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CASE REPORT

A rare case of knee joint mucormycosis with pathological fracture after COVID-19 infection

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Abstract

Mucormycosis is a fungal infection that generally occurs in patients with some degree of immunosuppression, such as patients with malignancies, diabetes, HIV infection, or patients who require the administration of immunosuppressive drugs.

The final diagnosis is established by collecting some tissue from the infectious process and isolating the fungus using lab cultures.

The treatment of mucormycosis is complex and consists of trying to reduce risk factors, rigorous surgical debridement, and specific antifungal treatment.

We present the case of a 54-year-old male patient with a background of SARS-COV2 infection (moderate form), that started 3 months prior to presentation to our hospital, initially treated at home.

The patient presented to the Orthopaedics Department of the University Emergency Hospital of Bucharest with pain and total functional impotence in his left knee as a result of a trauma that occurred about 2 months before the presentation to the hospital, at that moment with progressive worsening of the symptoms. Clinical and imaging examination established the diagnosis of pathological supra-intercondylar fracture of the left femur.

The purpose of this case report is to present the risk of infection with an opportunistic agent as a result of immunosuppression induced by COVID-19 or its treatment with immunosuppressive agents necessary to combat the inflammatory process. The patient presented with a moderate form of COVID-19 treated at home with non-steroidal anti-inflammatory drugs and antibiotics to prevent a bacterial superinfection.

Mucormycosis remained a challenging situation for the physician, regardless of his medical specialty, both in terms of diagnosis and treatment. In this case, COVID-19 is one of the risk factors that contributed to the appearance of mucormycosis.

Keywords: mucormycosis, Covid-19 infection, pathological fracture

Introduction

Mucormycosis is a fungal infection that generally occurs in patients with some degree of immunosuppression, such as patients with malignancies, diabetes, HIV infection or patients who require the administration of immunosuppressive drugs [1]. The incidence of this disease is difficult to establish, but the increased number of cases of diabetes worldwide and of malignancies, together with the use of new immunosuppressive therapies, predispose to an increase in the number of cases [2]. Regarding its terminology, this disease was initially called mucormycosis and then the term zygomycosis was adopted. Currently, because of molecular biology studies, the term mucormycosis has been universally accepted [3]. Mucormycosis refers to a group of fungi and from these the most involved are *Rhizopus*, *Mucor* and *Rhizomucor* [4].

In the following, the reference will be made to the *Mucor* species because it represents the most frequently involved fungus in the appearance of the disease. Spores can be identified in nature, but also in microbiology laboratories and can be involved in the contamination of samples causing false positive results. The most common site of infection is rhino-orbito-cerebral or pulmonary by inhaling spores directly from the environment and transporting them by the cilia. Another way of infection is direct inoculation in a blood vessel and their transportation through the circulatory system. The presence of areas of infarction and tissue necrosis are a sign of advanced local invasion [5].

The main risk factors involved in the appearance of mucormycosis are malignant hematological diseases and infections associated with bone marrow transplantation [4], diabetes, especially diabetic ketoacidosis [6], in-hospital infections, infections associated with disasters. There are reported

cases of mucormycosis associated with COVID-19, but no association between them can be demonstrated yet [7,8]. The question that arises when we refer to COVID-19 is whether mucormycosis is a consequence of the disease or of the treatment with steroids and tocilizumab [9].

The main sites of infection are rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, central nervous system and rarely hematogenous dissemination in other tissues like bone and cartilage.

The final diagnosis is established by collecting some tissue from the infectious process and isolating the fungus using lab cultures. Germ isolation is sometimes difficult and often associates negative cultures. The diagnosis should be suspected after clinical examination and especially in patients with severe neutropenia. Recent studies highlighted the importance of PCR tests on histopathological specimens [10]. Other newer methods used in the diagnosis of mucormycosis, cited in specialized literature, are matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) [11].

The treatment of mucormycosis is complex and consists of trying to reduce risk factors, rigorous surgical debridement, and specific antifungal treatment [12].

COVID-19 is the world's leading health problem at present, being declared pandemic shortly after the description of the first cases in Wuhan, Hubei Province, China. The main signs and symptoms of COVID-19 are fever, myalgia, cough, headache, sore throat, rhinorrhea, nausea, vomiting, diarrhea and sensory abnormalities of taste and smell [13]. In addition, many complications have been described in literature. The most common complications are pneumonia with respiratory failure, pulmonary thromboembolism, cardiovascular complications, neurological complications, and inflammatory complications. Secondary infectious

complications are not routinely present in patients with COVID-19, and data currently provided by the scientific community are limited, without being able to demonstrate a direct association between the two conditions.

Several opportunistic secondary infections can be attributed to both treatment with biological agents, glucocorticoids or poor immune status of patients admitted to intensive care units and clinical-biological changes induced by COVID-19 infection [14].

