THERAPEUTIC ADVANCES in
Infectious Disease

Case Report

Aspergillus granulosus femoral osteomyelitis in a cardiac transplant patient: first reported case and literature review

Ther Adv Infect Dis

2024, Vol. 11: 1–9

DOI: 10.1177/20499361241231482

Alessandro Giacinta, Zorba Blázquez, Paloma García Clemente, Álvaro Pedraz, Pilar Escribano, Jesús Guinea, Patricia Muñoz and Maricela Valerio

***Abstract*:** *Aspergillus* osteomyelitis is a rare complication of extrapulmonary invasive aspergillosis, which usually presents as spondylodiscitis. The clinical picture is usually paucisymptomatic and of long evolution, which leads to diagnostic difficulties, especially in immunosuppressed patients presenting a delayed systemic host response. We report a case of femoral osteomyelitis caused by *Aspergillus granulosus* in a heart transplant recipient successfully treated with a combined surgical and antifungal approach. A 65-year-old heart transplant male presented with left knee pain lasting 3 months. X-ray and magnetic resonance imaging identified a lesion with aggressive characteristics at the distal third of the left femur, due to which the patient underwent excisional surgery. *Aspergillus granulosus* was cultured from the removed material and antifungal treatment with oral isavuconazole was started. Chest imaging excluded pulmonary aspergillosis, while the positron emission tomography/computed tomography (PET/CT) identified a remnant of a prosthetic vascular graft sewn to the proximal third of the right axillary artery, through which a catheter-based micro-axial left ventricular assist device was implanted previously as bridge to transplant therapy. The patient presented a rapid clinical improvement with complete functional recovery following the surgical treatment and the antifungal therapy and finally underwent surgical removal of the residual vascular graft. This is the first reported episode of long bone osteomyelitis due to *A. granulosus* that occurred in a heart transplant recipient without pulmonary infection and was successfully treated with isavuconazole. The PET/CT was useful in supporting the diagnostic process and follow-up. Cryptic fungal species can cause invasive infections, particularly in immunocompromised patients. Molecular methods are crucial in fungal identification.

Keywords: *Aspergillus granulosus*, case report, heart transplantation, invasive aspergillosis, invasive fungal infection, osteomyelitis, solid organ transplantation

Received: 24 August 2023; revised manuscript accepted: 23 January 2024.

Correspondence to:
Patricia Muñoz
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Calle Dr. Esquerdo, 46, Madrid 28009, Spain

Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

pmunoz@micro.hggm.es, maricevа@ucm.es

Alessandro Giacinta
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Division of Infectious Diseases, Department of Medicine, University of Udine, Udine, Italy

Zorba Blázquez
Department of Cardiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Paloma García Clemente
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Introduction

Aspergillus is a filamentous fungus ubiquitous in nature, which, following inhalation of spores (conidia), can cause respiratory tract infections or disseminate extra-pulmonary.

These types of infections rarely affect immunocompetent patients, while they are a common occurrence in the immunocompromised population, particularly in the case of patients undergoing onco-haematological therapies or in recipients of haematopoietic stem cell transplantation or solid organ transplantation.[1,2]

Invasive aspergillosis is an opportunistic infection that mainly affects the respiratory tract and lungs following the inhalation of conidia.

Among the extrapulmonary manifestations of invasive aspergillosis, osteomyelitis is a rare complication, and more than half of the cases present as spondylodiscitis.[3,4]

Álvaro Pedraz
Department of Cardiac Surgery, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Pilar Escribano
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

School of Health Sciences, HM Hospitals, Universidad Camilo José Cela, Madrid, Spain

Jesús Guinea
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

School of Health Sciences, HM Hospitals, Universidad Camilo José Cela, Madrid, Spain

Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

Maricela Valerio
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

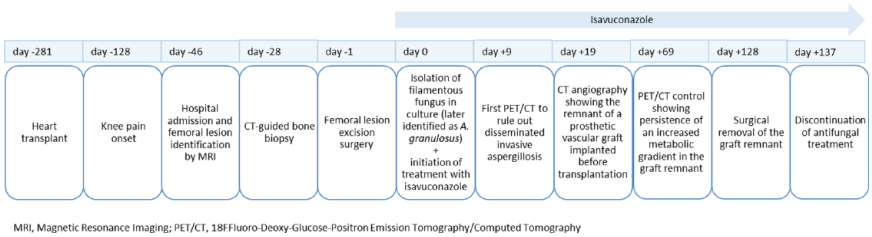

Figure 1. Clinical evolution. Timeline of the evolution of the case depicting the main events concerning the episode described, including onset of symptoms, hospital admission, diagnosis and management.

