Case report

doi: http://dx.doi.org/10.22265/acnef.6.1.314

Clinical course of mycosis produced by exophiala xenobiotica in renal transplanted patient at the University Hospital of Burgos

Curso clínico de micosis producidas por Exophiala xenobiotica en paciente trasplantado renal en el Hospital Universitario de Burgos

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Resumen

Las micosis por Exophiala xenobiotica comprenden un amplio espectro clínico en pacientes inmunosuprimidos, desde infecciones localizadas, hasta diseminadas. Son incluidas como etiología de las feohifomicosis, actualmente consideradas como infecciones fúngicas emergentes en pacientes trasplantados de órgano sólido. Presentamos 2 casos de micosis por Exophiala xenobiotica en paciente trasplantado renal, una micosis cutánea localizada y una infección sistémica con afectación del sistema nervioso central.

Palabras clave: anfotericina B, dermatomicosis, exophiala, feohifomicosis, itraconazol, trasplante de riñón.

doi: http://dx.doi.org/10.22265/acnef.6.1.324

Abstract

Mycosis by exophiala xenobiotica comprise a broad clinical spectrum in immunosuppressed patients, from localized to disseminated infections. They are a recognized etiology of phaeohyphomycosis, currently considered as emerging fungal infections in transplanted solid organ recipients. We present 2 cases of mycosis by exophiala xenobiotica in kidney transplant recipients, a localized cutaneous mycosis and a systemic infection with central nervous system involvement.

Key words: amphotericin B, dermatomycoses, exophiala, itraconazole, kidney transplantation, phaeohyphomycosis.

doi: http://dx.doi.org/10.22265/acnef.6.1.324

Citation: Marín Franco JA, Sáez Calero MI, Palacios Ball JB, López Martínez JL, Terán Redondo M, Yépez León G, Abáigar Luquín P. Curso clínico de micosis producidas por Exophiala xenobiotica en paciente trasplantado renal en el Hospital Universitario de Burgos. Rev. Colomb. Nefrol. 2019;6(1):63-68.
doi: http://dx.doi.org/10.22265/acnef.6.1.324
Correspondence: Antonio José Marín Franco, amarinf@saludcastillayleon.es
Received: 08.10.18 • **Accepted:** 26.11.18

http://dx.doi.org/10.22265/acnef.6.1.314

Introduction

Numerous members of the genus Exophiala can cause human and animal mycoses. Most of these infections are cutaneous and superficial, but they can also cause life-threatening systemic infections. Among the known species that produce human mycoses we found: Exophiala dermatitidis, Exophiala xenobiotica and Exophiala oligosperma as the most frequently isolated in immunosuppressed patients[1-3].

We present 2 cases of mycosis due to Exophiala xenobiotica in kidney transplanted patients, one localized cutaneous mycosis and one disseminated mycotic infection with involvement of the central nervous system (cerebellar).

Presentation of clinical case 1

A 60-year-old patient with a history of juvenile idiopathic arthritis (psoriatic arthropathy) and a kidney transplant in November 2011 due to secondary renal amyloidosis; under treatment with prednisone 5 mg every 12 hours, tacrolimus 2 mg every 24 hours and mycophenolate 250 mg every 12 hours. After 6 years of immunosuppressive treatment he reported the appearance of nodules in the right hand. The patient denies contacts with plants, fertilizers, gardening work, and also denies prior lesions as an entrance door. Physical exploration revealed a non-painful fluctuating tumoration in the back of the right hand, at the level of the metacarpophalangeal joint of the third finger of 2 cm in diameter, without apparent tendinous involvement.

Given the persistence of the lesions, one month after the first assessment, a puncture of the lesion was performed with aspiration of 1.5 ml of fluid, apparently inflammatory/purulent, with negative result for Gram stain, bacterial culture, fungal culture, Mycobacterial culture and crystals.

The evolution of the lesions was torpid, a progressive increase in size was observed with the appearance of an ulceration on a lump that covers the 2nd, 3rd and 4th metacarpophalangeal spaces, with drainage for bacteria and fungi.

An ultrasound of the lesion was performed, in which a highly vascularized mass on metacarpals from the 2nd to the 5th fingers was observed, with multiple hypoechoic lesions in the subcutaneous fat layer with a collection greater than 22x10 mm, probably related to cellulitis-abscesses without tendinous or articular affectation. Given the poor evolution, surgical debridement was performed and the sample was sent to anatomical pathology (Figure 1).

