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Chronological aggregation of subcutaneous mycosis in renal transplant recipients

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SUMMARY

We present four cases of subcutaneous invasive mycosis in renal transplant recipients that happened in our Unit during a period of eight months. The Microbiology Department did not find any fungi when they studied possible reservoirs and vectors for transmission. We speculate about the reasons of this chronological aggregation. We discuss the treatment that we used for these infections.

Key words: ***Chronological aggregation. Renal transplantation. Subcutaneous mycosis.***

AGREGACIÓN CRONOLÓGICA DE CUATRO CASOS DE MICOSIS SUBCUTÁNEA INVASIVA EN RECEPTORES DE TRASPLANTE RENAL

RESUMEN

Presentamos cuatro casos de micosis subcutánea invasiva que fueron diagnosticados en nuestra unidad durante un período de ocho meses. El estudio realizado por los servicios de Microbiología y Medicina Preventiva no detectó los posibles reservorios y vectores de la transmisión. Especulamos sobre las razones de esta agregación cronológica. Discutimos el tratamiento usado para tratar este tipo de infección fúngica y la evolución favorable.

Palabras clave: ***Agregación cronológica. Trasplante renal. Micosis subcutánea.***

INTRODUCTION

Invasive subcutaneous mycosis is an infection that particularly affects immunosuppressed patients, and among those, transplanted patients.[1-10]. Few cases have been described of renal transplanted patients in whom the diagnosis is delayed as a result of heterogeneous presentation[1-10], with no existing guidelines for a standardized therapy.

We present four cases of non-yeast saprophytic fungal subcutaneous infection in renal transplant recipients, diagnosed at our unit during a limited time of eight months.

CASE PRESENTATION

Case 1

Fifty-two years old male patient, with a renal transplant in June of 2001. He had acute tubular necro-

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Table I.

Cases	Surgery	Antifungal therapy	Recurrrence	Recurrence therapy
1. Aspergillus sp	Yes	1. Liposomal Amphotericin B, 21 days (3 mg/kg/d). 2. Itraconazole (400 mg/d).	Yes 2 months	1. Surgery 2. Liposomal Amphotericin B, 21 days (3 mg/kg/d). 3. Itraconazol 6 months (400 mg/d). 4. Local amphotericin B infiltration (3 infiltrations).
2. Alternaria sp	Yes	1. Liposomal Amphotericin B, 14 days (3 mg/kg/d). 2. Itraconazole 6 months (400 mg/d).	No	
3. Phoma sp	Yes	1. Liposomal Amphotericin B, 14 days (3 mg/kg/d). 2. Itraconazole 6 months (400 mg/d).	Yes 1 month	1. Local amphotericin B infiltration (1 infiltration). 2. Itraconazole therapy was continued.
4. Alternaria sp	Yes	1. Liposomal Amphotericin B, 14 days (3 mg/kg/d). 2. Itraconazole 6 months (400 mg/d).	No	

sis (ATN) treated with four doses of anti-thymocytic globulin (ATG) (total 350 mg). Maintenance immunosuppressant therapy included tacrolimus, mycofenolate mofetil (MMF), and steroids. He had a stable renal function with serum creatinine (sCr) of about 2 mg/dL. He developed diabetes mellitus post-transplantation.

In June of 2002, he had a 10 cm in diameter indurated red-purple lesion on his back, with no fever or any other symptom (Fig. 1). Ultrasound and magnetic resonance imaging showed a nodular lesion in the subcutaneous soft tissue. The biopsy showed a granulomatous infiltrate of the soft tissue with branched septate hyphae structures with areas of venous invasion. Sabouraud's culture revealed Aspergillus sp. growing. Further clinical and imaging workup did not reveal any other involved organs or tissues.

Management was based on surgical debridement of the lesion and liposomal amphotericin B followed by itraconazole (Table I).

He was switched to oral cyclosporin and MMF was withdrawn. A month later, he had a recurrence of the lesion having another surgical excision. Later on, a second regimen of liposomal amphotericin B was administered together with 3 local injections of amphotericin B, and itraconazole was sustained (Table I) with no further recurrences and with stable renal function.

