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Редкая локализация аваскулярного некроза при лечении новой коронавирусной инфекции глюкокортикостероидами

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АННОТАЦИЯ

Развитие аваскулярного некроза костных структур, индуцированного лечением новой коронавирусной инфекции глюкокортикоидами, является довольно распространённым осложнением терапии, при этом чаще всего встречается поражение головок бедренных костей. Своевременное выявление аваскулярного некроза важно в рамках профилактики развития артритов и других осложнений.

В работе представлен клинический случай пациентки в возрасте 54 лет, госпитализированной по поводу новой коронавирусной инфекции, с жалобами на выраженные боли в обоих коленных суставах через 2 недели от начала болезни. По результатам магнитно-резонансной томографии был выявлен выраженный аваскулярный некроз костей, формирующих коленный сустав, с обеих сторон. Консервативная терапия, включающая приём нестероидных противовоспалительных препаратов и ингибиторов костной резорбции из группы бисфосфонатов, дала выраженный положительный результат. При повторном осмотре через 3 месяца болей нет, сохраняются небольшие ограничения движений в коленных суставах. По данным магнитно-резонансной томографии обоих коленных суставов отмечено значительное уменьшение ранее выявленных изменений.

Побочные эффекты глюкокортикоидов (нарушение толерантности к глюкозе, повышение артериального давления, тахикардия, эрозивно-язвенное поражение желудочно-кишечного тракта, нарушения сна и др.) широко известны, однако остеонекроз костных структур коленных суставов, вызванный приёмом стероидов, редко попадает в поле зрения клиницистов. Приведённый клинический случай подчёркивает комплексный характер патогенеза остеонекроза и демонстрирует широкий спектр осложнений при терапии кортикостероидами.

Ключевые слова: клинический случай; аваскулярный некроз; остеонекроз; коронавирусная инфекция; коленный сустав; магнитно-резонансная томография.

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Rare localization of avascular necrosis during treatment of COVID-19 with glucocorticosteroids

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ABSTRACT

The development of bony avascular necrosis induced by glucocorticoid treatment of COVID-19 is a common adverse effect, with femoral head being the most commonly affected. Timely detection of avascular necrosis is important in the prevention of osteoarthrosis and other complications.

We present a clinical case of a 54-year-old patient hospitalized for novel coronavirus infection with complaints of severe pain in both knees 2 weeks after the disease onset. Magnetic resonance imaging revealed pronounced changes in both knees, corresponding to avascular necrosis. The results of conservative therapy, including non-steroidal anti-inflammatory drugs and bisphosphonate bone resorption inhibitors, produced a pronounced positive result. At follow-up examination 3 months later, there was no pain, but the knee joints still had slight restrictions of movement. Magnetic resonance imaging showed a significant decrease in the previously detected changes.

The side effects of glucocorticoids (impaired glucose tolerance, increased blood pressure, tachycardia, gastrointestinal erosive ulcers, sleep disorders, etc.) are widely known, but knee osteonecrosis caused by steroid intake rarely comes to the attention of clinicians. This clinical case emphasizes the complex nature of osteonecrosis pathogenesis and demonstrates a wide range of complications in corticosteroid therapy.

Keywords: case report; avascular necrosis; osteonecrosis; COVID-19; knee joint; magnetic resonance imaging.

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糖皮质激素治疗新型冠状病毒感染罕见局限性缺血性坏死

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简评

糖皮质激素治疗新型冠状病毒感染引起的骨结构缺血性坏死是一种相当常见的治疗并发症，其中最常见的是股骨头病变。对于预防关节炎和其他并发症，及时检测缺血性坏死是很重要的。

这项研究展示了一名54岁的患者的临床案例，她因新冠状病毒感染住院，并在发病后两周内抱怨双膝关节疼痛。磁共振成像扫描显示，形成膝关节的骨骼在两侧都有明显的血管性坏死。使用非甾体抗炎药和双磷酸盐骨吸收抑制剂的保守治疗有显著的积极效果。3个月后复查时，没有疼痛，但膝关节的活动仍有轻微限制。两个膝关节的磁共振成像显示，先前确定的变化明显减少。

