ORIGINAL ARTICLE

FUNGAL INFECTIONS IN KIDNEY-TRANSPLANTATION PATIENTS. EXPERIENCE OF THE RENAL ABLATION AND IMPLANT UNIT, DR. COSME ARGERICH GENERAL HOSPITAL.

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SUMMARY

Infections in kidney transplant patients are one of the main causes of morbidity and mortality in this patient population. Fungal infections are a diagnostic challenge and require a high index of suspicion. The elaboration of risk scores is of great help, but they often require the use of early therapy given the diagnostic difficulties and high mortality. In this article we present the experience of our Hospital and illustrative clinical cases that can be a contribution to the transplant community.

KEY WORDS: kidney transplant mycosis

INTRODUCTION

Fungal infections in renal transplant recipients account for approximately 5% of all infections and are an important cause of morbidity and mortality. This figure varies according to the immunosuppression regimens used, the geographical area, the time of appearance of the infection and epidemiological factors. [1-2]

Immunosuppressive agents have effects on the impact of infections in this population and the personal history of each patient determines additional risk factors, especially if they present multiple rejections that require higher doses of immunosuppression.

Deep mycoses and locally invasive mycoses are a major problem in transplant patients and have a high morbidity and mortality that varies according to the series reported and arrives, in some series , up to 63% mortality, a fact that depends on additional risk factors, such as comorbidities, chronic rejection and reactivation of immunomodulatory viruses. [1-4]

Multiple immunosuppressive agents are used in transplant patients to prevent rejection and prophylaxis against multiple microbial agents with the consequent appearance of adverse effects and interactions, as well as resistance to the antimicrobials used. [3-5]

As is known , transplant infections depend on the net state of immunosuppression and epidemiological exposure.

The net state of immunosuppression is the interplay of multiple factors such as dose and type of immunosuppression, the presence of acute and chronic rejection, nutritional status, underlying disease such as diabetes or autoimmune conditions that already receive prior immunosuppression, and the presence of infection by immunomodulatory viruses such as those belonging to the Herpes virus group, which due to the variable degree of latency frequently reactivate and cause greater immunosuppression , as occurs with Cytomegalovirus after the first month after transplantation. favoring the appearance of opportunistic infections in general

The chronology of appearance of infections in transplantation allows the aetiological agent to be inferred and in the case of fungal infections, except for Candida and Aspergillus, they are observed after the sixth month post-transplantation unless there is an extraordinary epidemiological risk. [5-6]

The incidence of fungal infections in solid organ transplants is in the small intestine 11.6 % , in the lung 8.6 %,

in the liver 4.7%, in the heart 4.0%, in the pancreas 3.4% and in the kidney 1.3%.
The prevalence of fungal infections in TOS of 5 to 50% is quite similar in heart transplantation and somewhat higher in liver transplantation.
In both groups, 80% of invasive fungal infections are caused by Candida and Aspergillus .
Non - Aspergillus mycelial fungi are causal agents in approximately 37%, with a mortality of 43%; could be dematiaceous fungi or hyaline fungi such as Fusarium spp . or Scedosporium spp . Mortality due to invasive mycelial fungal infections it is 43 % compared to 7% in skin and soft tissue infections. [6-8]
Fungal infections can be primary or reactivation of latent infection. [8] One of the main problems in diagnosis is the decrease in the inflammatory response in immunosuppressed patients and the presence of invasive disease without detectable fungemia is frequent .
The potential etiological agents in these individuals are multiple, the pulmonary processes can evolve rapidly and become a medical emergency, especially in cases of Pneumocystis pneumonia . jirovecii , Aspergillus spp. Y Cryptococcus neoformans and to a lesser degree Nocardia asteroides, decrease in the inflammatory response decreases the clinical manifestations and the radiological findings are often not evident, and the use of computed axial tomography is mandatory. Fever is absent in 40% of fungal infections and , in general, at the time of clinical presentation they are already disseminated diseases.

MATERIAL AND METHODS

In the Renal Transplant Unit of the Dr. Cosme Argerich General Acute Hospital, in the Autonomous City of Buenos Aires, Argentina, 1226 transplants were performed with 61 episodes of fungal infections : (deep, disseminated and locally invasive mycoses) 30 men, 30 women (aged between 19 and 69 years, mean age 41.8 years and 1 episode of confection by two different agents (see graph 1) with an incidence of 5.1%. 85% were episodes of deep mycosis and the 13% locally invasive mycoses.

Superficial mycoses were excluded from this review. The etiological agents were, in order of frequency: Cryptococcus neoformans 36%, histoplasma capsulatum 28 % , Aspergillus spp. 11.5 _ % Candida spp. 10 % , Purple eo cillium lilacinu m 6.6 %, other agents (6.6%) such as Trichophyton rubrum , which produced an abscess in a transplant patient another patient with confection by dematiaceous and mucoral fungi and a third patient with Trichoderma infection longibrachiatum. (see graph 2).
The majority of disseminated and locally invasive fungal infections were 87% after 80 days post - transplant

Agent	< 30 days	30-180 days	> 180 days
C. neoformans	-	-	22
H. capsulatum	-	-	17
Candida	2	3	1
Purpureocillium spp.	-	-	4
Aspergillus	2	-	5
Hyalohi fomycetes	-	-	1
Mucor sp.	-	-	1*
Dematiaceous fungi	-	-	1 *
T. rubrum	-	-	1
T. longibrachiatum	-	-	1

; the causative agents of early infections (from the first to the sixth month) were Candida and Aspergillus, as is frequently observed in this period and they were associated with additional risk factors, such as neutropenia, sepsis due to resistant organisms and prolonged use of antibiotics.
Overall mortality was 29%, and in the group of deceased patients it was, depending on the aetiological agents, 80% by Histoplasma capsulatum, 16% Cryptococcus, 4% Candida and Aspergillus

Mortality attributable to fungal infection was relatively low (19%) and was associated with additional risk factors and the presence of comorbidities, severe chronic liver disease due to B and C viruses, acute and chronic rejection, acute pancreatitis, sepsis, and diabetes.
In the literature , mortality associated with fungal infection varies from 20 to 100%, a variation probably related to the etiological agent , delay in diagnosis, comorbidities, and degree of host immunosuppression and as risk factors. additional, are recognized: the presence and reactivation of immunomodulatory viruses , infections and fungal infection.