Aspergillus osteomyelitis is a rare infection that can affect both immunocompetent and immunocompromised individuals. The number of cases is rising due to the increase in the number of patients at risk. It most commonly affects the vertebrae, less frequently the cranial bones and ribs and rarely involves the long bones. The clinical picture is usually paucisymptomatic and of long evolution, which leads to diagnostic difficulties, especially in immunosuppressed patients presenting a delayed systemic host response.[5]

Furthermore, there is a lack of recent guidelines on the best therapeutic approach for *Aspergillus* osteomyelitis.

While *Aspergillus fumigatus* is the most common fungal pathogen, *Aspergillus granulosus* can also cause invasive aspergillosis.[6,7] *Aspergillus granulosus* is a cryptic species belonging to the *Usti* section and whose main microbiological characteristics include poor conidiation and the preponderance of colourless large aggregates of globose to elongate Hülle cells distributed randomly.[7,8]

No cases of osteomyelitis due to this pathogen have been reported to date. We report a case of femoral osteomyelitis caused by *A. granulosus* in a heart transplant recipient successfully treated with a combined surgical and antifungal approach.

Case presentation

A 65-year-old male who underwent a heart transplant in June 2022 for hypertrophic cardiomyopathy presented in February 2023 (on day −46 of diagnosis) at a tertiary hospital in Madrid (Spain) with pain in the left knee of 3 months of evolution. Timeline of the clinical evolution of the case is summarized in Figure 1.

Among the post-transplant medical history, he developed right-predominant primary graft failure, renal failure, right jugular thrombosis and SARS-CoV-2 pneumonia. He also developed post-cardiotomy pericarditis with severe pericardial effusion with tamponade requiring a pleuropericardial window. *Cutibacterium acnes* was isolated from the pericardial fluid culture. In pre-transplant screening, the patient tested positive for the interferon-gamma release assays QuantiFERON®-TB Gold (Qiagen, Venlo, Limburg), so he received prophylactic treatment with isoniazid for 9 months.

Finally, approximately 2 weeks before the onset of knee pain, the patient underwent left inguinal hernioplasty with mesh placement.

Physical examination at hospital admission on day −46 revealed a significant swelling of the left knee, painful, in the absence of erythema and other inflammatory signs. Knee ultrasound confirmed major joint effusion, which determined functional limitation to leg flexion and consequent knee flexion attitude without an impairment of the distal nerve bundles.

Blood tests showed a slight increase in C-reactive protein (CRP 48.3 mg/L) and erythrocyte sedimentation rate (ESR 62 mm/h) without other alterations and a normal leukocyte count.

The patient was receiving standard immunosuppression with tacrolimus, mycophenolate mofetil and prednisone and the immunosuppression levels were within the range of efficacy and tolerability.

X-ray and magnetic resonance imaging (MRI) identified a lesion with aggressive characteristics at the distal third of the left femur associated with intense bone oedema over the entire diaphysis

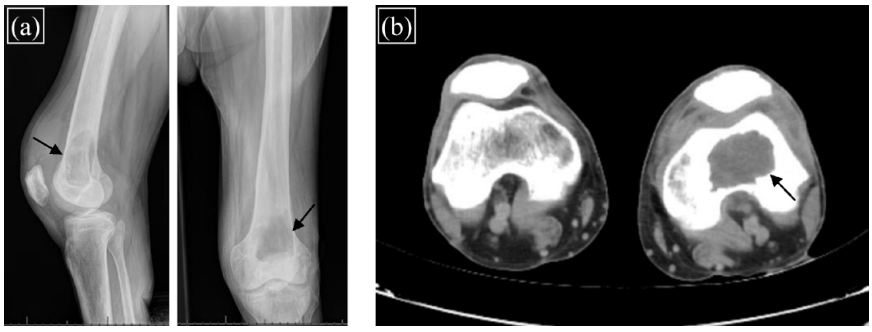

Figure 2. (a) Anterolateral X-ray of the left femur and the knee showing an osteolytic lesion of the distal metaphysis of the femur. (b) CT scan of both femurs and knees showing an osteolytic lesion of the distal metaphysis of the left femur. Arrows indicate the site of the lesion.
CT, computed tomography.

and metaphysis and part of the femoral epiphysis and adjacent adipose tissue with periosteal thickening [Figure 2(a)].