糖皮质激素的副作用（糖耐量受损、血压升高、心动过速、胃肠道侵蚀性溃疡、睡眠障碍等）广为人知，但由类固醇引起的膝关节骨结构的骨坏死却很少引起临床医生的注意。这个临床病例强调了骨坏死发病机制的复杂性，并展示了皮质类固醇治疗的广泛并发症。

关键词：临床病例；缺血性坏死；骨坏死；冠状病毒感染；膝关节；磁共振成像。

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BACKGROUND

The novel coronavirus infection, discovered in Wuhan, China, in December 2019, has triggered a global pandemic. The use of glucocorticosteroids (GCSs) to treat novel coronavirus infection is pathogenetically justified and widespread [1]. However, even a single dose of GCS can cause the development of avascular necrosis [2]. The literature describes several clinical cases of femoral head avascular necrosis in patients treated with GCS [3, 4]. However, the cases of osteonecrosis in other areas, particularly the knee joints, are mentioned much less frequently [5]. Early diagnosis of this pathology is critical for preventing arthritis and other complications [6].

This paper describes a clinical case of avascular necrosis of the bone structures of both knee joints that developed while treating coronavirus infection with GCS.

CLINICAL CASE

Patient

A 54-year-old woman with complaints of severe cough and fever up to 39.5 °C for 6 days was hospitalized with the novel coronavirus infection. A chest CT revealed lung damage of >30%. The PCR test for SARS-CoV-2 RNA was positive. The medical history was insignificant.

During the hospital stay, the patient received parenteral dexamethasone at a daily dose of 20 mg for 5 days, followed by a 2-day break and subsequent reintroduction of dexamethasone at a daily dose of 12 mg for 5 days. Additionally, the patient received anticoagulant and antisecretory therapy.

On Day 15 of the disease, the patient experienced severe pain and substantial limitation of knee joint movement, which persisted at night. The knee joints were nontender on palpation. On Day 17 of the disease, the patient was discharged because of positive changes. Nonsteroidal anti-inflammatory drugs (NSAIDs) were recommended for treating knee joint pain.

Magnetic resonance imaging (MRI) of both knee joints was performed 1.5 months after hospitalization due to persistent pain and limited movement in the knee joints.

Instrumental findings

MRI of the left knee joint: lesions in the distal parts of the femoral diaphysis and femoral condyles (with involvement of the articular surface) as well as in the patella, inhomogeneously hyperintense on PD-weighted (proton-weighted) images with fat suppression and hypo-/isointense on T1-weighted images (T1WI), with an irregular ("geographic") shape and yellow marrow signal areas visualized in the central parts (Fig. 1). MRI of the right knee joint: similar lesions of the bone marrow of both femoral condyles, with involvement of the distal metaepiphysis and articular surface of the lateral condyle as well as the patella. A perilesional "double line" sign is visualized over a short distance for some lesions (Fig. 2).

The following diagnosis was made on the basis of medical history and identified MRI changes: "Avascular necrosis of the bone structures of both knee joints."

Diagnosis and treatment

On the basis of MRI findings, medical history, and clinical pattern, the patient was diagnosed with avascular necrosis of the femoral and tibial condyles of both knee joints. Thus, the following conservative therapy (physiotherapy) was prescribed: magnet therapy and phonophoresis with NSAID-containing gel, NSAID therapy (tablets) for pain (as needed), vitamin D preparations, and bisphosphonate bone resorption inhibitors.

