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# Mucormycosis osteomyelitis after anterior cruciate ligament reconstruction

TREATMENT AND OUTCOMES OF 21 REPORTED CASES

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## Aims

Our purpose was to describe an unusual series of 21 patients with fungal osteomyelitis after an anterior cruciate ligament reconstruction (ACL-R).

## Methods

We present a case-series of consecutive patients treated at our institution due to a severe fungal osteomyelitis after an arthroscopic ACL-R from November 2005 to March 2015. Patients were referred to our institution from different areas of our country. We evaluated the amount of bone resection required, type of final reconstructive procedure performed, and Musculoskeletal Tumor Society (MSTS) functional score.

## Results

A total of 21 consecutive patients were included in the study; 19 were male with median age of 28 years (IQR 25 to 32). All ACL-R were performed with hamstrings autografts with different fixation techniques. An oncological-type debridement was needed to control persistent infection symptoms. There were no recurrences of fungal infection after median of four surgical debridements (IQR 3 to 6). Five patients underwent an extensive curettage due to the presence of large cavitary lesions and were reconstructed with hemicylindrical intercalary allografts (HIAs), preserving the epiphysis. An open surgical debridement was performed resecting the affected epiphysis in 15 patients, with a median bone loss of 11 cm (IQR 11.5 to 15.6). From these 15 cases, eight patients were reconstructed with allograft prosthesis composites (APC); six with tumour-type prosthesis (TTP) and one required a femoral TTP in combination with a tibial APC. One underwent an above-the-knee amputation. The median MSTS functional score was 20 points at a median of seven years (IQR 5 to 9) of follow-up.

## Conclusion

This study suggests that mucormycosis infection after an ACL-R is a serious complication. Diagnosis is usually delayed until major bone destructive lesions are present. This may originate additional massive reconstructive surgeries with severe functional limitations for the patients.

**Level of evidence: IV**

## Introduction

Infection after an arthroscopic anterior cruciate ligament reconstruction (ACL-R) is rare, and usually induced by pyogenic bacteria.[1-3] Arthroscopic washout and antibiotic therapy are the standard treatments with effective results, and generally without serious structural or functional consequences.[4-6]

Fungal osteomyelitis is extremely rare, potentially aggressive, and with devastating complications, sometimes leading to severe joint and bone compromises that may risk the patient's limb or even life.[78] Mycotic infections have a very low incidence, and usually involve immunocompromised patients.[9] However, during the last 18 years, some case reports of fungal infections after ACL

**Table I.** Demographics and clinical data.

| Pt | Sex | Age at ACL-R, yrs | ACL graft | Previous surgeries, n | Affected bone | Bone loss, cm | Fungal culture | Time between ACL-R and diagnosis, days | Reconstructive surgery | Follow-up, yrs | MSTS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 25 | H | 16 | Femur | 15.5 | NEG | 95 | APC | 10 | 22 |
| 2 | M | 26 | H | 7 | Tibia | 19 | R | 33 | TTP (femur)+ APC (tibia) | 8 | 11 |
| 3 | M | 25 | H | 8 | Tibia | N/A* | R | 55 | HIA | 4 | 24 |
| 4 | M | 29 | H | 3 | Femur | 9.5 | R | 28 | APC | 9 | 19 |
| 5 | M | 32 | H | 2 | Tibia | 15 | R | 66 | APC | 5 | 19 |
| 6 | M | 32 | H | 3 | Tibia | N/A* | R | 24 | HIA | 4 | 26 |
| 7 | M | 22 | H | 6 | Tibia | 11.5 | NEG | 36 | APC | 4 | 12 |
| 8 | F | 27 | H | 6 | Femur | 10.5 | R | 98 | APC | 11 | 22 |
| 9 | F | 35 | H | 3 | Tibia | N/A* | NEG | 105 | HIA | 7 | 24 |
| 10 | M | 52 | H | 3 | Tibia | 13 | R | 75 | APC | 6 | 11 |
| 11 | M | 26 | H | 3 | Femur | 13.5 | R | 83 | TTP | 7 | 19 |
| 12 | M | 29 | H | 2 | Tibia | N/A* | R | 64 | HIA | 14 | 26 |
| 13 | M | 25 | H | 4 | Femur | 15 | R | 33 | TTP | 10 | 11 |
| 14 | M | 31 | H | 1 | Tibia | N/A* | R | 49 | HIA | 7 | 24 |
| 15 | M | 29 | H | 3 | Femur | 14.5 | R | 57 | TTP | 9 | 22 |
| 16 | M | 23 | H | 6 | Tibia | 14 | R | 93 | APC | 7 | 19 |
| 17 | M | 34 | H | 5 | Femur | 15.5 | R | 72 | APC | 4 | 14 |
| 18 | M | 22 | H | 7 | Femur | 16.5 | R | 65 | TTP | 7 | 11 |
| 19 | M | 27 | H | 6 | Femur | N/A* | R | 71 | Amputation | | |
| 20 | M | 32 | H | 5 | Tibia | 10 | R | 47 | TTP | 5 | 22 |
| 21 | M | 28 | H | 3 | Femur/tibia | 12 | R | 30 | TTP | 6 | 21 |
| Median (IQR) | | 28 (25 to 32) | | 4 (3 to 6) | | 14 (11.5 to 15.6) | | 36 (64 to 75) | | 7 (5 to 9) | 20 (13 to 23) |