CRYPTOCOCCOSIS

Cryptococcosis is a serious fungal infection that primarily affects immunocompromised patients with impaired cell-mediated immunity; it is associated with high mortality and is the third leading cause of fungal infections in this patient population.
Cryptococcus neoformans is an environmental fungus,

which has virulence factors such as the polysaccharide capsule, among others, which inhibits phagocytosis. [9-10]
Transplanted patients present alterations in cell-mediated immunity, the initial pulmonary infection (usually undiagnosed) causes the dissemination of the disease, meningitis is the main clinical manifestation (50%) and usually presents with fever and headache, with minimal inflammatory reaction of the CSF, so it is not frequent for the patient to present signs of meningeal irritation , the characteristics of the cerebrospinal fluid reveal a minimal inflammatory reaction with cells with lymphocyte predominance, minimal protein in the spinal cord and generally without glucose alterations, and the presence of abundant characteristic capsulated yeasts . [10-11]
The sensitivity of cerebrospinal fluid culture is 100% and 85%, detection of polysaccharide antigen; antigorachia it is of prognostic value and, together with antigenemia, supports the diagnosis.
Transplanted patients exhibit a significant frequency of skin lesions, the immunosuppressants that are frequently used are calcineurin inhibitors , tacrolimus and cyclosporine A; the latter is a natural macrolide with antifungal activity , it is toxic to Cryptococcus neoformans in vitro (by calcineurin inhibition) and has the ability to suppress fungal growth at 37 °C but not at 24°C.
This temperature-dependent inhibition could prevent infection in the central nervous system with the potential to affect exposed and lower temperature sites such as skin and soft tissues.
Mortality in this population is high, 20 to 35%, compared to HIV-positive patients (14.3%), probably due to the high frequency of central nervous system involvement, spread of the disease, delay in diagnosis and the lowest index of suspicion due to the low frequency of infection.
Treatment of cryptococcal meningitis consists of the amphotericin induction regimen. liposomal (3-4 mg/K/day intravenously plus flucytosine 100 mg K/day divided into 4 doses orally, for 14 days.
In countries such as Argentina where flucytosine is not available, fluconazole is used in doses of 800 mg IV and / PO , in both cases fluconazole 400-800 mg is continued orally for 6 to 12 months. [12]

Case 1: (Fig 1) kidney transplant patient, 6 years of evolution prior to admission, with a history of hypertensive nephropathy, multiple rejections, the last one was treated with high doses of corticosteroids 6 months before admission, was left with permanent deterioration renal function and chronic rejection. He had a history of arterial and venous insufficiency of both lower limbs. He consulted a few months earlier due to ulcers in the lower limbs interpreted as of mixed vascular origin given the patient's history. Given the persistence of rapidly worsening lesions, a scarification of the ulcers was performed and the presence of yeasts compatible with Cryptococcus was confirmed by direct examination **(Fig 2-3-4)**. spp. Computed axial tomography (CAT) of the brain, chest, and abdomen revealed no lesions, except for mild homogeneous hepatomegaly . The chemical physical examination of the cerebrospinal fluid was normal and the culture was negative as well as the blood cultures. Antigenemia was positive with titers of 1/10,000 . The patient died months later with a diagnosis of sepsis due to gram- negative bacilli.

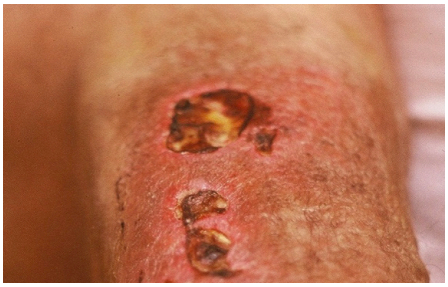

Fig 1.

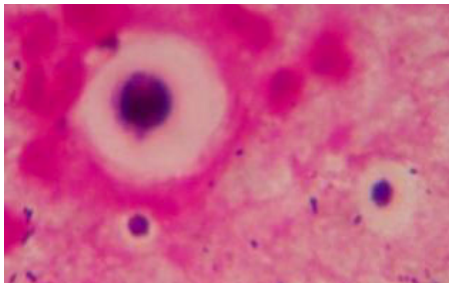

Fig 2: tincion de Giemsa.

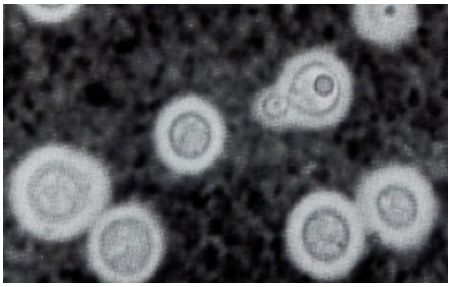

Fig 3: tinta China.

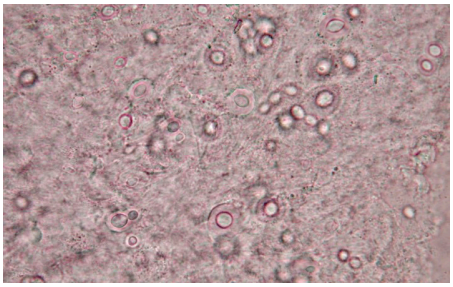

Fig 4: examen de Fresco.

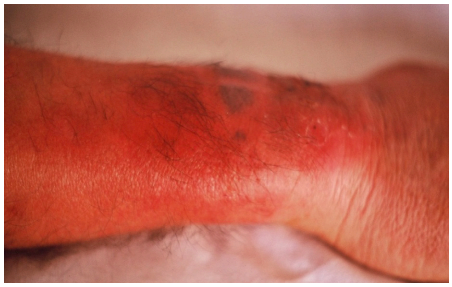

Fig 5.

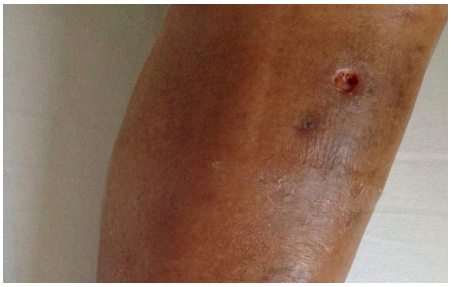

Fig 6.

Case 2: (Fig. 5) Male, kidney transplant, with cadaveric donor, smoker, worked in waste processing, with no recent history of rejection, treated for tuberculosis one year earlier, with biopsy diagnosis of chronic rejection and chronic liver disease due to virus C. He reported a blunt trauma one month before the appearance of the lesion on the right wrist, the lesions had a violaceous erythematous appearance, without phlogosis, not suppurative and painless. The presence of yeasts compatible with Cryptococcus was evidenced. sp in material extracted for cytodiagnosis that was confirmed by culture. Central nervous system involvement was also ruled out in this patient with negative fluid cultures. cerebrospinal fluid and blood cultures were negative. Antigenemia of 1/5000. Complete CT scan revealed no lesions.

Case 3: (Fig 6) Renal transplant, with cadaveric donor, history of renal failure secondary to obstructive uropathy and chronic venous insufficiency of the lower limbs. Good renal function with no history of acute or chronic rejection. He presented localized pain in the anterior face of the left leg. Slightly indurated nodular appearance, which presented softening and purulent material drained. Positive direct test with the presence of yeasts and positive culture for Cryptococcus neoformans . There was no involvement of the central nervous system, lungs or other parenchyma, blood cultures were negative and antigenemia It was positive in low titer 1/5000. He presented good evolution.

These three cases of opportunistic infection by Cryptococcus neoformans , with cutaneous involvement without systemic involvement, are probably due to the pre-existence of sites of lower resistance such as arterial and venous vascular insufficiency or trauma in immunosuppressed patients.

The immunosuppression used in the three cases was calcineurin inhibitors such as cyclosporine and tacrolimus .

Cyclosporin A binds to an intracellular receptor (cyclophilin) and forms an active complex that binds to and inhibits calcineurin phosphatase activity .

Calcineurin participates in the control of ribonucleic acid (RNA) transcription for the synthesis of pro - inflammatory cytokines (IL-2, IFN-gamma, IL-4 - IL-5 and TNF - ß) , inhibits proliferation of T cells and prevents clonal expansion of T helper and cytotoxic cells without affecting suppressor T lymphocytes.