On day −28, a computed tomography (CT)-guided biopsy of the lesion was performed, but the histological examination did not show any abnormal features [Figure 2(b)].

At the same time, the patient underwent a transesophageal echocardiogram, with no infectious endocarditis signs nor other pathological findings and a chest CT scan, with bilateral pulmonary calcified granulomas, already known, excluding the suspicion of malignancy.

On the microbiological profile, the patient presented a serum 1,3-β-D-glucan of 180.2 pg/mL (determined with Wako β-glucan test, cut-off value of 11.0 pg/mL) and a negative serum galactomannan index (GMI), equal to 0.21 ng/mL.

Finally, at the beginning of April 2023 (on day −1), the patient underwent surgery to remove the bone lesion, described as purulent in appearance, with subsequent filling with polymethylmethacrylate.

A filamentous fungus was cultured from the removed material (Figure 3). The microscope preparations revealed Hülle cells and mycelia structure, but no conidial heads of *Aspergillus* were identified. The isolate was subcultured on potato dextrose agar at 30°C. After 5 days, the colonies appeared velvety, with a colour ranging from cinnamon to brown at the centre and white at the periphery. *Aspergillus* fruiting heads were scarce and located on long, smooth conidiophores. In the preparation, globose or coiled Hülle cells predominated. Based on these features, the isolate was tentatively identified as *Aspergillus* section *Usti*.

The definitive identification of the species as *A. granulosus* was reached by molecular methods. Genomic DNA was extracted from conidia suspensions with a DNeasy tissue kit (Qiagen GmbH, Hilden, Germany) and initially treated with lyticase (Sigma-Aldrich Corporation, St. Louis, MO, USA) for 2 h at 37°C. Polymerase chain reaction (PCR) amplifications were carried out using the two pairs of primers *tub1* and *tub2*, specifically by the amplification and sequencing of the β-*tubulin* gene, and Basic Local Alignment Search Tool (BLAST) searches of the sequences were performed using the National Center for Biotechnology Information BLAST database to accomplish an accurate species identification; specific details concerning PCR conditions can be found elsewhere.[9]

Therefore, in the immediate post-operative period, it was decided to start antifungal treatment with oral isavuconazole (day 0).

The European Committee On Antimicrobial susceptibility testing (EUCAST) antifungal microdilution method for moulds (EUCAST E.Def 9.4; clinical breakpoints V10) was performed on the *A. granulosus* isolated, resulting in a minimum inhibitory concentration (MIC) values of 0.5 mg/L for amphotericin B, 1 mg/L for posaconazole and isavuconazole and 2 mg/L for itraconazole and voriconazole. No breakpoints are