*We did not resect the epiphysis.

ACL-R, anterior cruciate ligament reconstruction; APC, allograft prosthesis composite; H, hamstrings; HIA, hemicylindrical intercalary allograft; MSTS, Musculoskeletal Tumor Society score; NEG, negative; R, Rhyzopus; TTP, tumour type prosthesis.

arthroscopic surgery in immunocompetent patients have been published.[10-14] This type of infection is frequently misdiagnosed due to its rarity, and mild insidious initial presentation, delaying clinical suspicion by the surgeon. Compared to pyogenic, fungal infections usually progress through a more indolent course, leading to massive bone destruction.[15,16]

Our hypothesis was that fungal osteomyelitis after an ACL-R is a serious complication, which originates a severe bone loss requiring major reconstructive procedures that may affect functional outcomes. Our purpose was to describe an unusual series of 21 patients with fungal osteomyelitis after an ACL-R.

## Methods

We present a case-series of consecutive patients treated at our institution due to a severe fungal osteomyelitis after an arthroscopic ACL-R from 2005 to 2015. Patients were referred to our institution from different areas of our country with a persistent septic arthritis following an arthroscopic ACL-R.[17]

The inclusion criteria were patients referred to our department after an ACL-R with hamstring autograft with a fungal osteomyelitis. All the patients were immunocompetent. In total, 21 consecutive patients were included in the study; 19 patients were male with a median age of 28 years (IQR 25 to 32) at the time of the reconstructive surgery. None of these patients presented lymphopenia, renal failure, diabetes, immunosuppressive therapies such as corticosteroids or monoclonal antibodies, or chronic diseases.

Patients were admitted to our hospital and a detailed medical history and blood tests analysis were performed. Plain radiographs, MRI, and CT were performed.

According to medical records from the referring institutions, the types of graft and the surgical fixation techniques used to reconstruct the ACL were determined. We analyzed the period of time from the primary ACL-R until the final diagnosis and number of procedures performed during that interval, in addition to the amount of bone resection required, method used to reach the final diagnosis, type of final reconstructive procedure performed, and final mucormycosis infection control.

Once admitted, the surgical treatment began with an extensive debridement in order to control the limb threatening persistent infection. An open knee arthrotomy by a medial parapatellar approach, sinovectomy, removal of fixation devices and graft, curettage, or bone resections according to the amount of bone necrosis were performed. When possible, the articular joint was
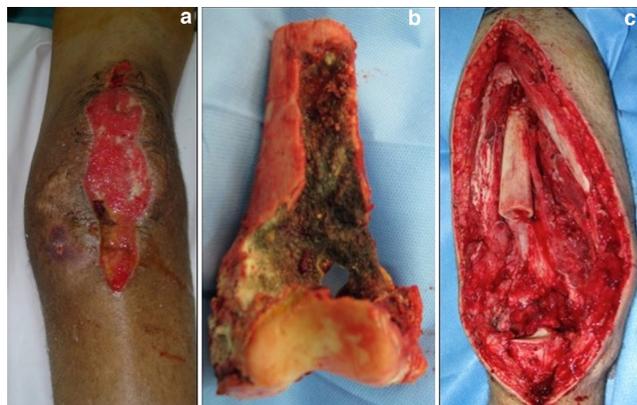
**Fig. 1**