Tacrolimus is a macrolide that forms an intracytoplasmic complex with an immunophilin (FKBP) capable of also blocking the phosphatase activity of calcineurin.

These immunosuppressants also exhibit synergy with other antifungal agents in vitro , and could prevent to some degree the involvement of the central nervous system, which is the most frequent manifestation of this mycosis.

HISTOPLASMOSIS

Histoplasma capsulatum is a dimorphic fungus the mycelial phase is found in the environment and presents its infective forms, macroconidia and microconidia 13 that when inhaled reach the terminal bronchioles where they transform into yeasts inside the macrophages.

In immunosuppressed patients, the infection is usually due to reactivation, although primary infection or reinfection may be possible.

Reactivation of infection in transplant patients residing in endemic areas occurs through histoplasmas that persist latent in mediastinal lymph nodes and spreads via the lymphohematic pathway. [14-15]

Most forms are disseminated and involve multiple parenchyma: lung , liver , spleen , bone marrow, and skin.

The control of disease progression depends on cell-mediated immunity, where interferon gamma plays a fundamental role in the integrity of macrophages and the production of CD4 T lymphocytes.

The production of pro-inflammatory cytokines (Interleukins , tumor necrosis factor) and infected macrophages that promote the formation of granulomas, this immune response is impaired in patients receiving immunosuppressive treatment and glucocorticoids. [15]

Severe disseminated forms are frequent in HIV-positive patients with a CD4 count of less than 50 cells and in transplant patients, the evolution is 3 to 4 weeks with general symptoms such as fever, asthenia, weight loss and, less frequently, gastrointestinal involvement.

Cutaneous involvement is very common in Latin America, but unlike maculopapular , nodular, or ulcerative lesions that are frequently seen in HIV-positive patients, in this population, it presents as panniculitis.

Skin involvement in our population (90%), unlike the world literature, is due to the characteristics of the clades that circulate in Argentina, and the clinical presentation as extensive panniculitis with a tendency to softening and exulceration is characteristic and It is due to the use of corticosteroids as part of the treatment. [17-18]

Disseminated forms present lymphadenopathy , fungemia , bone marrow and reticuloendothelial system involvement, and extension to multiple parenchyma.

Laboratory findings are; pancytopenia , mild elevation of transaminases, elevated LDH. Due to hepatic and splenic infiltration.

Fungemia determines miliary -type pulmonary infiltrates.

Although it is not frequent, cases of interstitial nephritis and adrenal compromise have been reported.

The progressive disseminated forms have high mortality and presentation as hemophagocytic syndrome is frequent , characterized by multi- organ failure , liver failure, encephalopathy, pancytopenia , disseminated intravascular coagulation and clinical manifestations of septic shock. [17-19]

The need for rapid diagnosis in immunosuppressed patients to lower mortality rates requires speeding up the same with the detection of Histoplasma antigens capsulatum. [20-21]

the gold standard is the cultivation of clinical specimens but these require 2 to 4 weeks for development with a maximum of 8 weeks revealing on Sabouraud 's media or dextrose agar slightly cottony white brownish colonies with a yellowish reverse at 25 C, and the presence of macroconidia and conidiophores .

At 37 degrees the transformation of the saprophytic phase to the yeast phase occurs .

The positivity of blood cultures (sensitized by the lysis-centrifugation technique), of bone marrow in disseminated forms is from 74 to 80% and of lung specimens from 67 to 70%.

Cytodiagnosis and histopathology are very useful tools that allow a rapid diagnosis of mucosal skin lesions, direct examinations reveal the presence of ovoid yeast-like elements with the characteristic polar staining compatible with Histoplasma. capsulatum and the presence of moderately loose granulomas depending on the immune status of the patient.

Serological tests such as complement fixation, immunodiffusion , and enzyme- linked immunosorbent assay are not very helpful in disseminated forms, since they are not detected before 4 to 8 weeks after infection and sensitivity and specificity are low in organ transplant recipients. solids.

The enzyme-linked immunosorbent assay detects IgG and IgM antibodies and used in conjunction with antigen detection greatly increases sensitivity.

Histoplasma circulating polysaccharide antigen detection techniques capsulatum , by Enzyme linked immunosonbent Assay , ELISA has a sensitivity of 96% and a specificity of 90% and is commonly used on serum or urine, bronchoalveolar lavage , and cerebrospinal fluid samples. They are rapid non-invasive sensitive and specific techniques in immunosuppressed patients and detect more than 90% of the disseminated forms.

Serum polysaccharide antigen clearance is used as a useful tool for monitoring clinical response.

The use of the polymerase chain reaction (PCR) is used in samples of serum, urine and tissues, but the standardization of the method is still lacking.

Treatment depends on the severity at the time of diagnosis, the extent and spread of the disease, the degree of immunosuppression, and the clinical form. 23

Agents used are azoles , itraconazole voriconazole and posaconazole , fungicidal drugs, act by inhibiting the synthesis of ergosterol , which is part of the membrane of the fungus, and polyenes such as amphotericin liposomal that produces membrane rupture and apoptosis by complexing with ergosterol .

Amphotericin Liposomal is preferably used in kidney transplant patients because it is much less nephrotoxic compared to amphotericin deoxycholate and, according to some series, the use of this preparation significantly improves the prognosis.

Disseminated forms require rapid establishment of a fungicidal treatment with amphotericin . initial liposomal and as soon as the patient's symptoms improve, azoles are continued , which must be received for 12 months in all clinical presentations of transplant patients.

In exceptional cases in which the clinical presentation is predominantly mucosal skin, treatment with oral itraconazole can be started, at a dose of 400 mg per day, with close monitoring for any variation in the patient's clinical conditions, since in our experience Despite the good general condition of the patient, conceptually they are disseminated forms and the use of amphotericin at the beginning and the change to azole drugs improves the prognosis if the patient remains stable.

Case 1: 29 years old, male , rural worker. Chronic renal failure of unknown cause, for which he received a cadaveric kidney transplant 5 years prior to admission. He was admitted due to fever, general deterioration, weight loss, and the appearance of nodules on the back of the right foot, the knee on the same side, the trunk, and the upper eyelid.

Immunosuppressive treatment: prednisone in decreasing doses, cyclophosphamide and azathioprine . Presented six months before hospitalization , reactivation of Cytomegalovirus infection . Malnourished, with edema, decreased adipose tissue, scaly dermatitis and onychodystrophies associated with vitamin deficiencies , Cushingoid facies , globular abdomen and atrophic striae on both flanks . On the back of the right foot, 3 nodules 3 to 4 cm in diameter were observed , of a firm consistency, adhered to superficial planes, covered by red-violet skin and cold **(Fig .1)** . In the right knee , ulcer of 10 cm in diameter, with clear edges, granulomatous background, reddish, barely covered by yellowish secretion and fibrin.