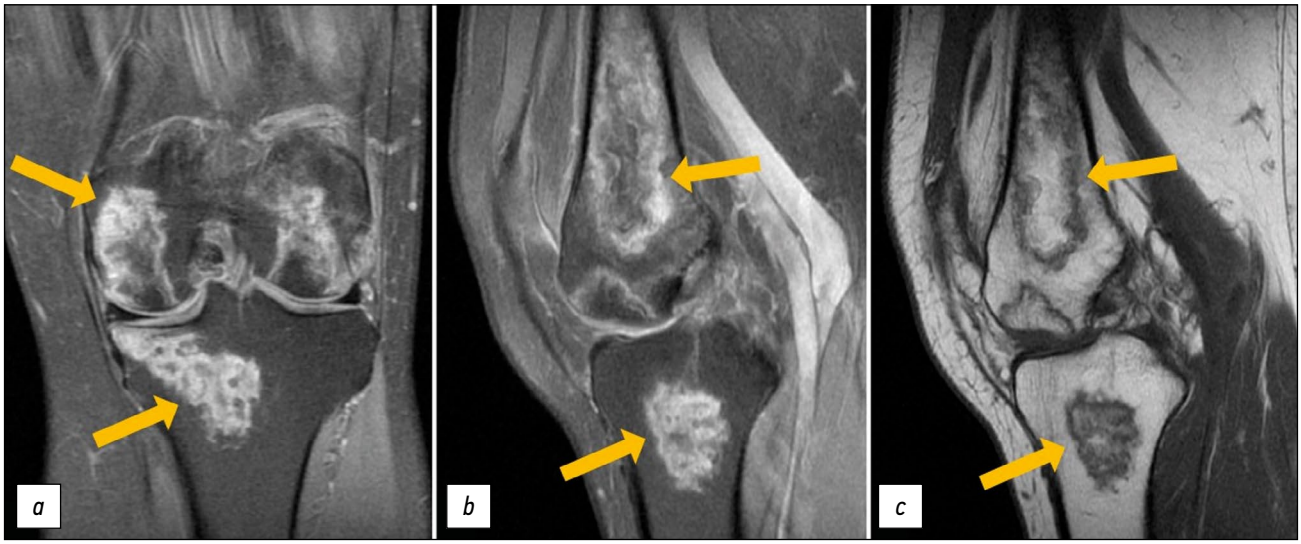

Fig. 1. Primary MRI of the left knee joint: PDWI with fat suppression in the coronal (*a*) and sagittal (*b*) plane and T1WI in the sagittal plane (*c*). The arrows indicate areas of bone marrow edema in the form of a heterogeneous, irregularly shaped ("geographic") MRI signal of femoral and tibial condyles.

The therapy resulted in substantial positive changes after 3 months: The pain had subsided, but some limitations in knee joint movement remained (the patient could not do a deep squat).

A follow-up MRI of both knee joints revealed positive changes: Previously identified lesions had become substantially less severe (Figs. 3 and 4).

DISCUSSION

The prevalence of osteonecrosis in patients with the novel coronavirus infection ranges from 5% to 58% [7]. Damage is more common to the femoral head than to the bone structures of the knee joints and other bones.

Secondary osteonecrosis of knee joint bone structures, particularly avascular necrosis, most commonly affects both femoral condyles, as in the clinical case presented here. Conversely, primary osteonecrosis affects only one of the condyles [8].

Avascular necrosis can develop as a result of GCS treatment, kidney disease, or hematological diseases. Some authors believe that drugs used to treat coronavirus infection, such as lopinavir and ritonavir, can contribute to the development of osteonecrosis [9]. In our case, this pathology most likely developed as a result of GCS treatment for coronavirus infection.

GCSs, which play an important role in treating novel coronavirus infection, are an independent risk factor for