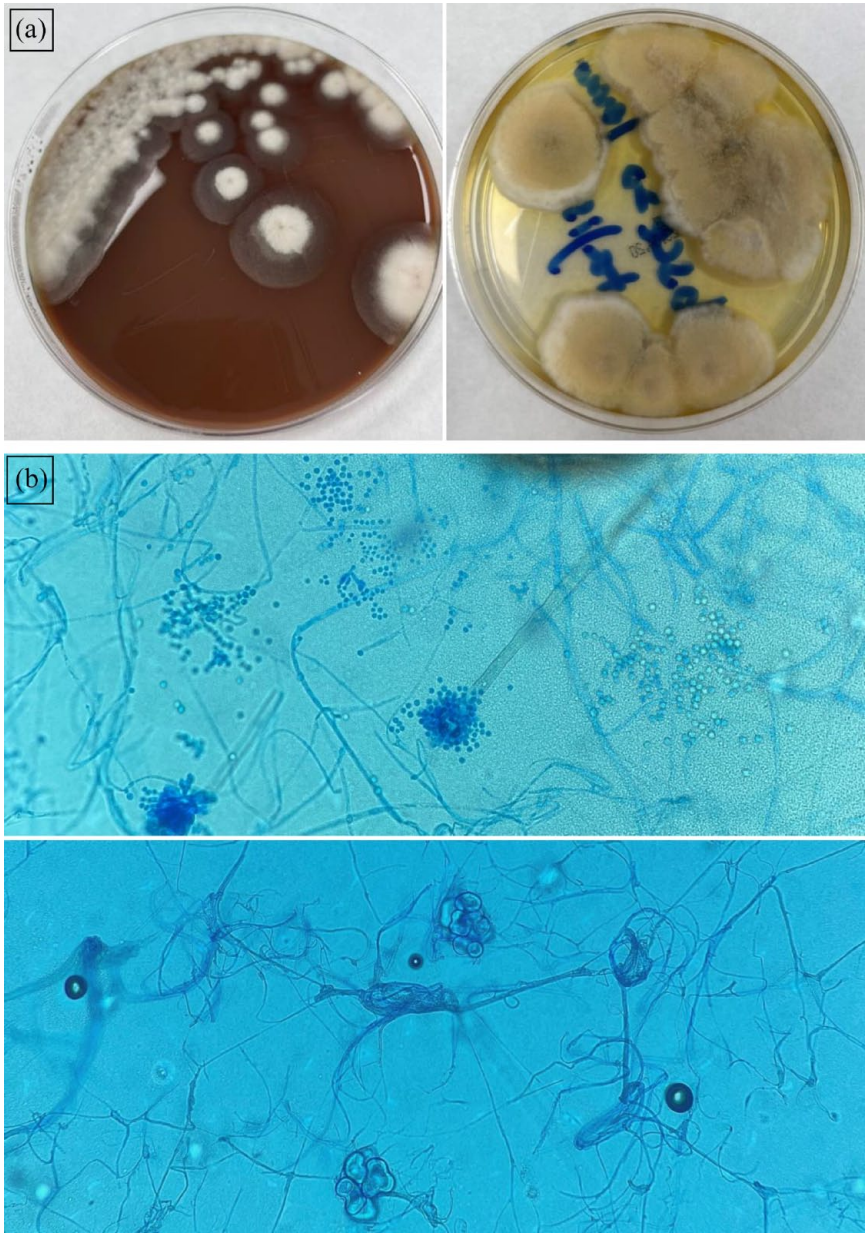

Figure 3. (a) Culture sample of the excised femoral lesion. On the left, white colonies on chocolate agar media. On the right, cinnamon–brown colonies on PDA medium. (b) Lactophenol cotton blue preparation of culture sample of the excised femur lesion. At the top, relatively sparse conidiophores are seen with poorly defined phialides (20×). At the bottom, globose to elongated Hülle cells are seen in clusters (40×).
PDA, potato dextrose agar.

available to interpret the MIC values against *A. granulosus*.[7]

Histological examination of the excised lesion described a chronic, granulomatous inflammatory process with abundant histiocytes and multinucleated giant cells presenting acute central inflammation with focal granulomatous necrosis. Periodic acid-Schiff (PAS) and Grocott stains allowed observing the presence of fungal structures consisting of septate hyphae branching at an acute angle.

To rule out a potential disseminated invasive aspergillosis, a ^{18F}Fluoro-Deoxy-Glucose-PET CT (PET/CT) was performed on day +9, showing an increased metabolic gradient (defined as standardized uptake value, SUV) in the site of the excised

femoral lesion (SUV max 6.78) and the right retropectoral region, in the path of the right axillary artery and vein with a maximum SUV of 8.02 [Figure 4(a) and (b)]. This find was then identified by CT angiography as a remnant of a prosthetic vascular graft sewn to the proximal third of the right axillary artery, through which a catheter-based micro-axial left ventricular assist device (Impella 5.0, Abiomed USA-Massachussetts) was previously implanted as bridge to transplant therapy [Figure 4(c)].

The patient presented a rapid clinical improvement with complete functional recovery following the surgical treatment. The antifungal therapy was kept unchanged until the PET/CT control was performed on day +69 at the start of treatment. Due to the persistence of an increased metabolic gradient (SUV max 11.16) in the graft remnant attached to the anterior aspect of the right axillary artery and in the heterogeneous intermediate-density tissue adjacent to it, it was considered appropriate to surgically remove the graft remnant and continue isavuconazole, which the patient was still taking with excellent tolerance.