(Fig 2) Hepatomegaly and splenomeglia homogeneous by ultrasound. Chest CT: no injuries

Erythrocyte sedimentation rate 120 mm in the first hour; hematocrit 30%; red blood cells 4.2× 106/ µl; hemoglobin

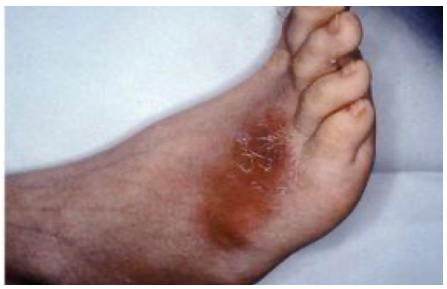

Fig 1: nodules skin lesions on the dorsum of the right foot.

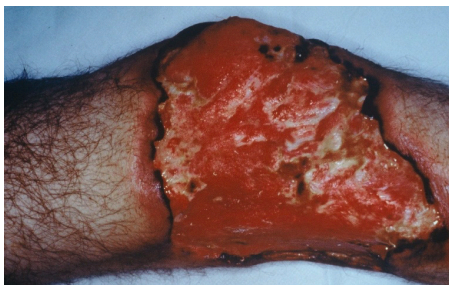

Fig. 2: ulcer of the right knee, with a red and granulomatous background.

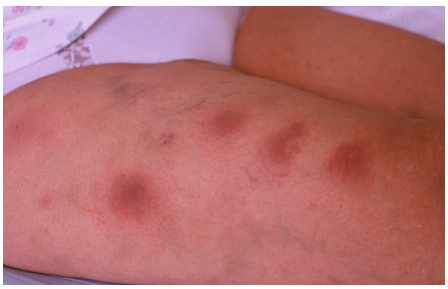

Fig. 3: nodular lesions on the thighs.

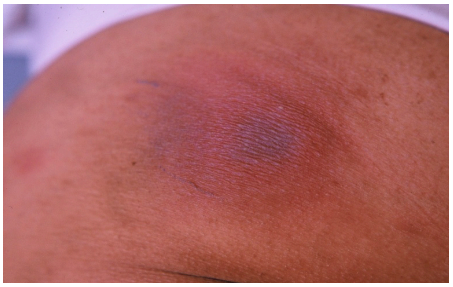

Fig. 4: abscessed lesion in the gluteus.

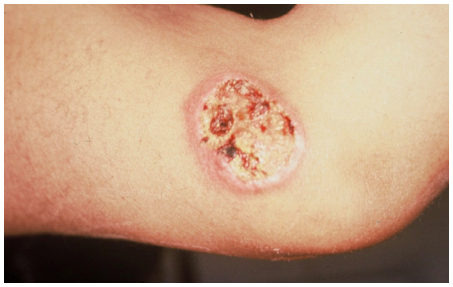

Fig. 5: exulcerated lesion on the elbow.

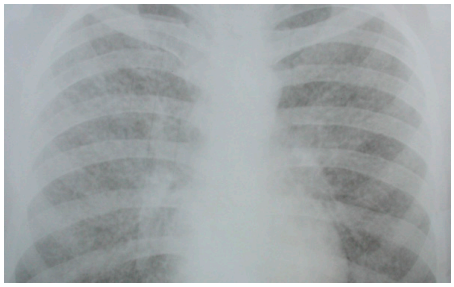

Fig.6: miliary/hematogenous involvement.

9g/dl; leukocytes 2,700/ µl ; neutrophils 83 %; eosinophilic 3 %; basophils 0%; lymphocytes 8%; monocytes 6%; platelets 79,000/ µl ; blood glucose 120mg/dl; uremia 160mg/dl; creatinine 4.1mg/dl; total cholesterol 176 mg/dl; total protein 5.6 g /dl; albumin 1.7 g/dl; globulins 3.9 g/dl; gamma globulins 2.1 g/dl (polyclonal hypergammaglobulinemia); prothrombin time 58%; total bilirubin 1 mg/dl; direct bilirubin 0.3 mg/dl; glutamicooxalacetic transaminase 78 U/ml; glutamicopyruvic transaminase 106 U / ml; alkaline phosphatase 528 U/ml.
Diagnosis of Histoplasmosis, direct examination with the presence of stains compatible with Histoplasma , culture of Hsitoplasma scarification material capsulatum

Case 2: 49-year-old woman with a history of renal TX due to an obstructive urological problem, 10 years before admission. History of multiple treatments for rejection, and renal biopsy confirmation of chronic rejection. Immunosuppression : prednisone 4mg, azathioprine and cyclosporine. Lesions on the anterior face of both thighs with a nodular appearance, indurated, erythematous - violaceous, slightly painful, 2 to 3 cm in diameter **(Fig. 3)**, and another on the right buttock, 7 cm in length, erythematous violaceous with central softening and purulent content. **(Fig 4)** No lung involvement, hepato -splenomegaly, involvement of the three series: anemia, leukopenia and thrombocytopenia , serum albumin 2 g/dl. The aspiration puncture of the gluteal lesion was performed: diagnosis of histoplasmosis by direct examination with Giemsa stain, compatible yeasts and Histoplasma diagnosis. capsulatum, confirmed by the cultures of the material obtained, in addition to the positivity of the blood cultures by lysis-centrifugation. Within a year of completing treatment, breast cancer was diagnosed.

Case 3: 51-year-old woman with a history of kidney transplant, kidney failure due to lupus nephropathy, kidney transplant with a cadaveric donor 4 years prior to admission, admitted in poor general condition, severe malnutrition, anemia, thrombocytopenia , leukopenia, injury to the outside of the right elbow, 4 cm in diameter, exulcerated, with a granulomatous appearance covered by serofibrinous secretion . Fig 5. Impairment of Glasgow level of consciousness from 13 to 15, with minimal pleocytosis 50 cells with lymphocyte predominance in cerebrospinal fluid, mild hyperproteinorrhachia 50 g/dl with normal glycorrhachia . miliary involvement on chest x-ray due to hematogenous spread. Fig. 6 The diagnosis of histoplasmosis was confirmed by scarification of the elbow lesion and Giemsa staining . The blood cultures by lysis-centrifuge were positive, despite the clinical manifestations and the deterioration of the level of consciousness, no development of the liquid was obtained. cerebrospinal.

Case 4: 42-year-old woman who received a kidney transplant from a cadaveric donor, presented a painless erythematous lesion with a slightly phlegmatic appearance on the left hand, which mainly compromised the palm of the hand and fingers, with a violaceous appearance, indurated and swollen . Fig 7. who did not respond to the conventional antibiotic treatment instituted, which is why a skin biopsy was performed, the diagnosis was confirmed by direct examination of material obtained by puncture, with Giemsa staining Fig. 8 and culture positive

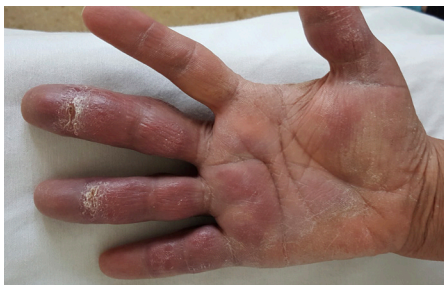
Fig 1.