Materials and Methods

We present the case of a 54-year-old male patient with a background of SARS-COV2 infection (moderate form), that started 3 months prior to presentation to our hospital, initially treated at home. The patient was admitted to the Orthopedics Department of the University Emergency Hospital of Bucharest with pain and total functional impotence in the left knee.

Case Report

The patient presented to the Orthopedics Department of the University Emergency Hospital of Bucharest with pain and total functional impotence in his left knee as a result of a trauma that occurred about 2 months before the presentation to the hospital, at that moment with progressive worsening of the symptoms. Clinical and imaging examination established the diagnosis of pathological supra-intercondylar fracture of the left femur.

The patient was admitted to the Orthopedics Department for diagnosis and specialized treatment. From the personal pathological antecedents, it should be mentioned that the patient was known with bilateral polycystic kidney and renal failure without the need for hemodialysis. Also important was the fact that he has had arterio-venous fistula necessary for hemodialysis since

2018. From recent personal history it appeared that in early November 2020 the patient developed specific symptoms for COVID-19 and the PCR test result for SARS-COV2 infection was positive.

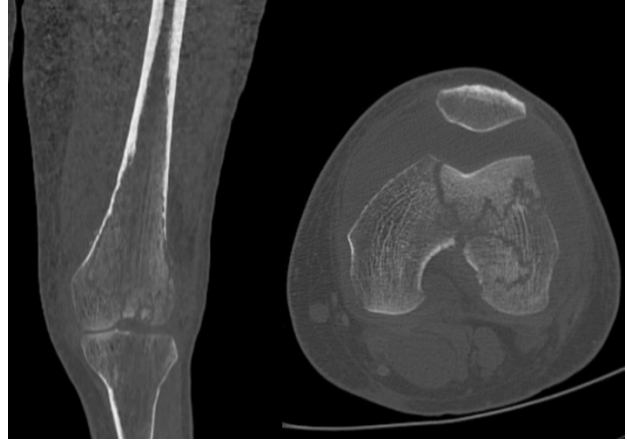


Fig. 1 CT images



Fig. 2 Macroscopic image of the swollen knee

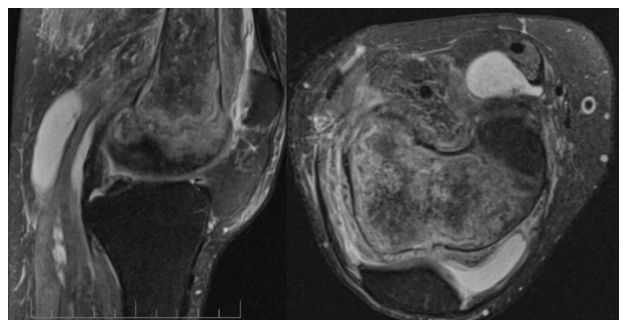


Fig. 3 MRI images of the knee

The patient's clinical condition was initially good, and it was decided to follow the treatment with azithromycin 500 mg per day and paracetamol 500 mg every 12 hours at

home with periodic reassessment by the family doctor. The patient's condition worsened with the appearance of mucopurulent expectoration and the patient was treated with levofloxacin cp 500 mg per day. After 10 days from the onset of symptoms, the patient's state of health worsened and presented oligo-anuria. He went to the emergency room, in another hospital for a specialized consultation. At the time of presentation, the patient had a creatinine value of 18 mg/ dl and was diagnosed with acute renal failure and metabolic acidosis with the need for hemodialysis. Following dialysis sessions, the patient's condition was favorable. During the hospitalization in the nephrology department, the patient suffered a trauma by accidental precipitation from the same level, without signs of fracture at the time of hospitalization. Subsequently, the algo-functional syndrome worsened, leading to total functional impotence. At the moment of hospitalization within the Orthopedics Department of the University Emergency Hospital of Bucharest, a joint puncture was performed with cultures for bacteria and fungi, both results being negative. Biologically, the value of hemoglobin was 8.2 g/ dl (normal value: 12.5-16.3 g/ dL), white blood cells (WBC) 10.3×10^3 u/ L (normal value: $3.6-10.2 \times 10^3$ u/ L), platelets (PLT) 462×10^3 u/ L (normal value: $152-348 \times 10^3$ u/ L), creatinine 4.15 mg/ dl (normal value: 0.7-1.3 mg/ dL), serum urea 76 mg/ dl (normal value: 19.26-49.22 mg/ dl), alkaline phosphatase 53 U/ L (normal value: 40-136 U/ L), C reactive protein (CRP) 13.6 mg/ L (normal value: 1-5 mg/ L). Due to the negative result after joint puncture, the patient was proposed for an incisional biopsy with the sending of specimens for histopathological examination and immunohistochemistry. The histopathological result revealed quasi-total ischemic bone necrosis with fungal colonization and highlighting of fungal filaments in the necrosis areas.