Clinical images of a 26-year-old male patient. a) Surgical wound after multiple open debridements. b) Radical bone resection showing an extensive area of cortical bone compromised by necrotic tissues. c) Intraoperative image after resecting the distal femur and proximal tibia, due to massive fungal contamination.
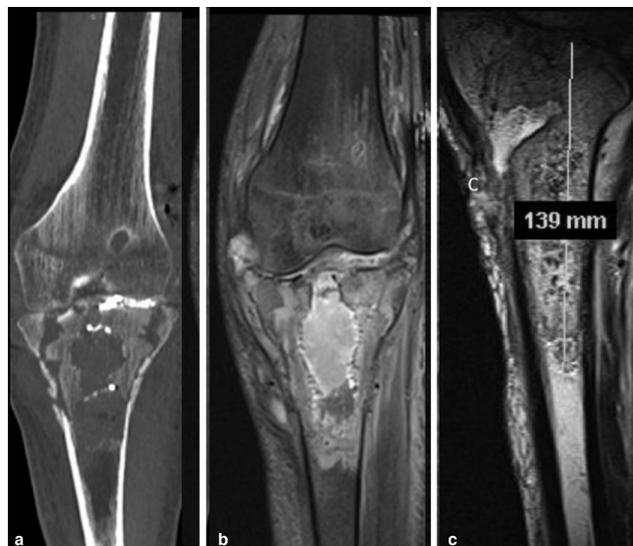


**Fig. 2**

MRI and CT scan images of a 52-year-old male patient show bone and soft tissue compromises at 75-day follow-up. a) A CT scan shows intracavitary and medial cortex lesion of the proximal tibia. b) MRI coronal views show a central cavitary lesion of the proximal tibia surrounded of bone oedema and soft tissue compromise. c) MRI sagittal view, showing the tibial tunnel of the primary anterior cruciate ligament surgery, and a massive bone lesion of 139 mm.

preserved. In those cases, with severe compromises, the entire distal femur or proximal tibia epiphysis were removed. Frozen section samples were referred for histopathology analysis, and aerobic, anaerobic, mycobacterial, and fungal cultures were done from joint fluid, synovial lining, ACL graft, and bone. A contained cement spacer was placed in patients treated with curettages to avoid an articular joint collapse. A segmental uncontained cement spacer was placed in patients treated with a massive bone resection of the compromised epiphysis to stabilize the joint. The cement spacer was mixed with local Amphotericin B (200 mg Amphotericin per 40 gm of bone cement). Antifungal intravenous treatment was started after surgery with Liposomal Amphotericin (5 mg per kg per day). The whole treatment lasted for about three months. Patients were followed with plain radiographs, serial ESR, and CRP laboratory tests.

The extent of bone resection to control bone infection was measured with plain radiographs. At least two months free of antifungal therapy was required to plan the reconstructive salvage surgery. The amount of bone losses determined the type of reconstructive procedure needed. They were classified as hemicylindrical intercalary allografts (HIAs) with the addition of morcellized bone to fill the cavity, allograft prosthesis composites (APCs), and tumour type prosthesis (TTP). Infection was considered to be eradicated once clinical and laboratory parameters were within normal values. The functional evaluation was performed with the revised Musculoskeletal Tumor Society (MSTS) rating system (Table I).[18]

The Clinical Research and Bioethics Committee of the aforementioned hospital approved the study, in accordance with the Declaration of Helsinki of 1975 as revised in 2008.[19]

**Statistical analysis.** Categorical variables are presented as absolute numbers with percentages. Numerical data are presented as medians and interquartile ranges (IQRs). The statistical analysis was conducted using STATA v.14.2 (StataCorp, College Station, Texas, USA)

## Results

The clinical presentation showed a persistent serious drainage from previous wounds in 16 patients (eight from proximal tibia and eight from distal femur) (Figure 1a to b). Five patients claimed pain with limited range of motion. MRI showed that initial bone infectious compromises were at the tibial or femoral tunnels (Figure 2).