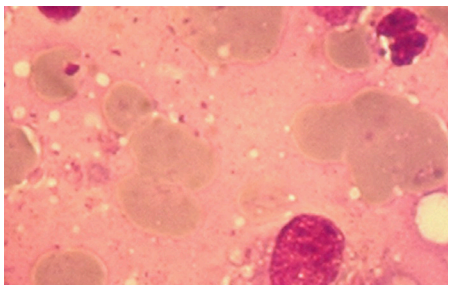
Fig 2: tincion de Giemsa

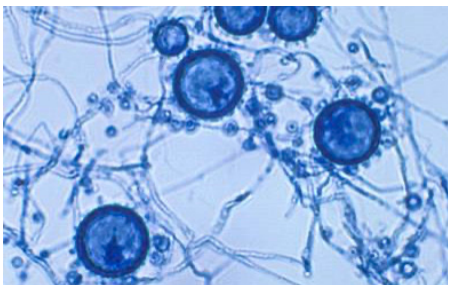
Fig 3: tinta China

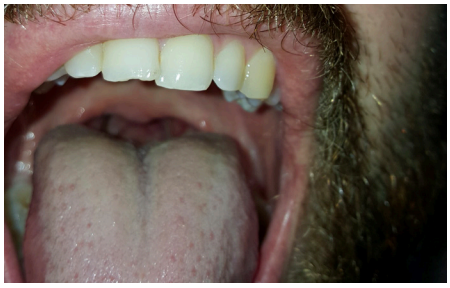
Fig 4: examen de Fresco

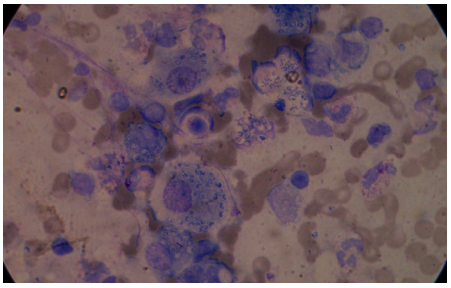
Fig 5.

for Histoplasma capsulatum from skin biopsy. **(Fig 9)**. The patient did not present evidence of dissemination of the infection. He responded favorably to treatment with azoles.

Case 5: A 28-year-old male patient with a 2-year history of kidney transplant from a cadaveric donor, kidney failure secondary to rapidly evolving glomerulonephritis . Months before, pharyngitis began without evidence of bacterial plaques and granulomatous lesions and in some vesicular areas in the fauces, he was treated with amoxicillin- clavulanic acid , which was discontinued when the swab of the fauces was negative for beta-hemolytic Streptococcus . The symptoms worsened and soon after began with discomfort in the nostrils, itching, formation of small crusts and nasal congestion Figure 10, always afebrile course . An axial computed tomography of the maxillary sinuses and facial massif was performed , where the perforation of the cartilaginous portion of the nasal septum and polypidean lesions with a granulomatous appearance were observed , the lesions of the nostrils were scarified, and the almost total resection of said lesions. in addition to the biopsy of the uvula by otorhinolaryngology. The pathological anatomy report revealed fragments of mucosa partially covered by squamous epithelium, in ulcerated sectors, and below it the presence of granulomas with extensive areas of central necrosis, surrounded by a palisade of epithelioid histiocytes with some giant cells and regular infiltrate. lymphocytic, with the presence at the intracellular level of small round or ovoid yeasts with a refringent halo compatible with Histoplasma sp Fig 11. The possibility of all tissue samples and blood cultures by lysis-centrifugation was confirmed . The general condition of the patient was always good and he did not present spinal cord or lung involvement. It evolved favourably. The presentation with mucosal skin involvement with compact granulomas as seen in the chronic disseminated form of the immunocompetent patient , (despite the positivity of the blood cultures in this case), is not a frequent presentation in transplant patients.

The incidence of histoplasmosis in kidney transplant patients, as mentioned above, is low, less than 0.5%, and mortality is close to 10 %. Rarer still is the involvement of the nasal mucosa and larynx in this population. Four cases have been reported in the literature, three kidney transplant patients and one liver transplant. In these cases except for the last patient, the infection presented after 4 years post-transplantation. Fever was an uncommon event and 3 of them presented evidence of dissemination, lung involvement and/or positive blood cultures despite the defensive manifestations of the clinical picture. It is an uncommon diagnosis in renal transplantation, and requires a high index of suspicion. [22]

ASPERGILLOSIS

Invasive Aspergillus infections are relatively infrequent (less than 10% depending on the transplanted organ) in solid organ transplant recipients, and are associated with a high rate of mortality and graft loss. [1-3]

The incidence is in heart transplantation from 3 to 27%, with a mortality of 36 to 67%, in kidney transplantation, from 1.2 to 4%, with a mortality of 4 to 25%, liver transplantation the incidence is from 1 to 4.7% with a mortality of 83 to 88% and in lung transplant: from 8.3 to 23.3%

and mortality of 4.2%.

Taking into account the devastating consequences of invasive aspergillosis in some types of transplants such as lung, some centers consider the use of prophylaxis, which is still controversial, especially if we take into account the multiple interactions between azoles and some immunosuppressants, in addition to the probable selection of resistant fungal pathogens particularly Candida spp . and other filamentous fungi.

Invasive aspergillosis in solid organ transplantation recognizes additional risk factors 13, in lung transplantation: reactivation and/or infection by Cytomegalovirus , post-transplant hemodialysis, history of another case of API in the program at least 2 months prior to diagnosis, mechanical ventilation, use of extracorporeal membrane oxygenation ECMO.

In renal transplantation: bloodstream infections, chronic obstructive pulmonary disease, late recovery of renal function in the immediate post-transplant and/or deterioration of renal function, long period of hemodialysis prior to transplantation, protein caloric malnutrition, corticosteroids in high doses, severe infection due to immunomodulatory viruses and other opportunistic infections, in liver transplantation, MELD score, surgical reintervention, reactivation of Cytomegalovirus infection, kidney failure, hemodialysis, retransplantation, or transplantation in case of fulminant liver failure and in case of lung transplant is very important prior colonization with Aspergillus spp, early ischemia of the airway, reactivation of Cytomegalovirus and rejection.

Diagnosis includes staining of biopsy materials or bronchoalveolar lavage with methenamine silver, Gomori or PAS with a sensitivity of 20 to 70% depending on the specimen obtained and the inoculum and the detection of galactomannans by EIA, blood samples have less sensitivity than material obtained by bronchoalveolar lavage ranging between 67 and 100%.

The polymerase chain reaction -PCR- still requires further standardization.

In all cases, strong clinical suspicion and the evaluation of additional risk factors are fundamental tools that significantly improve the prognosis and make it possible to institute early therapy, a modality that was initially used in transplant patients, they are treatment doses in the face of minimal clinical evidence, with laboratory evidence and based on risk scores.

All the scores used in the diagnosis are based on the measurement of risk and the use of laboratory surrogates, in this case the detection of galactomannans , always in the context of neutropenia.

Their positivity is evidence of angionvasion: a late event with high mortality. [25-26]

The identification of fungal pathogens is very important due to the emergence of strains intrinsically resistant to azoles of Aspergillus fumigatus . due to mutations, and from other species in Aspergillus fumigatus complex ; which includes A. lentulus , A. viridinutans and A. calidoustus , the latter being intrinsically resistant to azoles and is an emerging when antifungal prophylaxis is used .

Lastly, the presence of Perergillus terreus , intrinsically resident to amphotericin . In this sense, the use of PCR and other molecular biology techniques such as MALDI-TOF are of great help in deciding the best therapeutic option.

