closest relatives under the age of 50 had a myocardial infarction, severe hypertension, thrombosis, which made it possible to suspect a possible family predisposition to «vascular accidents» in this family. This seems very likely, since in the last decade it has been established that genetically determined thrombophilia, coagulopathy, endothelial dysfunction, etc., play a certain role in the genesis of aseptic necrosis. A modern systematic approach to medicine has made it possible to establish the presence of some gene polymorphisms common to vascular disorders of various localizations. In particular, in our studies, the relationship of aseptic necrosis with polymorphisms of the genes of factors V and XIII of the blood coagulation system, the methylenetetrahydrofolate reductase gene, and platelet integrin genes in the pathogenesis of non-traumatic aseptic necrosis of the femoral head was previously proven. In relation to the observational data (patients 3,4), it is reasonable to assume that COVID-19 provoked and/or accelerated the implementation of a genetic predisposition to vascular disorders.

Of course, it is premature to draw conclusions regarding the genesis of osteonecrosis after suffering covid today. It is likely that many factors, including steroid and ischemic, act synergistically in this disease. The accumulation of information about such patients will allow in the future to form a more informed opinion on this issue.

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Литература


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Информация об авторах:
Хамидов Обид Абдурахманович — phd, заведующий кафедрой Медицинской радиологии ФПДО Самаркандского государственного медицинского института, Самарканд, Узбекистан. E-mail: o.xamidov@gmail.com; https://orcid.org/0000-0001-7458-3884
Равшанов Зафар Хазраткулович — клинический ординатор кафедры ФПДО Медицинской радиологии ФПДО Самаркандского государственного медицинского института, Самарканд, Узбекистан. E-mail: radiologyuz@gmail.com

Information about the authors:
Khamidov Obid Abdurakhmanovich — phd, Head of the Department of Medical Radiology FPE, Samarkand state medical institute, Samarkand, Uzbekistan. E-mail: o.xamidov@gmail.com; https://orcid.org/0000-0001-7458-3884
Ravshanov Zafar Khazratkulovich — resident of the Department of Medical Radiology, Samarkand state medical institute, Samarkand, Uzbekistan. E-mail: radiologyuz@gmail.com

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