Preoperatively, the patient received treatment with intravenous fluconazole. The best choice of treatment in this case was resection of the distal portion of the femur, rigorous excisional debridement of necrotic tissues, abundant lavage, and local instillations with fluconazole.

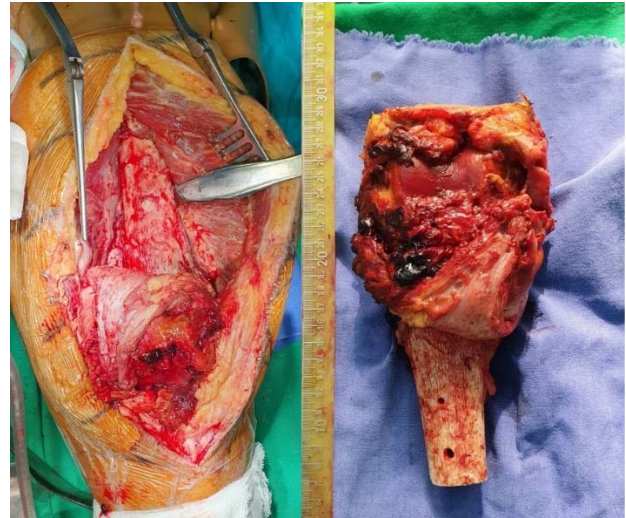


Fig. 4 Intraoperative images



Fig. 5 Postoperative X-ray

For an optimal functional result, Campanacci type arthrodesis with acrylic cement sleeve was performed on the resected segment.

The postoperative evolution of the patient was favorable, with the resumption of support on the operated pelvic limb. The patient had to return periodically for reassessment and continued treatment with fluconazole at home. It should be mentioned that during the hospitalization, the patient was evaluated for the detection of possible primary foci of mucormycosis with thoraco-abdominal-pelvic CT and brain MRI.

Discussion

The purpose of this case report was to present the risk of infection with an opportunistic agent, as a result of immunosuppression, induced by COVID-19 infection or treatment with immunosuppressive agents necessary to combat the inflammatory process. Our patient presented with a moderate form of COVID-19 infection treated at home with non-steroidal anti-inflammatory drugs and antibiotics to prevent a bacterial superinfection. We recalled that azithromycin, which was administered to the patient for 5 days, belongs to the antibiotic class of macrolides. Azithromycin is excreted predominantly in the bile and then in the feces, and very small amounts are detected in the urine [15,16]. Levofloxacin, which in our case was administered to the patient for 7 days, is eliminated by the kidneys in proportion of 87% as unchanged drug and less than 5% as metabolites. Levofloxacin treatment can be identified as a trigger for acute renal failure, especially if the dose has not been adjusted in dynamics compared to creatinine levels [17]. The immunosuppressive status of the patient could also be attributed to the chronic kidney disease, for which the patient was going to the nephrology

department [18]. Following the patient's history, it could be stated that the immune status was precarious due to chronic kidney disease and possibly, levofloxacin treatment that led to acute renal failure, and the need for hemodialysis created the necessary premises for a fungal infection such as mucormycosis. On the other hand, in the absence of a continuity solution at the knee joint, an anatomical quite rare site without the presence of another outbreak of mucormycosis in one of the favorite sites, which also brings into question the connection with COVID-19 infection. To the multitude of clinical-biological changes induced by the SARS-COV2 virus, the risk of fungal infections, in the absence of immunosuppressive treatment, can also be added. At present, cases of mucormycosis associated with COVID-19 infection are reported in literature without being able to demonstrate a direct association between them [8,9]. This case report aimed to draw new research directions on the relationship between mucormycetes infections and SARS-COV2 virus infection.

Conclusions

Mucormycosis remains a challenging situation for the physician, regardless of his medical specialty, both in terms of diagnosis and treatment. In the case of the presented patient, COVID-19 infection was one of the factors that contributed to the appearance of mucormycosis along with the associated pathologies. The treatment of joint mucormycosis is challenging for the orthopedic surgeon, requiring radical surgical treatment, especially in cases with pathological bone fractures and equally preoperative, intraoperative, and postoperative antifungal drug treatment. After resection of the proximal portion of the femur, reconstruction with acrylic cement rod and sleeve, according to the Campanacci

technique, and remediation of the outbreak together with local instillations with fluconazole, the patient had good local and general evolution, without signs of local recurrence at 30 days.

In order to identify a statistically significant association between COVID-19 infection and mucormycosis, a larger group of patients is required.

Conflict of Interest statement

The authors state no conflict of interest.

Informed Consent and Human and Animal Rights statement

An informed consent has been obtained from all individuals included in this study.

Authorization for the use of human subjects

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the review board of the University Emergency Hospital Bucharest, Romania.

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None.

Disclosures

None.

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