Other techniques such as the lateral flow device together with quantitative PCR are a promising tool in this patient population. [4-24-25]

Treatment: voriconazole is the first option in the treatment of invasive Aspergillus infections despite the multiple interactions with commonly used immunosuppressants such as cyclosporine, tacrolimus and sirolimus and its main adverse effects such as hepatotoxicity , neurological and psychiatric disorders, much less frequently observed . with isavuconazole .

Amphotericin Liposomal is the second option in the treatment of this condition.

The use of echinocandins is still under study and does not provide convincing data. [27-28]

CANDIDA

It is the most common invasive fungal infection in the population of solid organ transplant recipients.

With a cumulative incidence of 1.9%, it generally occurs during the first 3 months post-transplantation 30-31 except in distant periods in which risk factors reappear, such as bloodstream infections , antibiotic selection pressure , intra- abdominal and urinary tract infections.

candida albicans it is the isolated microorganism in 50% of cases; candida krusei and C. guillermondii are less common in solid organ transplant recipients , risk factors for invasive Candida disease are age, broad-spectrum and prolonged antibiotic therapy, presence of central venous catheters, long- term bladder catheter, parenteral nutrition, diabetes, post-transplant dialysis requirement, surgical corrections and infections related to urological procedures such as fistulas, lymphocele , placement of ureteral catheters for prolonged periods, recent infection and/or reactivation of Cytomegalovirus and slow recovery of post-transplant renal function, colonization or infection due to contamination of the preservation fluid in which the organ is transported before transplantation, can have catastrophic consequences such as suture dehiscence, mycotic aneurysm and graft loss with high mortality. [29]

Diagnosis of invasive Candida infection is based on isolation of the organism from sterile sites.

The sensitivity of blood cultures is close to 70% but it is not a diagnosis of invasion, but in patients with proven invasive disease, the use of 1-3 beta D glucan increases the sensitivity and specificity to 70 and 87%, respectively. The possibility of blood cultures plus the detection of 1-3 beta D glucan greatly increases the sensitivity of the diagnosis up to 98%.
Species identification is critical in deciding treatment and has predictive value in prognosis.
Germ tube identification is a rapid method to identify Candida albicans and C. dubliniensis , the peptide nucleic acid in situ hybridization techniques fluorescent hybridization loops (PNA-FISH) identify C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, and C. krusei . in blood cultures.
Chromogenic agar is very useful and quickly distinguishes the presence of Candida albicans , C tropicalis and Candida krusei through the production of different pigments. twenty-one.Susceptibility can be predicted based on species and local epidemiology.
Fluconazole resistance in Candida albicans is less than 1% while C. parapsilosis and C. glabrata they usually exhibit resistance to fluconazole and voriconazole in the order of 3 and 8%, respectively. Almost all isolates are sensitive to echinocandins and amphotericin.
Echinocandins have rapid fungicidal activity and are 75 % effective. [37-39]
Due to their efficacy, safety profile, and few interactions with immunosuppressants, they are the first choice, especially if there was prior exposure to azoles .
In mild to moderate disease, 3 to 5 days of treatment with echinocandins can be administered and then treatment with fluconazole can be discontinued , except if infection with resistant isolates is suspected.
Locally invasive mycoses present 79% skin involvement, soft tissues and joints, 21% can cause invasive systemic infection, with frequent involvement of the central nervous system.
This spread depends on the immune status of the transplant patient and additional risk factors, diabetes, diabetic ketoacidosis , high-dose corticosteroid therapy, and neutropenia. The causal agents are frequently dematiaceous fungi such as Exophiala , Phialophora , Cladophialophora, Dactylaria, Alternaria. [32-33]
Front door is usually by traumatic inoculation; they are environmental saprophytes and develop chronic nodular or cystic infections such as pheohyphomycosis subcutaneous or cystic , 34 common in diabetic patients , presenting as nodules subcutaneous cells of variable size located in the deep dermis, delimited , not painful, that spontaneously drain purulent material where the presence of yeasts and hyphae with brown pigments can be observed.

Most reported cases of pheohyphomycosis occur in patients with immunodeficiency, usually patients receiving chemotherapy or induced neutropenia. A high percentage of these infections recognize traumatic inoculation and occasional dissemination depending on the immune status of the patient.
These agents are characterized by the presence of melanin in the cell wall, which imparts the characteristic dark color of the conidia and hyphae. Melanin is a virulence factor in many fungal species such as Cryptococcus and Wangiella. dermatitis . [3-4]

Other infections caused by filamentous fungi in addition to Aspergillus or Mucorales are on the rise, for example Purpureocillium lilacinun (formerly called Paecilomyces lilacinus) in most reports as a potential cause of disseminated opportunistic infection with multiorgan involvement. In our series, it is a very frequent cause of locally invasive infection.
P. lilacinum It is a saprophytic hyaline fungus widely distributed in the environment, soil, decomposing material, water currents, streams and even in hospital water supplies. It is also known to persist in saline solutions or skin lotions and may be potentially resistant to processes of sterilization.

It is a frequent cause of keratomycosis , it has a tropism for ocular structures and in immunosuppressed patients it is a frequent cause of systemic infections with involvement of multiple parenchyma, especially in oncohematological patients , bone marrow transplantation, especially in the presence of neutropenia, and the administration of high-dose corticosteroids.
26.7% of purpureocillium infections occur in transplant patients and diabetics.
Infection by this agent requires a differential diagnosis with Aspergillus and other hyaline fungi since it can present a therapeutic problem due to the variable sensitivity to antifungals and the poor response to medical treatment, which is why it often requires surgical excision, being a growing therapeutic problem. .

The cases of infections in kidney transplant recipients reported in the literature are approximately 10 (9.9%).
The non-disseminated forms, despite the potential for systemic invasion, are 63.4 %, of these, 36.6% present cutaneous involvement and 23.8% deep dermis involvement.
The diagnosis is established through cultures in more than 97% of cases, in which whitish colonies are observed at first that turn purple or violaceous and the presence of phialides with fusiform conidia can be observed on microscopic examination and in specimens Tissue biopsy samples may occasionally present some degree of sporu-

lation (phialides and conidia), the appearance of these reproductive structures as observed in vitro evidences the local predisposing factors and the degree of immunosuppression of the patient.
Diagnosis through molecular biology with ribosomal subunit sequence analysis or proteomic profiling with MALDI-TOF/MS allows definitive identification.
Overall mortality is 21.8%, but in invasive clinical forms, 50% is attributable to Purpureocillium infection, most with hematogenous spread. The mortality of skin and soft tissue infections has low mortality (12.5% to 16.2 %) in the reported series.
The variable sensitivity to antifungals , even to amphotericin , is an emerging therapeutic problem, voriconazole , posaconazole and ravuconazole seem to be the best treatment options despite the fact that some cases of natural resistance to voriconazole have been described and many strains of Purpureocillium exhibit high MICs for itraconazole .
In our experience, cases of skin involvement and deep dermis required, in addition to medical treatment, surgical removal of the lesion. [37-38]

MUCORMICOSIS

It is an invasive fungal infection with high mortality and difficult and aggressive treatment. It affects immunocompromised hosts, especially those diagnosed with hematological diseases and bone marrow transplant recipients, but it also affects diabetic patients, major burn patients, patients with trauma and devitalized tissues, drug addicts, surgical patients and recipients of solid organ transplants.