On day +128, the patient underwent excision surgery. Through a subclavicular incision, the remnant of the prosthetic vascular graft placed in the sinus of the right axillary artery and vein was identified [Figure 5(a)]; after proximal and distal control of the axillary artery, the graft remnant was removed, inside which thrombotic material was found [Figure 5(b)].

Both the prosthetic vascular graft remnant and the thrombus were processed for culture and molecular examination by PCR, both of which have been negative.

The antifungal therapy was, therefore, discontinued after 137 days of treatment.

The patient presents excellent clinical conditions and a complete resolution of the initial clinical picture.

Discussion

We present this case because it is the first reported episode of long bone osteomyelitis due to *A. granulosus* that occurred in a heart-transplanted recipient without simultaneous pulmonary infection and was successfully treated with isavuconazole.

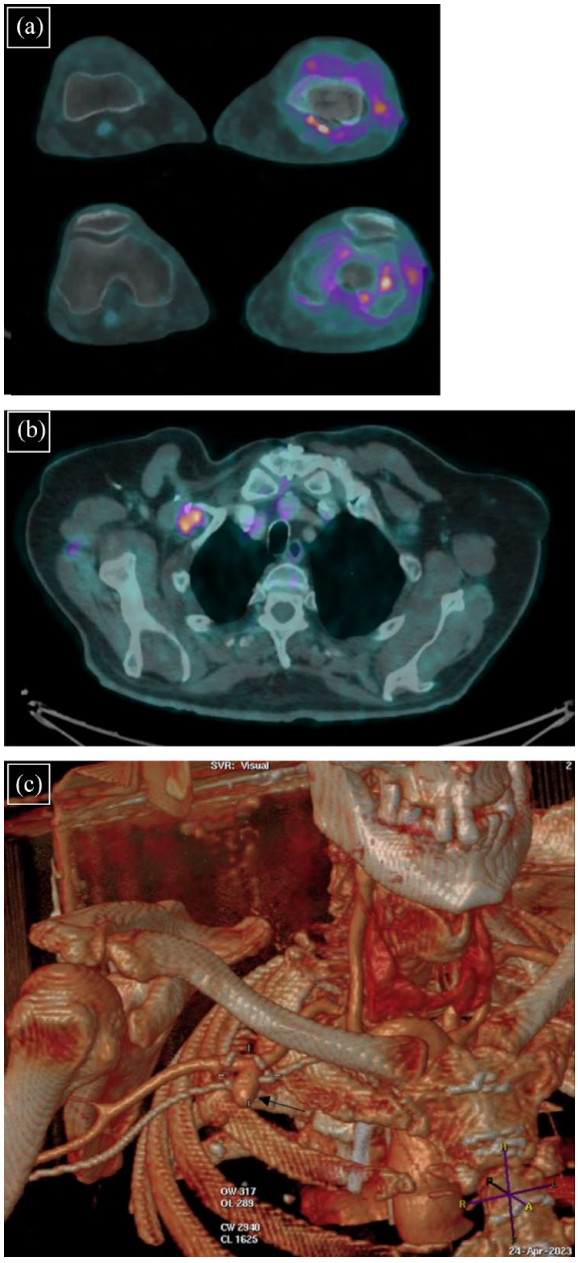

Figure 4. (a) PET/CT of both femurs and knees after the surgical excision showing a nonspecific metabolic lesion in the left distal femur, with peripheral hypermetabolism and adjacent soft tissue, compatible with known fungal infection. (b) Chest PET/CT showing a focal uptake in the right retropectoral region, in the path of the axillary artery and vein. (c) CT angiography showing the remnant of the prosthetic graft sewn to the proximal third of the right axillary artery, located superficially to the *pectoralis minor* and in the interval between the sternocostal and clavicular heads of the *pectoralis major* (black arrow).
CT, computed tomography; PET, positron emission tomography.