The report of anatomical pathology describes a suppurative granulomatous inflammatory process in relation to deep cutaneous mycosis (presence of spores and septate hyphae with branches at an acute angle) that contact the surgical margins; it was classified by morphological determination as Exophiala xenobiotica and treatment was started with posaconazole 300 mg every 24 hours for 19 weeks. Given the interaction of this drug with tacrolimus, it required dose adjustment of the calcineurin inhibitor to maintain adequate levels, with a dose reduction of 75%.

The patient is currently followed-up by the outpatient service with a favorable evolution. Table 1.

Presentation of clinical case 2

A 50-year-old male with a functioning renal transplant since December 1995, with a history of HCV liver cirrhosis; in immunosuppressive treatment with cyclosporine 75 mg every 12 hours, azathioprine 25 mg every 24 hours and methylprednisolone 8 mg every 24 hours. In the second year post-transplant, he presented nodular lesions of grayish color in the front of the left thigh with progressive expansion through the lower limb. The skin nodules were removed, and it was requested their characterization to the service of anatomical pathology.

Anatomical pathology describes suppurative granulomatous dermatitis of fungal etiology (Figure 1). By morphological determination it was classified as Phaeohifomicosis caused by Exophiala xenobiotica and treatment with itraconazole was initiated, presenting hepatotoxicity 4 weeks after starting treatment, which is why it was replaced by systemic

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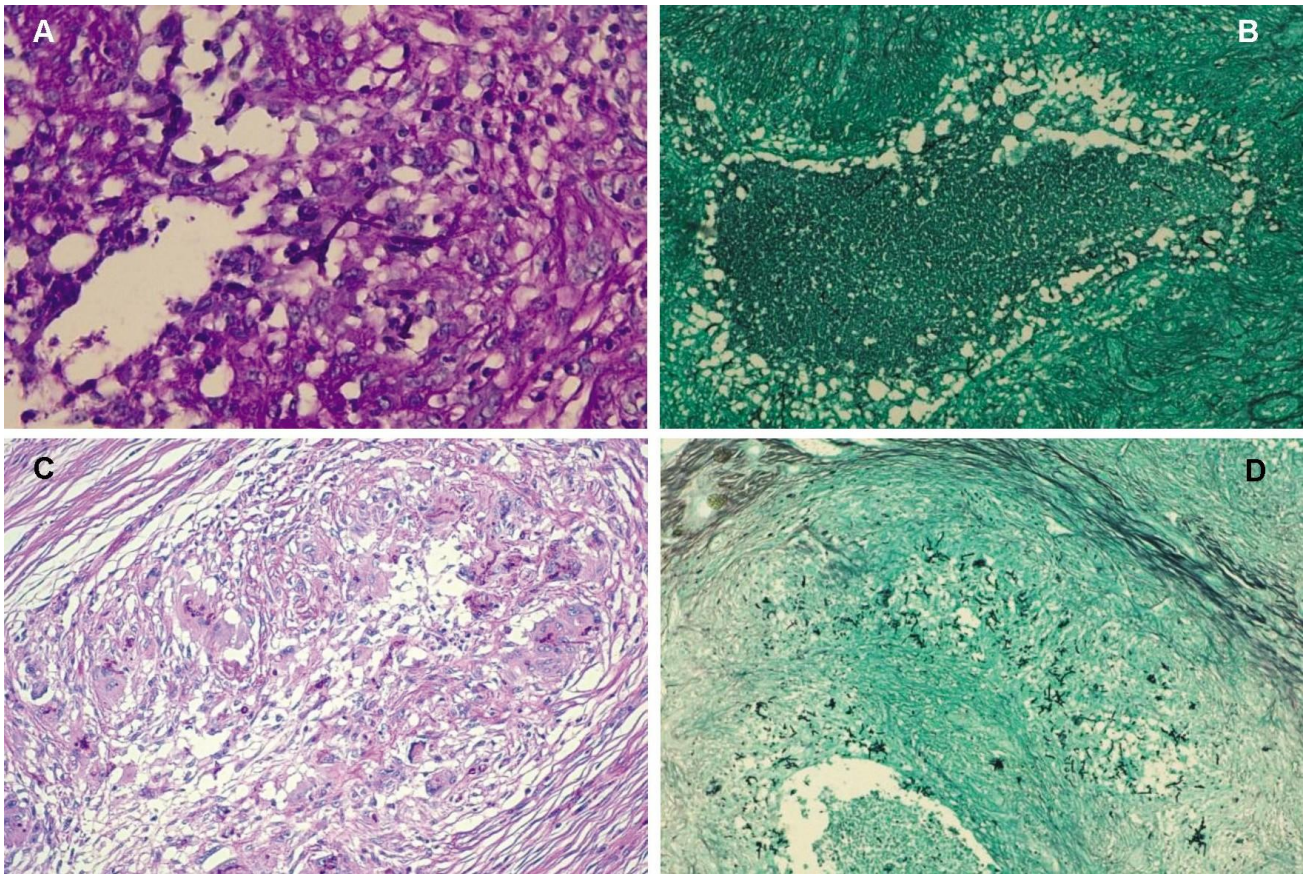