In this population, the rate of post-transplant infection is 2 to 14% (5). It is associated with prolonged hospital stays and with lower survival 2 years after diagnosis, and 2 to 6% of invasive fungal infections correspond to mucormycosis. [6]

The most frequent form of presentation is rhinocerebral (33%), followed in order of frequency by pulmonary involvement (25.9%), disseminated forms (14.5 %), involvement of the transplanted kidney (11.5%), skin involvement (7.5%) and other less common sites such as gastrointestinal, peritoneum and vascular prostheses. 39-40
The disseminated forms are those with the highest mortality, following in importance the involvement of the central nervous system, lung and transplanted kidney. (76 to 42%). The diagnosis of the disease can be microbiological if there is fungal growth in sterile samples .
Serological tests have not shown utility. Microbiological diagnosis is complicated because cultures are often negative except for skin samples.
Blood cultures have poor sensitivity, and the culture yield of airway biopsies is low (30%) .The presence of a non-septate filamentous fungus in non- sterile samples is not a diagnostic criterion for disease, 19 ; in these cases the confirmation diagnosis is histopathological. [32]
For this reason, at the slightest clinical suspicion , an immediate biopsy of the lesions is mandatory. Direct microscopic examination is a technique that is simple to perform, rapid , sensitive, inexpensive, and specific when calcofluor white staining is used , which greatly sensitizes the diagnosis. Mucorales are identified by the presence of ribbon-like hyaline filaments with hyphae with irregular walls and variable diameter, although somewhat wider compared to other hyaline filamentous fungi, these grow irregularly branched at angles greater than 45 with no or very few septa.
Identification can be carried out by immunohistochemical techniques and molecular procedures. [41-42]
Treatment includes correction of predisposing factors, antifungal therapy , extensive surgery, and reduction of immunosuppression. In patients receiving combined treatment with lipid-formulated amphotericin and posaconazole , the survival rate appears to be higher.

Case 1: 48-year-old male patient, kidney transplant recipient 4 years before admission, with a history of chronic kidney failure due to diabetic nephropathy, immunosuppressive treatment: prednisone 4 mg, cyclosporine A and azathioprine . No recent history of rejection. He had been hospitalized 6 months prior for urosepsis with good evolution. He worked in gardening tasks. He consulted for extensive injuries, the first **(Fig-11)**. in the deltoid area of fluctuating appearance, not painful, without phlogosis with sites of spontaneous drainage of purulent material. The other lesion **(Fig-12)** was found on the same arm on the back of the hand near the arteriovenous fistula used for dialysis , where indurated nodular lesions were observed, not painful, without phlogosis of 4 and 5 cm in diameter. united at the base with drainage sites of pus and desiccated crusts. in direct fresh examinations, the presence of coenocytic thick filaments with thick irregular branching compatible with mucorales could be observed in the first lesion , **(Fig 13)**. in the lesion on the back of the hand, the presence of thinner septate filaments of irregular branching with the presence of pigments compatible with dematiaceous fungi. **(Fig 14)**. Although the patient presented figures of hyperglycemia, he did not present diabetic ketoacidosis. CT scans of the brain, paranasal sinuses, chest, abdomen, and pelvis showed no lesions. Cultures revealed characteristic colonies but organisms could not be typed. **(Fig 15)** The evolution of the patient was favorable, the deltoid lesion was drained , with an extensive surgical incision, with drainage of abundant puru-

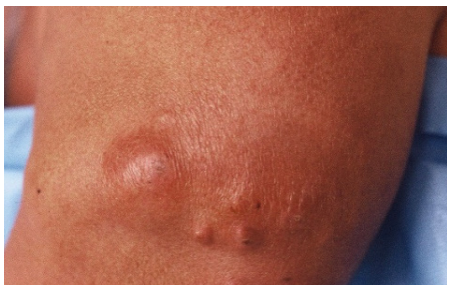
Fig. 11: lesion fluctuante en zona deltoidea.

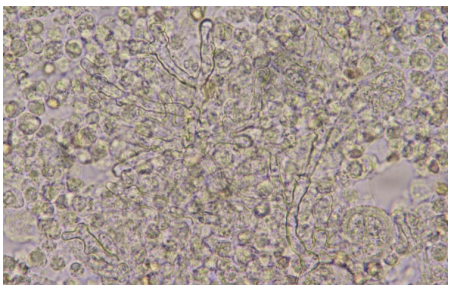
Fig. 13: filamentos gruesos no tabicados.

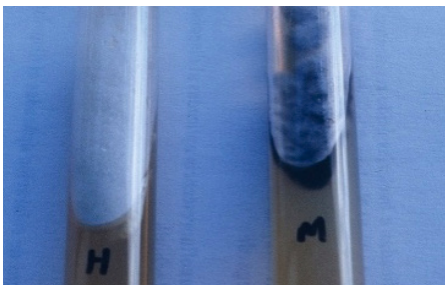

Fig. 15: cultivos.

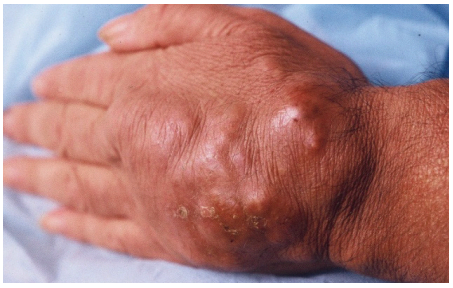
Fig. 12: lesiones pseudoquísticas en mano.

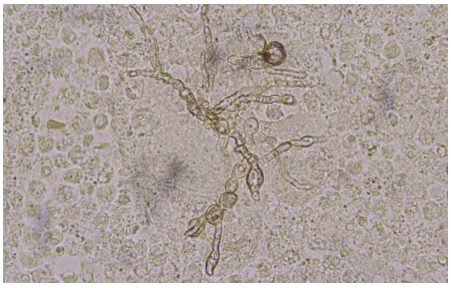
Fig 14: filamentos tabicados pigmentados.

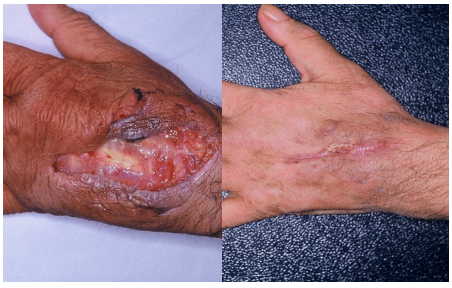
Fig. 16-17

lent material, and the infectious tumors on the back of the hand were surgically resected. Both lesions healed for the second time without requiring plastic surgery. Figures. [16-17]

Case 2: A 57-year-old patient who received a kidney transplant, 3 months before admission, a history of chronic kidney failure due to hypertensive nephropathy, good post-transplant evolution , with recovery of kidney function, presented urinary tract infection due to multiresistant gram-negative bacilli, required prolonged treatment with intravenous antibiotics and after 14 days of treatment, in the place where he had the venoclysis , he presented multiple lesions with an exophytic , indurated, non-suppurative vegetating appearance, the largest of 3.5 cm and others of smaller size but with similar characteristics with small scabs. showing scant seropurulent material that drained spontaneously. **(Fig 18)**. Material was taken for direct examination culture where filaments and the presence of septate hyphae were evidenced, **(Fig 23)**. confirmed Purpureocillium infection lilacinum , (formerly: Pacylomyces lilacinus) with the characteristic colonies and the identification with the cultures. **(Fig 20-21-22)** treatment with itraconazole was started with little response, it was only possible to obtain a cure with the surgical excision of the lesions. **(Fig 20)**. The possible contamination and/or traumatic inoculation of the elements used in the fixation of the venous catheter was not ruled out.