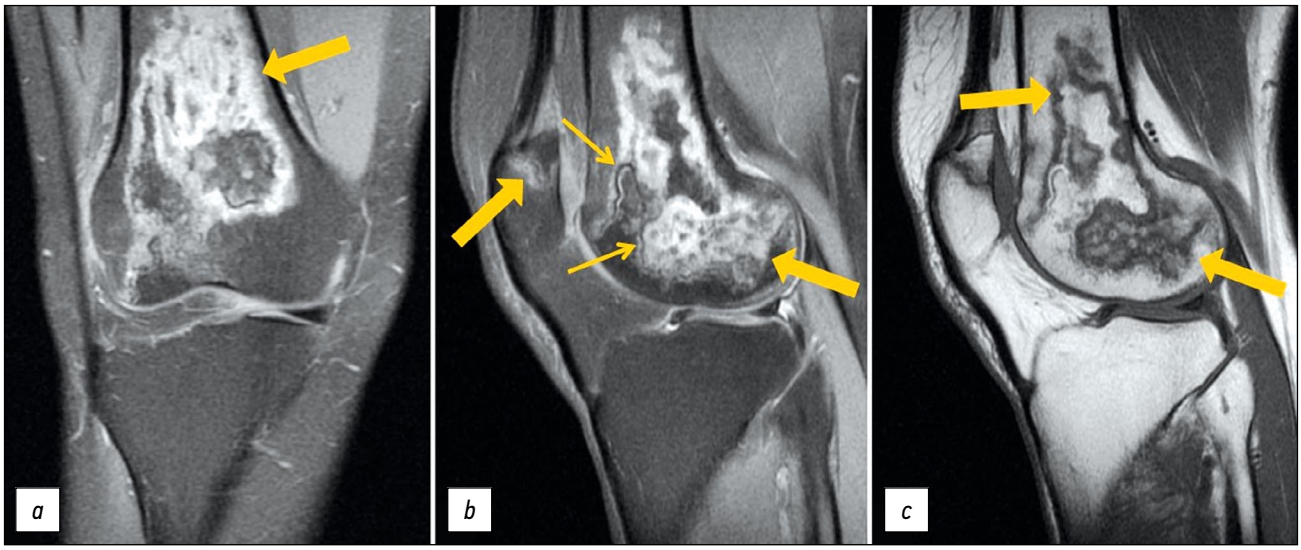

Fig. 2. Primary MRI of the right knee joint: PDWI with fat suppression in the coronal (*a*) and sagittal (*b*) plane and T1WI in the sagittal plane (*c*). Thick arrows indicate areas of bone marrow edema in the form of a heterogeneous, irregularly shaped ("geographic") MRI signal of femoral condyles and patella; thin arrows indicate the "double line" sign in the form of internal hyperintense (granulation tissue) and external hypointense (osteosclerosis) lines on PDWI.