Infection symptoms began at a median time of 23 days after the ACL-R. The median time between the ACL primary surgery and final diagnosis was 36 days (IQR 64 to 75).

Original ACL-Rs were performed with hamstrings autografts in all patients with different fixation systems: transfixiant metal pins in ten patients, bioabsorbable transfixiant in eight patients, and femoral endobutton in three patients. In 12 patients, implants were from the USA and in nine patients the implants were from Argentina.

A median of four arthroscopic or open surgical debridements (IQR 3 to 6) were done before a fungal osteomyelitis was diagnosed. In total, 18 patients underwent an open debridement at the original institution. In only two cases patients were referred with persistent mucormycosis infection already diagnosed. Fungal cultures were available after an average of 21 days and were positive for *Rhizopus microsporus* in 16 patients, while histopathology samples revealed non-septate hyphae, typical of the order of *Mucorales* in all cases (Figure 3). In addition, five patients
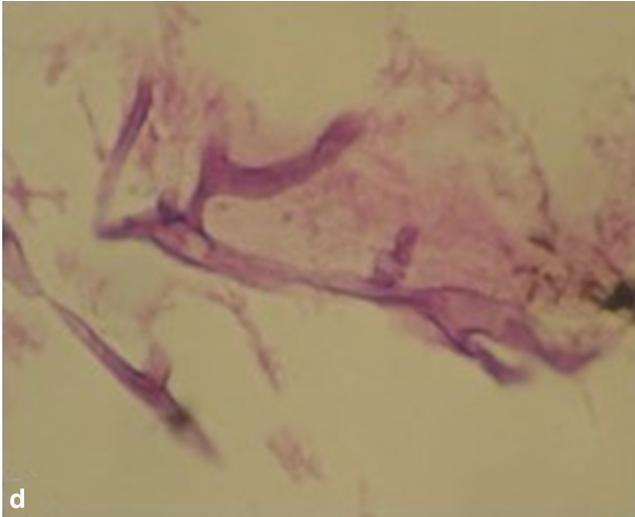
**Fig. 3**

*Mucoraceous hyphaes* are seen in this bone biopsy specimen (hematoxylin and eosin; original magnification × 400).
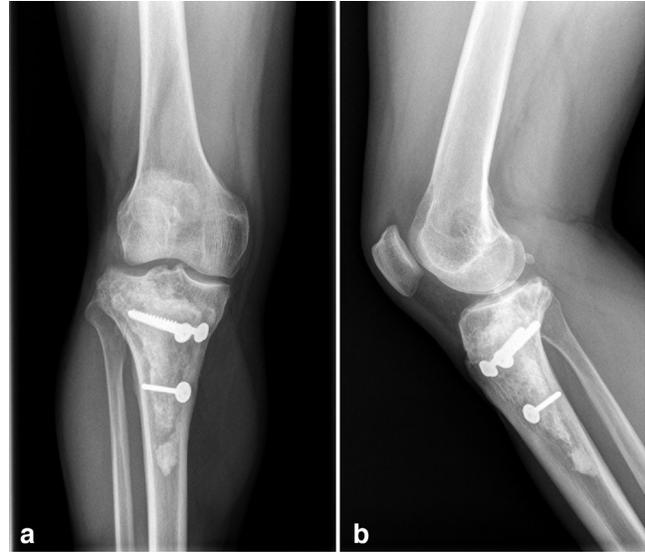