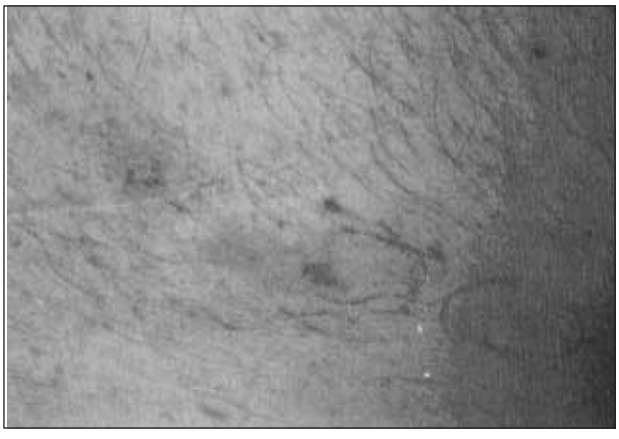

Fig. 1.

Case 2

Sixty-six years old male patient, with active hepatitis C virus (HCV) infection. He had a renal transplant on January of 2001. He has been on immunosuppressive therapy with tacrolimus, MMF, and steroids. The biopsy on day 13 after transplantation showed grade IIb acute rejection (Banff's classification), and treated with seven doses of ATG (700 mg in total), with a progressive decrease of sCr down to 3 mg/dL. He developed diabetes mellitus post-transplantation. In June of 2002, we consulted for the appearance of skin lesions on his right leg, with no other symptoms. One of them was pinkish and fleshy and the other one was an exudative papule. The biopsy showed dermic granulomatous inflammation with sporulated mycotic forms with isolated short

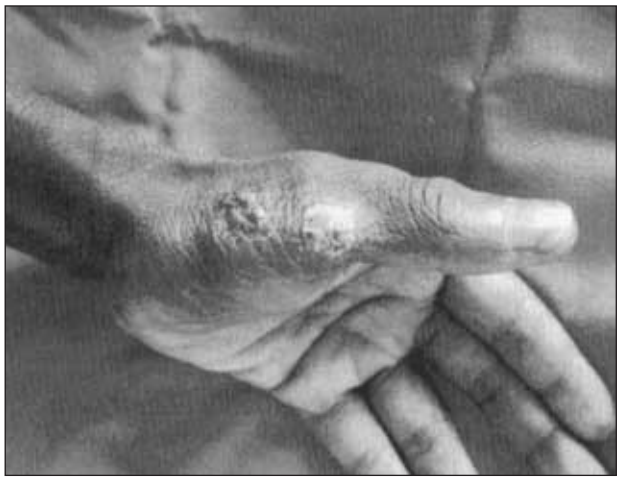

Fig. 2.

hyphae, engulfed by multinucleated giant cells or free cells within the dermis. The spores had a double capsule with a grayish-black color. In the culture Alternaria sp. grew. Surgical debridement of the lesion was done followed by liposomal amphotericin B and itraconazole (Table I). MMF was withdrawn and was switched to oral cyclosporin, with no recurrence of the infection and renal function stability.

Case 3

Fifty-two years old male patient receiving a renal transplant on April of 2001. He received treatment with tacrolimus, MMF, and steroids, with a favorable course with stable sCr (1.8 mg/dL). On august of 2002, we presented with two warty hyperkeratotic lesions, one on his left hand (Fig. 2) and the other one on his right leg. The biopsy showed brown hyphae with irregular septa accompanied by subcutaneous granulomatous reactions. Phoma sp. was isolated at the culture. There were no other signs of infection. Excision of the lesion was undertaken, MMF was discontinued, and lisosomal amphotericin B was started followed by oral itraconazole (Table I). After evidencing lesion spreading to deep layers by ultrasound, a local infiltration with amphotericin B was done. After completing the treatment, the patient has remained free of disease with stable renal function.

Case 4

Fifty-eight years old male patient with diabetic nephropathy, and renal transplant on June of 2001. He had a renal biopsy on day 5 post-transplantation showing grade IIb acute renal rejection (Banff's classification). He was treated with steroids boluses and four doses of ATG (750 mg in total), with a final SCr of 2 mg/dL. Maintenance immunosuppression was tacrolimus and MMF. This later drug was discontinued 10 months after transplantation because of anemia and leucopoenia. On January of 2003, two keratotic nodular lesions were seen on both legs (Fig. 3). The histology showed sporulated mycotic forms with septate hyphae. The spores had double grayish-black capsule. Alternaria sp. grew at the culture. Disease extension studies were negative.

Therapy was switched to oral cyclosporin and treatment with lisosomal amphotericin B was started followed by itraconazole (Table I). After completing treatment, the infection has not recurred, and renal function remains stable.