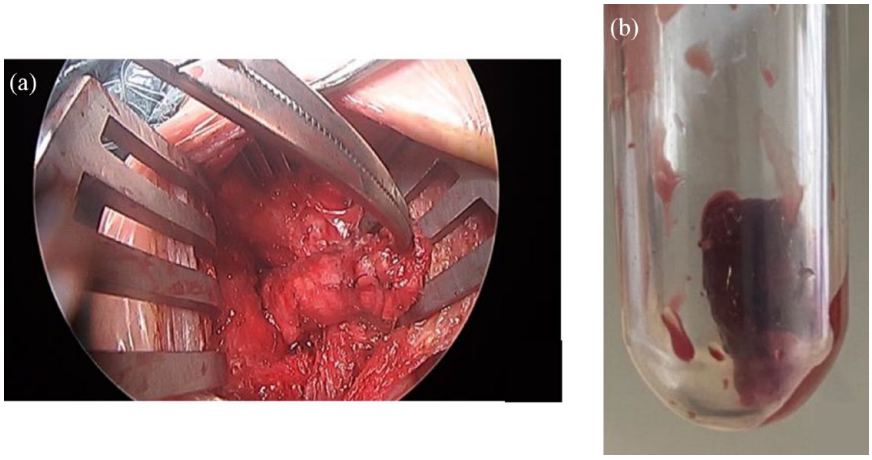

Figure 5. (a) Remnant of the prosthetic vascular graft sewn to the right axillary artery. (b) Thrombotic material found within the prosthetic vascular graft.

Aspergillus osteomyelitis is associated with predisposing conditions of the host, primarily immunosuppression caused by pathologies such as chronic granulomatous disease or induced following chemotherapy or transplantation of solid organs and haematopoietic stem cells.[10]

Our patient received immunosuppressive therapy for the heart transplant performed a few months before the first symptoms of osteomyelitis appeared.

Aspergillus osteomyelitis can develop by three mechanisms: (1) direct inoculation secondary to injury, surgery or epidural injection, (2) contiguous dissemination from pleuropulmonary infection or (3) haematogenous dissemination from coexisting pulmonary infection or intravenous injection.[4]

We cannot exclude that our patient presented a haematogenous dissemination originating from a remnant of the prosthetic vascular graft implanted prior to transplantation. However, microbiological tests of the excised remnant were negative (direct stain, culture and PCR), yet the patient had been receiving isavuconazole for more than 4 months at the time of their performance.

The main risk factor for the development of *Aspergillus* osteomyelitis of long bones, in particular of the tibia and femur, is chronic granulomatous disease following haematogenous dissemination from a pulmonary focus and it mainly affects the younger sections of the population.[4,11] However, Gamaletsou *et al.* reported that between patients with femoral and tibial *Aspergillus* osteomyelitis, there was a high proportion of solid organ transplant recipients as well, like in our case. *Aspergillus fumigatus* is by far the most frequently isolated pathogen, while there are no reported cases of osteomyelitis caused by *A. granulosus*.[4,7,12]

To the best of our knowledge, this is the second reported case of any type of infection due to *A. granulosus* in a heart transplant patient.[6]

Aspergillus granulosus is a species of fungus in the genus *Aspergillus* from the *Usti* section, formerly belonging to the now obsolete section *Versicolores*.

Previously, *Aspergillus* species were categorized into groups based on morphological characteristics. *Aspergillus granulosus* can be difficult to identify morphologically due to poor conidiation. It is characterized by its buff to pale brownish colony, by conidia that are only slightly roughened (finely echinulate or verruculose), by sparse conidial production in some isolates and by the preponderance of colourless aggregates of globose to elongate Hülle cells at maturity, giving a granular appearance to the colony. No defined breakpoints exist for this organism. Currently, thanks to the data obtained with molecular analysis, *A. granulosus* has been placed in the *Aspergillus* section *Usti*.[7,8]

The etiologic agent identification in the current report required a more detailed examination of the morphologic features combined with amplification and sequencing, emphasizing the crucial

role of molecular characterization to achieve an accurate species identification, as previously reported.[13]

We believe that the identification of a cryptic species as the etiological agent of osteomyelitis of the long bones, as described in this case, may depend on an underreporting of cases in the past due to the lack of appropriate identification methods.