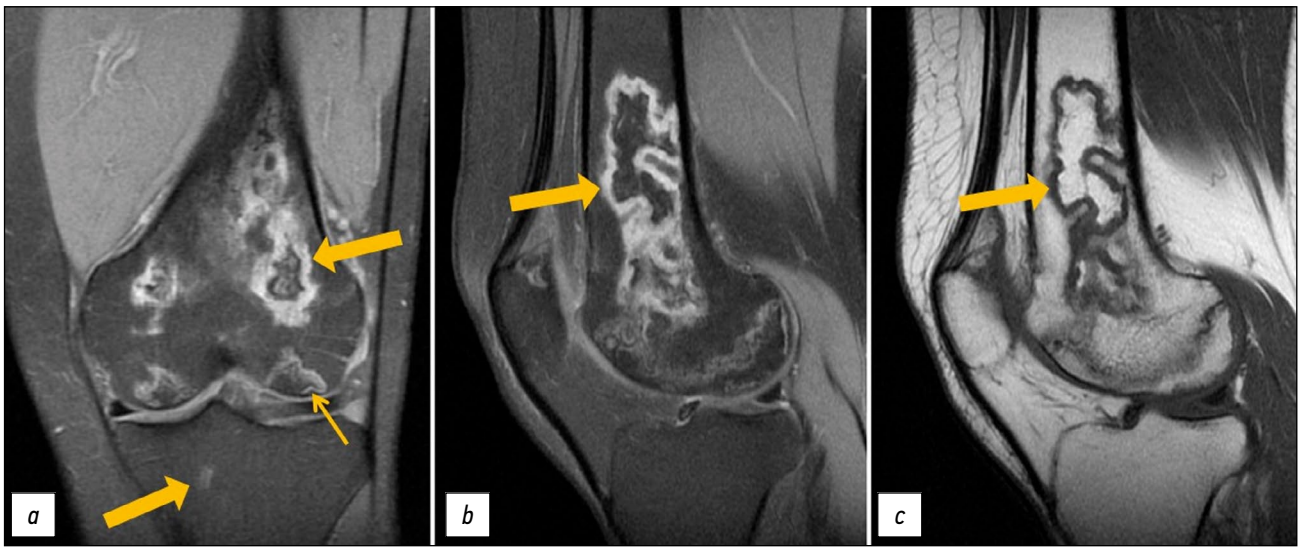

Fig. 3. Follow-up MRI of the left knee joint: PDWI with fat suppression in the coronal (*a*) and sagittal (*b*) plane and T1WI in the sagittal plane (*c*). Thick arrows indicate areas of bone marrow edema in the form of a heterogeneous, irregularly shaped ("geographic") MRI signal of femoral condyles and patella; the thin arrow indicates the "double line" sign in the form of internal hyperintense (granulation tissue) and external hypointense (osteosclerosis) lines on PDWI.

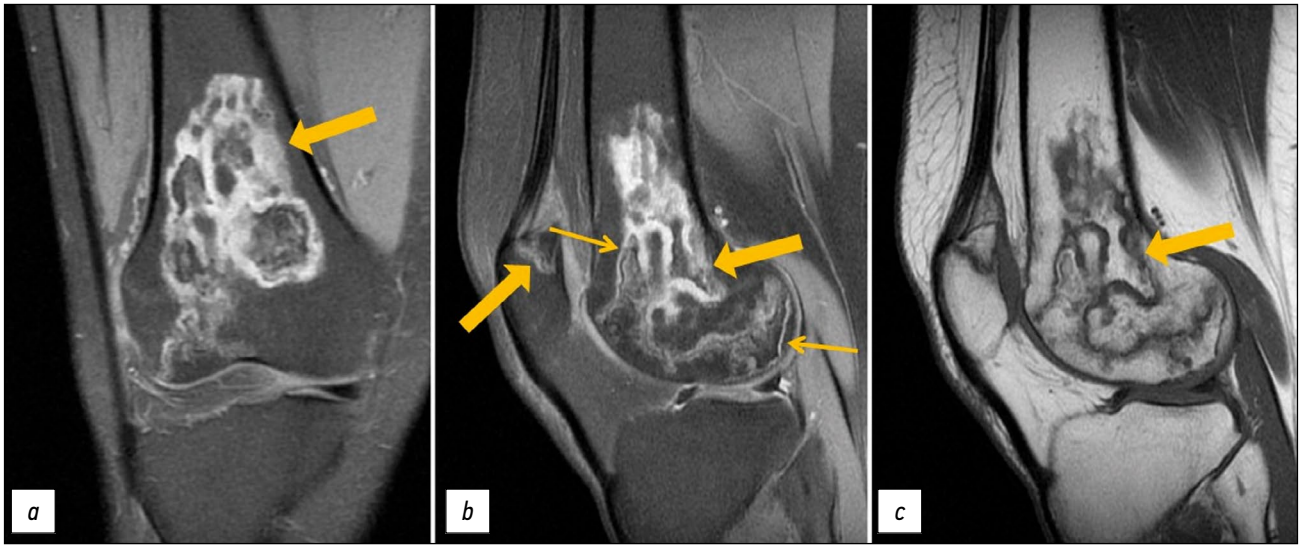

Fig. 4. Follow-up MRI of the right knee joint: PDWI with fat suppression in the coronal (*a*) and sagittal (*b*) plane and T1WI in the sagittal plane (*c*). Thick arrows indicate areas of bone marrow edema in the form of a heterogeneous, irregularly shaped ("geographic") MRI signal of femoral condyles and patella; thin arrows indicate the "double line" sign in the form of internal hyperintense (granulation tissue) and external hypointense (osteosclerosis) lines on PDWI.

developing avascular necrosis. At the same time, the pathogenesis of osteonecrosis in these patients is unclear: In addition to GCS therapy, independent causes may include vascular thrombosis, adipocyte hypertrophy, fat embolism, hypercoagulopathy, endothelial destruction, and leukocyte aggregation [7, 10]. However, we could not find clinical cases of osteonecrosis due to the above factors in the literature [7, 9].