Figure 1. Histochemical stains of skin biopsy: **A). PAS 40x**. Muchopolysaccharides of "Y shaped" septate hyphae are evidenced. **B). Gomori or Grocot's methenamine silver 10x.** Granuloma with necrotizing center, septated hyphae (in black) are observed in the periphery of the necrotic center. **Case 2: C). PAS 40x**. Granuloma with giant cells, septated hyphae and spores. **D). Gomori or Grocot's methenamine silver 10x**. Granuloma with septated hyphae (in black).

Table 1. Comparative table between different clinical courses.

Characteristics	Infección micótica localizada	Infección micótica diseminada
Age of the patient at diagnosis of the mycosis	60	50
Patient gender	Male	Male
Time from transplant to the onset of the mycosis	6 years	3 years
Year of diagnosis	2017	1997
Initial infection	Dorsum of the left hand	Left lower limb (Thigh)
Identification	Exophiala xenobiotica	Exophiala xenobiotica
Initial treatment	Posaconazol	Itraconazol (4 weeks)
Second line of treatment	It was not necessary	- Intravenous amphotericin B liposomal. - Intravenous amphotericin B liposomal and intrathecal
Longer duration of the treatment	Posaconazole 19 weeks	(Anfotericina B) 3 weeks y 4 days
Resolution of the case	Favorable evolution	Skin lesions persist and the patient dies from other causes.

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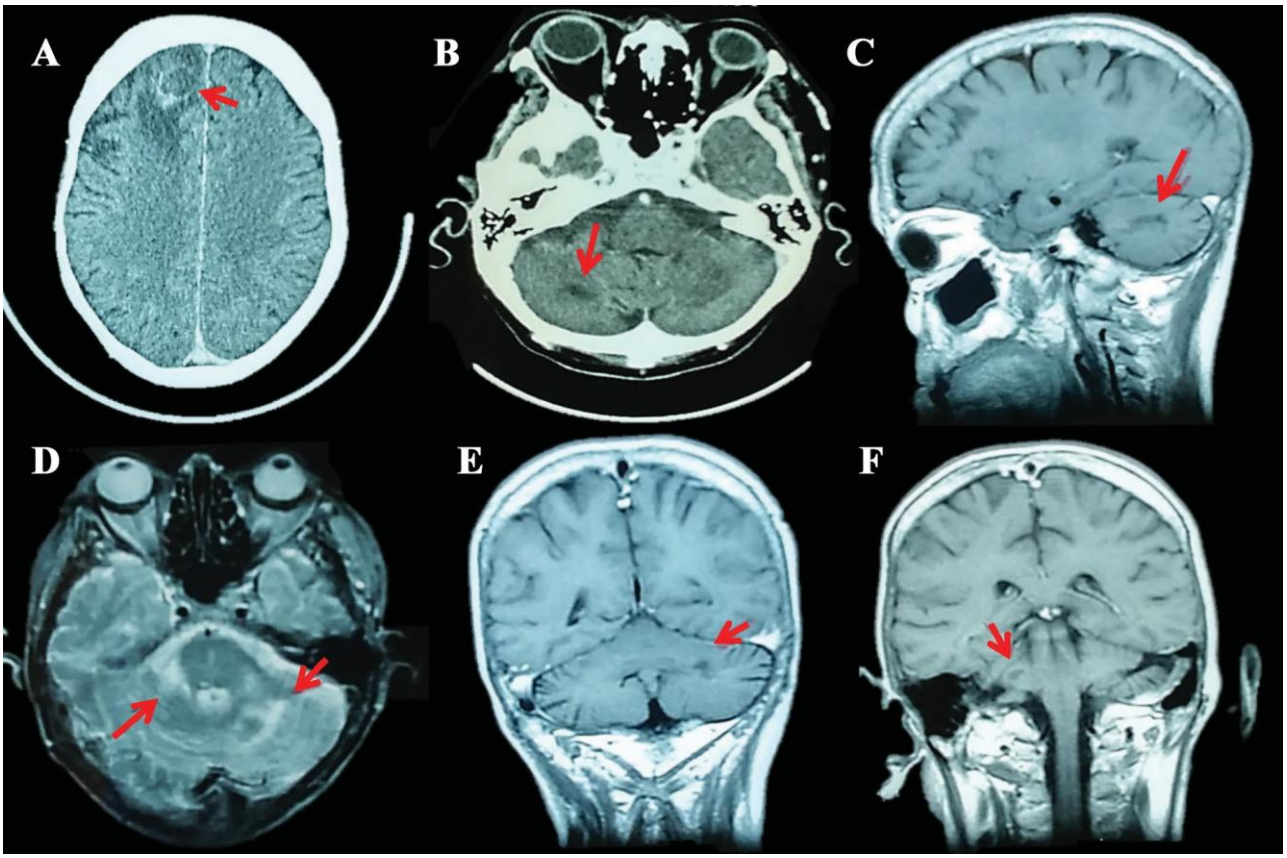