Case 3: 34-year-old male patient 1 year after the transplant, (history of renal failure of unknown aetiology), with good evolution of renal function without a history of rejection, He presented a nodular-looking lesion of 1 cm in diameter, on the left leg. **(Fig 24)**. Referred riding without major protections and close contact with equines. An aspiration puncture of the lesion was performed, obtaining purulent material that was completely drained. Purpureocillium infection was confirmed through cultures. lilacinum . He restored ad integrum with the maneuver performed.

TRICHODERMA LONGIBRACHIATUM

It is a ubiquitous, brown, filamentous fungus that grows on wood and soil. Microscopically, it presents hyaline, septate , branched hyphae, the presence of conidiophores, and long right-angled branches ending in phialides. T. longibrachiatum usually causes infection in reptiles and rarely in humans. The species involved in infections in immunosuppressed patients are T. viride, T. koningii, T. pseudokoningii and T. longibrachiatum . There are 9 cases reported in the literature, all in immunosuppressed patients with skin infections with hematogenous spread, especially in patients receiving bone marrow transplants or acute leukemia. Due to the frequent skin involvement, the diagnosis in most cases is through cytodiagnosis, biopsy and cultures of the material obtained. In locally invasive mycoses, it is mandatory in these patients to exclude disseminated forms and routine blood cultures by lysis-centrifugation and complete CT scan should be done. [43]

Case 1: a 40-year-old patient, diagnosed with renal failure of unknown aetiology, undergoing dialysis treatment 2 years prior to kidney transplantation with a cadaveric

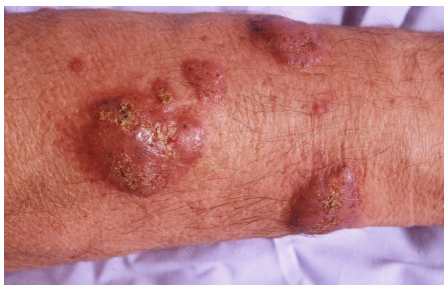

Fig. 18: lesiones exofiticas

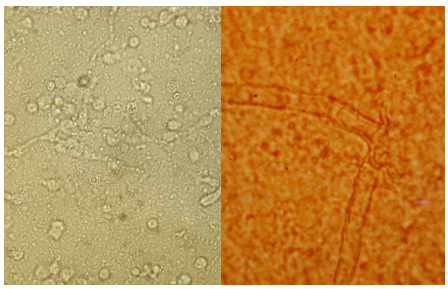

Fig. 19

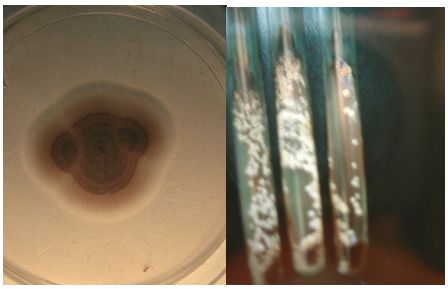

Fig. 20- 21: colonias de Purpureocillium ligeramente amarromadas de bordes liláceos.

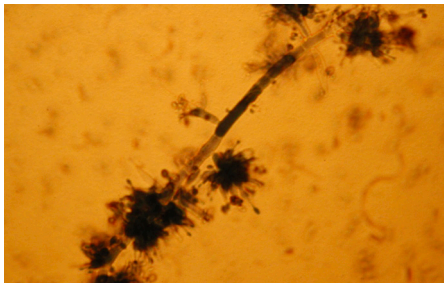

Fig. 22: micelio de fructificación Conidióforo de Purpureocillium.

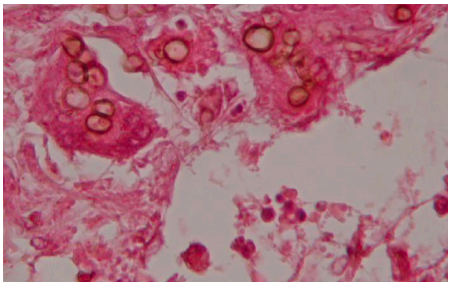

Fig. 23

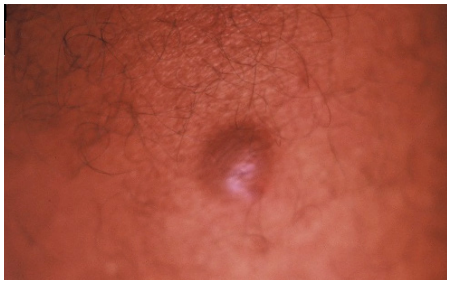

Fig. 24

donor, multiple transfusions, and a history of continuous ambulatory peritoneal dialysis and several episodes of peritonitis. Hypertensive, with non- chagasic dilated cardiomyopathy. He was a gardener by profession, although he did not report a traumatic episode or suspicion of inoculation with vegetables. He received initial immunosuppressive treatment with thymoglobulin , cyclosporine, mycophenolate , and corticosteroids. He required immediate post-transplant dialysis but recovered kidney function. On admission, he had good kidney function, Urea 0.7 g/dl, creatinine; 1.8g/ dl, Hto: 23%, serum albumin 3.1 g/dl and total protein 6.4 g/l. I present a lesion on the external face of the right knee, a nodular lesion with an infiltrative aspect , granulomatous erythematous violaceous, 2 by 3 cm in diameter with compromise of the subcutaneous cellular tissue. Fig 24 and 25. In the purulent material obtained by spontaneous drainage and biopsy of the lesion, hyaline filaments were observed Fig 26. and the presence of Trichoderma was confirmed by culture longibrachiatum . Start treatment with itraconazole , without response, exeresis was decided surgery , Fig 27. with good recovery. the patient presented a diagnosis of primary cerebral lymphoma one year after the episode and died shortly after.

CONCLUSIONS

The diversity of etiological agents in transplant patients is very extensive.The chronology of the appearance of infections is of great help, but knowledge of the epidemiology of mycoses and of the multiplicity of factors that determine the real risk of infections (some of them with high mortality), the various clinical manifestations -which depend of the patient's immunological status- require a high degree of suspicion, the preparation and measurement of risk scores, and require diagnostic methodology, sometimes simple but effective, such as cytodiagnosis and direct examination of lesions from clinical samples.
Sometimes, state-of-the-art techniques are needed that provide us with the necessary support and the specificity and sensitivity required for the treatment to be fast and effective.
But the knowledge and experience that we have wanted to transmit during these almost 30 years of work at the Dr. Cosme Argerich General Hospital for Acute Patients, we hope will be useful to our young colleagues.

ACKNOWLEDGEMENTS:
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