**Fig. 4**

Reconstructive surgery with hemicylindrical intercalary allograft (HIA) in a 29-year-old male patient. a) Anteroposterior and b) lateral view radiographs of a cavitary lesion of the proximal tibia filled with fragmented allograft chips and a HIA fixed with screws after 14 years follow-up.
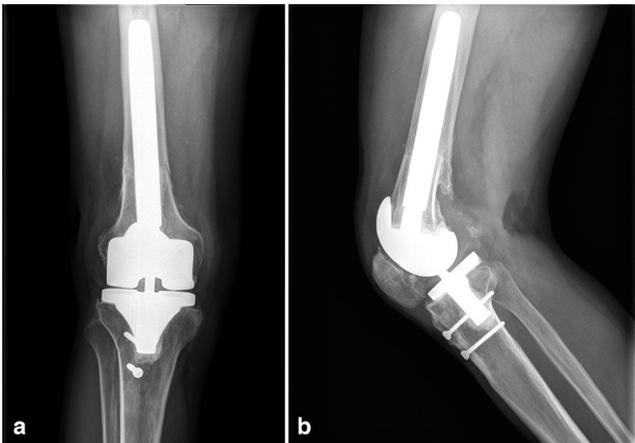


**Fig. 5**

Reconstructive surgery with allograft prostheses composite (APC) in a 25-year-old male patient. Anteroposterior and lateral radiographs show a femoral APC reconstruction at ten years follow-up.



**Fig. 6**

Reconstructive surgery with a tumor-type prostheses (TTP) in a 28-year-old male patient. An anteroposterior radiograph showing a TTP at six years follow-up.

presented a concomitant bacterial infection requiring specific intravenous antibiotic therapy. Bacterial cultures showed the presence of *Staphylococcus saprophyticus*, *Staphylococcus aureus*, and *Enterococcus*. An open surgical debridement was performed resecting the affected epiphysis in 15 patients, with a median bone loss of 14 cm (IQR 11.5 to 15.6) (Figure 1c). The remaining patients underwent an extensive curettage due to the presence of large cavitary lesions, preserving the epiphysis.

The surgical strategy to perform the reconstructive procedure was related with the joint compromise and bone preserved after repeated debridements. In five cases that showed a tibial cavitary lesion with both articular surfaces preserved, a bone reconstruction was performed combining fragmented bone allograft to fill the metaphyseal cavity, and a HIA to reconstruct the cortex (Figure 4). In eight cases (four tibiae and four femora, in which only one articular side of the joint was preserved) the reconstruction procedure consisted of an allograft prosthesis composite (APC) (Figure 5). A TTP was performed in seven patients (Figure 6). In one case, as a result of a bifocal bone loss (proximal tibial and distal femur), we performed a femoral TTP and, simultaneously, a tibial APC in order to recover bone stock. One patient underwent an above-the-knee amputation that was referred to our hospital in a bacterial

septic shock condition. No evidence of a recurrence of fungal osteomyelitis was seen in any patient after the oncological-type debridement performed in our institution at median of seven years (IQR 5 to 9) of follow-up. However, in three cases a second debridement was required due to an elevated ESR and CRP. One of these patients, with a tibial spacer, developed a distal femoral bacterial osteomyelitis resulting in a massive resection (Table I, patient 2). The remaining two patients underwent a routine debridement with a spacer exchange. Thereafter, the infection was eradicated and a reconstructive surgery was performed. A total of 20 patients underwent a massive reconstructive surgery achieving a functional limb according to the complexity of these type of procedures. The median MSTS score was 20 (IQR 13 to 23) out of a maximum of 30 points at median of seven years of follow-up (IQR 5 to 9).

## Discussion
Our results support that infection with mucormycosis after an ACL-R causes extremely damaging effects in those patients. A diagnosis is frequently difficult and delayed, originating extensive bone resections that may require demanding orthopaedic reconstructive procedures.[20] Treatment of mucormycosis needs to be aggressive, usually consisting of a combination of surgical debridement and antifungal agents and, in some cases, even amputation.[8]

All patients of the series were reconstructed with hamstring autografts. The literature reported a markedly higher bacterial infection rate in patients with a ACL-R with hamstrings autografts than with bone patellar tendon autografts.[21–23] We might consider that hamstrings are more prone to fungal infection than other graft types.