Figure 2. Cranial CT scan (A and B) and **MRI** (C, D, E and F): **(A and B): A)** Hypodense lesion with peripheral uptake and perilesional edema in the right frontal lobe compatible with abscess. **B)** Hypodense lesion localized in the right cerebellar hemisphere, with nodular aspect, without clear enhancement after administration of contrast that suggests an infectious lesion. **(C, D, E and F)**: Lesions localized in both cerebellar hemispheres, hypointense in T1 sequences **(C and E)** and hyperintense in T2 sequences **(D)**, with peripheral uptake after the administration of gadolinium **(G)**, in relation with abscesses.

amphotericin B that was maintained for 18 days, with little improvement of the skin lesions.

After 2 months he presented a clinical picture of dysarthria and clumsiness in the left hand, reason for which a cranial computerized tomography was performed, in which lesions of both cerebellar hemispheres suggestive of abscesses, probably related to fungal lesions were evidenced. Figure 2.

The immunosuppressive treatment was reduced and antifungal treatment was started with systemic amphotericin B and intrathecal amphotericin. 48 hours after starting treatment, the patient suffered a ventricular hemorrhage, remaining in a coma for several days, with subsequent progressive improvement, and was discharged to the minimal care center continuing without antifungal treatment, with persistence of few skin lesions. The patient died one year later due to probable decompensation of liver cirrhosis. Table 1.

Discussion and conclusions

Exophiala species can be found as a saprophytic germ mainly in the respiratory system, in immunocompetent subjects.

The infection in transplanted/immunosuppressed patients can be associated with previous injuries

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(weeks/months) in extremities (hands and feet), with vegetable fibers and spines during gardening works. The majority of the cases described refer to mild to moderate cutaneous monofocal infections. Systemic infections are rare[1-5].

The diagnosis is complex, requiring special techniques of microbiology and anatomical pathology to confirm it[1,2].

The optimal antifungal treatment is not yet specified; among the therapeutic options some experts recommend itraconazole or posaconazole in combination with surgical debridement in localized skin lesions and voriconazole in infections of the central nervous system. The average duration of the antifungal treatment reported in the literature is at least 12 weaks[1,4,5].

However, the selection of the antifungal agent is complicated in this type of patients, since the azoles inhibit CYP3A4 with different potency, with ketoconazole being the strongest, followed by itraconazole, posaconazole, voriconazole and fluconazole in decreasing order[1,6]. This decreases the metabolism of calcineurin inhibitors such as tacrolimus, increasing irregularly the levels of this drug. On the other hand, amphotericin-B is used in invasive mycoses and it is nephrotoxic. This toxicity is increased in transplanted patients due to the pre-existing renal dysfunction and the concomitant use of calcineurin inhibitors[1,6,7].

The experience that exists with this type of infections is very limited, the diagnosis is complex, requiring special techniques of microbiology and anatomical pathology to confirm it and the treatment to be used must be individualized to the patient's situation (type of transplant, type of immunosuppression, type of infection, personal antecedents and allergies)[1].

Conflict of interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent

The authors declare that patient data do not appear in this article

Contribution of the authors

Antonio José Marín Franco: main researcher.

María Isabel Sáez Calero: edition of the article, treating physician of one of the patients presented.

Pedro Abáigar Luquín: edition of the article, treating physician of one of the patients presented.

Johanna Beatriz Palacios Ball: anatomopathological diagnosis and edition of tissue photographs.

José Luis López Martínez: Radiologic diagnosis.

Magdalena Terán Redondo: collaborator.

Gabriel Yépez León: collaborator.

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