Osteomyelitis diagnosis can be challenging. Clinical presentation depends on the site of infection. The appearance of pain or hypersensitivity in a bony area in an immunocompromised patient should lead to the investigation of the presence of osteomyelitis, in particular, caused by *Aspergillus*. Although inflammatory markers (ESR and CRP) are usually elevated, the white blood cell count can often be normal, as we found in our case.

In the analysis conducted by Gamaletsou *et al.*,[4] among the cases in which serum GMI data were reported, most had negative GMI values, as we observed in our case.

To date, there is no gold standard for the radiological evaluation of *Aspergillus* osteomyelitis; however, MRI, as we observed in this case, would appear to be the most sensitive method for early diagnosis; in addition to osteolysis, bone destruction and bone erosion, it may show increased T2-weighted signal intensity.[4,10]

The culture and histology of tissue specimens obtained through CT-guided biopsies, especially in cases of non-contiguous infections, remain the most important diagnostic tool,[4,10], although in our case, it was not possible to reach a diagnosis in this way.

Zhu *et al.*[14] have shown that the use of PET/CT, although exposing patients to a high level of radiation, allows early identification of infectious focus and monitoring of response to treatment. In our case, PET/CT proved to be a valuable diagnostic tool which helped us to exclude other sites of infection and manage patient follow-up. It prompted us to proceed with surgery due to its persistent positivity.

Regarding treatment, Gabrielli *et al.*, who conducted the largest and most inclusive literature review, reported that the combination of surgery and antifungal therapy did not significantly affect patient outcomes compared to medical therapy alone. On the other hand, in the analysis by Gamaletsou *et al.*[4] and Koehler *et al.*,[10] combination therapy resulted in more favourable outcome with higher survival rate and lower recurrence rate.[12]

Infection in the vertebrae or bones other than the skull has also been reported to significantly decrease the chance of recovery.[12]

Surgery represents a fundamental step, especially in the case of vertebral involvement, given the greater risk of neurological complications that could derive from spinal cord impairment.[12]

In our case, we believe that the excellent clinical response of the patient can be attributed to the combination of early surgery and targeted antifungal treatment.

The guidelines of the Infectious Diseases Society of America (IDSA) for treatment of *Aspergillus* infections recommend surgery when possible for the management of *Aspergillus* osteomyelitis in combination with voriconazole.[15]

The most widely used drug in the treatment of *Aspergillus* osteomyelitis is amphotericin B, followed by itraconazole and voriconazole.[12] However, there would not seem to be greater advantages in the use of liposomal amphotericin B rather than voriconazole or itraconazole. Furthermore, the combination of antifungal therapy *versus* single agent would not bring significant changes in the outcome.[4]

Besides, the type and dosage of the antifungals administered require frequent modifications based on the result of the sensitivity tests, the plasma and tissue levels of the drug, and the drug–drug interactions.[10]

The IDSA guidelines recommend a minimum of 6–8 weeks of antifungal therapy, with longer courses (>6 months) frequently necessary, using voriconazole as first-line treatment for invasive aspergillosis.[15]

Considering the need for prolonged therapy times, the choice of antifungal should, therefore, consider the risk of long-term toxicity, especially in the case of amphotericin B, burdened by nephrotoxicity and by the lack of a formulation for oral administration.

Voriconazole can be administered for long periods and is available in an oral formulation with high bioavailability. However, in order to guarantee efficacy and sufficient bone penetration, it requires frequent monitoring of plasma levels. It is, in fact, susceptible to drug–drug interactions, especially with immunosuppressive drugs taken by transplant patients, and can lead to hepatotoxicity.[16]

In this context, isavuconazole, due to its better interaction profile, is a promising alternative for the treatment of *Aspergillus* osteomyelitis, as highlighted by Mertens *et al.* in a recent review and as confirmed in our experience, although data on bone penetration of isavuconazole are scarce.[16]

Conclusion

In our opinion, the optimal management of *Aspergillus* osteomyelitis involves the combination of targeted antifungal therapy and a surgical approach. PET/CT was relevant in our case, assisting in the diagnosis and follow-up. Isavuconazole is a valid alternative therapy thanks to its reduced drug–drug interactions, its tolerance and bioavailability profile and the possibility of oral administration. This case also recalls how the differential diagnosis must include cryptic fungal species, particularly in the case of immunocompromised patients. In these cases, molecular methods play a major role in allowing the identification of the species.