In this study, we found that previous infection management after ACL-R failed to control fungal infection, with delay in diagnosis and consequent dramatic bone losses. Therefore all patients showed extensive areas of massive bone necrosis that needed to be excised. However, in five cases, those procedures originated a cavitary bone loss that was filled with fragmented allograft and a structural HIA was added to restore cortical losses. In 15 patients, bone en-block epiphyseal resections were done, due to extensive bone compromises that needed an oncological type of reconstruction. One patient underwent amputation due to a severe clinical complication.

We detect that no patients of this series showed comorbidity factors, in contrast to the classical opportunistic appearance of this disease involving usually immunodeficient patients.[9]

We only found other four cases of fungal osteomyelitis due to *R. microsporus* with catastrophic bone destruction after ACL-R reported in the literature in addition to our series. In two cases the agent was a mucor of the *Rhizopus* species, and in the other two produced by the *Aspergillus* species. Only one study reported a follow-up of more than three years and had a distal femoral endoprosthesis placed in the patient's leg with a MSTS functional score of 15.[10,11,13,14]

We previously reported, in 2009, a small series of six patients with fungal osteomyelitis after an ACL-R.[12] Most ended with major reconstructive surgery. As far as we know, considering the rarity of this complication, there are no other reports of a series of patients with fungal osteomyelitis after an ACL-R. The contribution of this new study is the inclusion of 16 more patients, epidemiological data, and clinical outcome with a median of seven years of follow-up. *R. microsporus* has been shown to be a cause of serious infections after ACL-Rs in Argentina. A recent review of 40 *Rhizopus*-associated cases of osteomyelitis that developed after these surgeries from 2005 through 2017 in several regions across the country discussed different aetiologies.[24] Multiple practices that favour contamination during surgery with filamentous fungi were detected, therefore no unique cause could be identified. In addition, this was beyond the purpose of this study. Mucormycosis osteomyelitis post-ACL-R had a prevalence in Argentina of one case per million in habitants (range < 1 to 6 cases).[17,25]

ACL-Rs have been performed in Argentina for over three decades, but no cases of mucormycosis osteomyelitis were reported before 2005.[26] We were unable to identify a single origin of this fungal complication, but we might note that the initial bone compromises were always at the tibial or femoral tunnels, suggesting a potential factor of contamination through drilling cannulated devices. In a study published in 2017 we described the preventive measures based on our experience with fungal osteomyelitis.[27]

ACL-Rs in this series were done with different types of fixation, suggesting that these techniques are with mucormycosis osteomyelitis. In this study, the median time from the ACL-R to final diagnosis was 36 days (64 to 75), and the number of previous surgeries until the final diagnosis was also high, with a median of four procedures. These two parameters seem to be related with a much higher prevalence of bacterial over fungal infections, inducing erroneous original diagnosis. Despite the uncommon presentation of mucormycosis, early suspicion is mandatory in cases of persistent infection. Plain radiographs, MRIs, and CT scans should be indicated to identify necrotic bone areas. Histopathological frozen samples were positive for fungal infection in all cases.

There are several limitations for this study. This is a retrospective study including patients treated originally in other institutions. Patients arrived to our institution in different stages of the infection and after several surgeries. This was a heterogeneous group, as each patient underwent a different reconstructive method.

After a median of seven years of follow-up (5 to 9), no patient showed evidence of a recurred fungal infection. Since most patients were finally treated with reconstructive procedures usually done after oncological resections, functional outcomes were determined with the MSTS functional score system. Results obtained may be acceptable for a tumour

resection. However, patients in this series were young and physically active, complained of an unstable knee, and they ended with a reconstructive procedure with significant functional limitations. This results in extremely emotional outcomes for both the patient and surgeon, and additionally, potential medicolegal implications.

This study suggests that mucormycosis infection after an ACL-R is a serious complication. Diagnosis is usually delayed until major bone destructive lesions are present. This may result in additional massive reconstructive surgeries with severe functional limitations for the patients.

## Twitter

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