No agreement has been made on the duration of corticosteroid therapy or the dosage that increases the risk of osteonecrosis. Nonetheless, numerous studies suggest that controlling the cumulative dose of GCS is important in developing this pathology [11]. Thus, osteonecrosis of the bone structures of the knee joint was found to develop with a cumulative dose of prednisolone ranging from 1.012 to 6.562 g, [12, 13] whereas in other clinical cases, the cumulative dose of prednisolone was in the range of 0.9–1.413 g, with an average value of 1.156 g [14]. In our case, dexamethasone was used at a dose of 20 mg/day, followed by a decrease to 12 mg/day.

Agarwala et al. [14] describe a case of avascular necrosis in a 20-year-old woman after using methylprednisolone for 15 days. The patient experienced pain in the knees on Day 25 of the disease, with lesions of both condyles and the patella according to MRI. The same authors describe a case of a 16-year-old boy who developed pain in both hip joints and the right knee joint 4 months after the novel coronavirus infection when treated with methylprednisolone and dexamethasone for 19 days. In our clinical case, dexamethasone was used for 10 days with a 2-day break. The first complaints of knee pain occurred on Day 15 of the disease (Day 9 of GCS therapy), similar to the case of the abovementioned female patient, although our patient's age differed considerably.

Another clinical case refers to avascular necrosis of the right knee joint in a 78-year-old woman with a history of bilateral gonarthrosis, more pronounced on the left, as well as concomitant cardiovascular diseases and obesity [15]. The treatment included antibacterial drugs, hydroxychloroquine, antiviral drugs (lopinavir, ritonavir), and oxygen therapy. Two weeks after discharge, the patient reported that the pain in the right knee joint had worsened. During this period, the patient also received GCS therapy for 9 days for bronchospasm. Seven days later, the patient developed local edema of the right knee joint. MRI revealed osteonecrosis of the right femoral medial condyle. GCS therapy cannot be considered the sole cause of avascular necrosis in this case; the presence of concomitant diseases is also a risk factor for developing osteonecrosis. However, the brevity between coronavirus infection and developing avascular necrosis suggests an effect of GCS therapy. In our clinical case, the patient had no other risk factors for developing avascular necrosis other than taking GCS; however, as in the example above, arthralgia developed rather quickly during GCS therapy.

Conversely, the study by Sulewski et al. [16] indicates insufficient evidence of the direct effect of GCSs on the development of osteonecrosis. This study analyzed 10 patients with confirmed coronavirus infection and signs of avascular necrosis. The mean age of the patients was 61 years. Although only four out of ten patients received GCSs, all of them developed avascular necrosis on Day 14 of the disease, on average. Li et al. [17] obtained similar data in a meta-analysis, confirming the theory of multifactorial pathogenesis of avascular necrosis in patients with the novel coronavirus infection. A deficiency of angiotensin-converting enzyme 2, which can cause bone destruction as well as vascular thromboses, as in the case of osteonecrosis

development on GCS therapy, is a possible factor in the development of avascular necrosis in such patients. Thus, no clear consensus exists regarding the etiology and mechanism of avascular necrosis development in patients with novel coronavirus infection.

In our clinical case and cases presented by foreign authors, the treatment of avascular necrosis is primarily conservative, with the main goals of relieving pain, slowing the progression of osteonecrosis, and preventing fractures and arthritis. At the same time, no generally accepted treatment scheme is available [18]. In turn, some researchers confirm that combination therapy with bisphosphonates is effective for treating osteonecrosis, including in the early stages, as our clinical case demonstrates [19, 20].

Thus, early identification of patients at high risk of developing avascular necrosis because of the novel coronavirus infection is critical in preventing arthritis and other complications.

CONCLUSION

We present a clinical case of MRI-detected bilateral avascular necrosis of the bone structures of the knee joint during treatment of COVID-19 with GCSs. GCS therapy has well-known side effects, such as impaired glucose tolerance, increased blood pressure, tachycardia, erosive and ulcerative lesions of the gastrointestinal tract, and sleep disturbances. However, avascular necrosis of the bone structures of the knee joints caused by GCS therapy is rarely brought to the attention of clinicians. Our case not only highlights the complexities of the pathogenesis of osteonecrosis but also demonstrates the wide range of complications associated with GCS therapy.

ADDITIONAL INFORMATION

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