Declarations

Ethics approval and consent to participate

Our report did not require ethical board approval as it described the treatment of a single patient which does not meet the federal definition of human subjects research. This anonymized case was documented in the context of routine care, and the information presented was anonymized in accordance with the Declaration of Helsinki. The reporting of this study conforms to the Case Report (CARE) guidelines.

Consent for publication

The patient reported in this case report provided verbal and written informed consent for publication of the case.

Author contributions

Alessandro Giacinta: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing.

Zorba Blázquez: Writing – review & editing.

Paloma García Clemente: Investigation; Resources; Writing – review & editing.

Álvaro Pedraz: Resources; Writing – review & editing.

Pilar Escribano: Investigation; Resources; Writing – review & editing.

Jesús Guinea: Investigation; Resources; Writing – review & editing.

Patricia Muñoz: Resources; Writing – review & editing.

Maricela Valerio: Conceptualization; Supervision; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data are available as part of this article.

ORCID iD

Alessandro Giacinta https://orcid.org/0009-0006-9031-619X

References

1. Segal BH. Aspergillosis. *N Engl J Med* 2009; 360: 1870–1884.
2. Ben-Ami R, Lewis RE and Kontoyiannis DP. Enemy of the (immunosuppressed) state: an update on the pathogenesis of *Aspergillus fumigatus* infection. *Br J Haematol* 2010; 150: 406–417.
3. Horn D, Sae-Tia S and Neofytos D. Aspergillus osteomyelitis: review of 12 cases identified by the Prospective Antifungal Therapy Alliance registry. *Diagn Microbiol Infect Dis* 2009; 63: 384–387.
4. Gamaletsou MN, Rammaert B, Bueno MA, *et al.* Aspergillus osteomyelitis: epidemiology, clinical manifestations, management, and outcome. *J Infect* 2014; 68: 478–493.

5. Latgé JP and Chamilos G. *Aspergillus fumigatus* and Aspergillosis in 2019. *Clin Microbiol Rev* 2019; 33: e00140–e00118.

6. Fakih MG, Barden GE, Oakes CA, *et al*. First reported case of *Aspergillus granulosus* infection in a cardiac transplant patient. *J Clin Microbiol* 1995; 33: 471–473.

7. Sutton DA, Wickes BL, Romanelli AM, *et al*. Cerebral aspergillosis caused by *Aspergillus granulosus*. *J Clin Microbiol* 2009; 47: 3386–3390.

8. Samson RA, Varga J, Meijer M, *et al*. New taxa in *Aspergillus* section *Usti*. *Stud Mycol* 2011; 69: 81–97.

9. Escribano P, Peláez T, Muñoz P, *et al*. Is azole resistance in *Aspergillus fumigatus* a problem in Spain? *Antimicrob Agents Chemother* 2013; 57: 2815–2820.

10. Koehler P, Tacke D and Cornely OA. Aspergillosis of bones and joints – a review from 2002 until today. *Mycoses* 2014; 57: 323–335.

11. Galluzzo ML, Hernandez C, Davila MT, *et al*. Clinical and histopathological features and a unique spectrum of organisms significantly associated with chronic granulomatous disease osteomyelitis during childhood. *Clin Infect Dis* 2008; 46:745–749.

12. Gabrielli E, Fothergill AW, Brescini L, *et al*. Osteomyelitis caused by *Aspergillus* species: a review of 310 reported cases. *Clin Microbiol Infect* 2014; 20: 559–565.

13. Grant DC, Sutton DA, Sandberg CA, *et al*. Disseminated *Geosmithia argillacea* infection in a German Shepherd dog. *Med Mycol* 2009; 47: 221–226.

14. Zhu LP, Chen XS, Wu JQ, *et al*. *Aspergillus* vertebral osteomyelitis and ureteral obstruction after liver transplantation. *Transpl Infect Dis* 2011; 13: 192–199.

15. Patterson TF, Thompson GR 3rd, Denning DW, *et al*. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 63: e1–e60.

16. Mertens B, Van Daele R, Depypere M, *et al*. Isavuconazole in the treatment of *Aspergillus fumigatus* fracture-related infection: case report and literature review. *Antibiotics* (*Basel*) 2022; 11: 344.