DISCUSSION

Aspergillus, Alternaria and Phoma are ubiquitous and cosmopolitan fungi.[3-4, 7] Subcutaneous infection due to these fungi has been associated with common conditions such as diabetes mellitus, bronchial disease, burns, heart failure, and inflammatory diseases,[5, 7, 11], and generally to conditions characterized by an immunosuppressive state such as the one occurring in renal transplantation.[3-5,7-8, 11-13] In transplanted patients, the cumulative immunosuppression has been related to the risk of fungal infection, highlighting that tacrolimus was the most frequently used anti-calcineurin agent in the cases of transplanted patients with invasive subcutaneous mycosis reported in the literature.[3-4, 8-9, 11] Our four patients were on immunosuppressive therapy with tacrolimus at

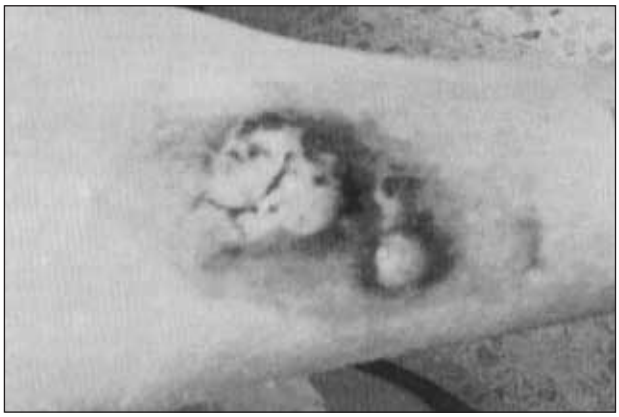

Fig. 3.

the time of infection, three on triple therapy with tacrolimus, MMF, and steroids, and one with double therapy with tacrolimus and MMF. Three of them had been treated with ATG, which might have increased the level of immunosuppression. The coexistence of diabetes mellitus in three patients, together with chronic HCV infection in one of them might have contributed to the development of fungal infection.

In the series we present, we may highlight the temporal aggregation of the four described cases, which were diagnosed in a period ranging from June of 2002 and January of 2003. We have not found in the literature any reference to this temporal clustering of cases with subcutaneous mycosis in renal transplanted patients such as the one reported here. However, temporal clustering does have been described of cases with systemic aspergillosis in renal transplanted patients in relation to an increase in filamentous fungi load in air conditioning systems.[14] During the nine years of life of our renal transplantation program, we have detected no case of invasive subcutaneous or systemic mycosis other than the four described cases, whose presentation coincided with the demolition of a building close to the hospital. This coincidence allows, at least, considering the hypothesis of greater levels of fungal particles in the environment as being the cause of the infections. The Microbiology and Preventive Medicine Departments did not find the source of the infection after studying the potential reservoirs and transmission vectors, so that we may only speculate on the basis of chronological aggregation. A possible association between higher environmental spores levels and the development of invasive mycoses has been described, although still is controversial.[14-19]

In our four cases, the skin lesions on the back, back of the hand, and legs, with no history of trauma were the only manifestations of the infection. A high mortality rate has been reported with disseminated disease secondary to subcutaneous mycosis,[5, 7] so that an aggressive therapy is recommended. Only in case 1, blood vessels invasion by fungi was detected, no patient showing any sign of systemic infection. Although treatment regimen is not adequately standardized for this type of fungal infections, most authors recommend surgical excision followed by systemic anti-fungal agents, besides suggesting a reduction of immunosuppressive therapy.[4, 7, 9-12]

First choice anti-fungal agents are azoles and amphotericin B, commonly using a combined therapy for a prolonged time (2-6 months).[4-6, 8-9, 11] Some anti-fungal agents such as terbinafine or 5-flucytosine are not as effective[5, 11] as azoles or amphotericin. There are new drugs such as voriconazole or caspofungin, which might be a good alternative, although more experience is needed.[6] Infection recurrence or persistence after completing the treatment is common,[9] then recommending to extend antifungal therapy, switch to another drug, or add a different one.[4-6, 9, 11-12] Local infiltration with amphotericin of azoles is a therapy that may be used in combination with systemic drugs, either as initial therapy of for recurrences.[20]

The therapeutic plan of our patients was based on liposomal amphotericin B and itraconazole (four patients), surgical excision (three patients), and local amphotericin B infiltration in two recurrences.

Besides, immunosuppression was reduced, with MMF discontinuation (three patients) and switching tacrolimus to oral cyclosporin (three patients). The clinical course in the four cases has been satisfactory, being disease free and with stable renal function.

Invasive subcutaneous mycosis is a rare condition in the renal transplanted population; however, the cases here presented oblige to consider the mycotic etiology in any skin lesion with a subacute course in renal transplanted patients.

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