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Note

Invasive scedosporiosis in lung transplant recipients: A nine-year retrospective study in a tertiary care hospital

Elisa Ibáñez-Martínez[a,b,◊], Amparo Solé[c,f,*,◊], Antonio Cañada-Martínez[d], Carlos F. Muñoz-Núñez[e], Amparo Pastor[c], Beatriz Montull[c], Patricia Falomir-Salcedo[b,f], Amparo Valentín[b,f], José Luis López-Hontangas[b,f], Javier Pemán[b,f]

[a] *Unidad de Biomarcadores y Medicina de Precisión, Instituto de Investigación Sanitaria La Fe, València, Spain*
[b] *Servicio de Microbiología, Hospital Universitari i Politècnic La Fe, València, Spain*
[c] *Unidad de Trasplante Pulmonar, Hospital Universitari i Politècnic La Fe, València, Spain*
[d] *Servicio de Bioestadística y Bioinformática, Instituto de Investigación Sanitaria La Fe, València, Spain*
[e] *Servicio de Radiología, Hospital Universitari i Politècnic La Fe, València, Spain*
[f] *Grupo de Investigación Infección Grave, Instituto de Investigación Sanitaria La Fe, València, Spain*

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ABSTRACT

Background: *Scedosporium* species and *Lomentospora prolificans* (*Sc/Lp*) are emerging molds that cause invasive disease associated with a high mortality rate. After *Aspergillus*, these molds are the second filamentous fungi recovered in lung transplant (LT) recipients.
Aims: Our objective was to evaluate the incidence, risk factors and outcome of *Sc/Lp* infections in LT recipients at a tertiary care hospital with a national reference LT program.
Methods: A nine-year retrospective study was conducted.
Results: During this period, 395 LT were performed. Positive cultures for *Sc/Lp* were obtained from twenty-one LT recipients. Twelve patients (incidence 3.04%) developed invasive scedosporiosis (IS). In 66.7% of the patients with IS the invasive infection was defined as a breakthrough one. The main sites of infection were lungs and paranasal sinuses. Most of the patients received combination antifungal therapy. The IS crude mortality rate after 30 days was 16.7%, and 33.3% after a year.
Conclusions: Our study highlights improved survival rates associated with combination antifungal therapy in LT recipients and underlines the risk of breakthrough infections in patients with allograft dysfunction on nebulized lipidic amphotericin B prophylaxis. In addition to pretransplant colonization, acute or chronic organ dysfunctions seem to be the main risk factors for IS.

Escedosporiasis invasora en receptores de trasplante de pulmón: un estudio retrospectivo de nueve años en un hospital de referencia

Palabras clave:
Scedosporium apiospermum
Lomentospora prolificans
Infección fúngica invasora
Escedosporiasis
Lomentosporiasis
Trasplante de pulmón

RESUMEN

Antecedentes: Las especies de *Scedosporium* y *Lomentospora prolificans* (*Sc/Lp*) son mohos emergentes que causan infecciones invasivas con una alta tasa de mortalidad. Después de *Aspergillus*, estos hongos filamentosos son los más frecuentemente aislados en pacientes receptores de trasplante de pulmón (TP).
Objetivos: Nuestro objetivo fue evaluar la incidencia, los factores de riesgo y la evolución de la infección por *Sc/Lp* en receptores de TP en un hospital terciario de referencia nacional para TP.
Métodos: Se realizó un estudio retrospectivo de nueve años.

* Corresponding author.
E-mail address: sole_amp@gva.es (A. Solé).
◊ Equal first authors.

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Resultados: Durante este período se realizaron 395 TP. Veintiún receptores de TP tuvieron cultivos positivos para *Sc/Lp*, y doce de ellos desarrollaron escedosporiasis invasiva (SI) (incidencia del 3,04%). Se observaron infecciones de brecha en el 66,7% de los pacientes con SI. Los principales focos de infección fueron el pulmón y los senos paranasales. La mayoría de los pacientes recibieron terapia antifúngica combinada. La tasa de mortalidad bruta de la SI a los 30 días fue del 16,7%, ascendiendo al 33,3% al cabo de un año.

Conclusiones: Nuestro estudio destaca la mejora de la tasa de supervivencia asociada a la terapia antifúngica combinada en TP y subraya el riesgo de infecciones de brecha en pacientes con disfunción de injerto en profilaxis con anfotericina B lipídica nebulizada. La colonización previa al trasplante junto con la disfunción aguda o crónica del injerto parecen ser los principales factores de riesgo de la SI.

The incidence of invasive infections by *Scedosporium apiospermum* complex and *Lomentospora prolificans* (*Sc/Lp*) in lung transplant recipients (LTR) is increasing.[4,11] In fact, *Sc/Lp* are the most recovered molds in respiratory samples after *Aspergillus* in LTR. These fungi are a major concern due to their high intrinsic resistance to antifungal drugs[4,10,13] and have been considered an absolute contraindication for transplantation in some programs.[16,17] In addition, therapeutic approach has a wide variability among centers and the evidence used is largely based on case studies which have shown highly inconsistent results.[14] Our aim was to evaluate the incidence, risk factors and outcome of *Sc/Lp* infection in LTR patients at La Fe University Hospital (Valencia, Spain), a tertiary care hospital with a national reference lung transplant (LT) program.

Clinical data of LTR from whom *Sc/Lp* was isolated during 2011–2019, were reviewed. Updated EORTC/MSG consensus definitions and International Society for Heart and Lung Transplantation (ISHLT) criteria were used to classify invasive scedosporiosis (IS) episodes as "proven", "probable" or "possible".[7,12] Colonization was defined as positive respiratory samples in asymptomatic patients with absence of characteristics of endobronchial/lung lesions.[1,9,11] *Sc/Lp* species were isolated and identified using the standard morphological methodology.[5] The antifungal susceptibility testing with a microdilution method (SensititreYeastOne, Thermo-Fisher, Madrid, Spain) was performed only on isolates causing therapeutic failure.

Thirty-day crude mortality and related mortality rates, as well as one-year evolution rate, were reviewed.

During the study period, a total of 395 LT were performed in our center. Standard immunotherapy consisted of oral cyclosporine (2.5 mg/kg/12 h), tacrolimus (0.15 mg/kg/12 h), intravenous mycophenolate mofetil (1500 mg/12 h during three weeks, and 1000 mg/12 h from then on) and methylprednisolone (0.5 mg/kg/day and tapering down during 3 months to 10 mg/day). Induction immunosuppression is not used in our center and, therefore, it was not used in these patients (i.e. anti-lymphocyte globulin or basiliximab). Acute cellular rejection (ACR) episodes associated with grade A2 or higher clinical symptoms were treated. In order to optimize immunosuppression maintenance, the first-line treatment of ACR consisted of intravenous methylprednisolone 10 mg/kg daily for 3 days, followed by prednisone, starting at 0.5 mg/kg/day and decreasing by 5 mg every five days until the baseline dose. Antifungal prophylaxis in LTR in our center consists of nebulized lipidic amphotericin B. Antifungal preemptive therapy in LT patients previously colonized with *Sc/Lp* in our center includes any combination of triazoles (voriconazole or posaconazole) and terbinafine. Isavuconazole had not yet been approved when this study started.

There were twelve invasive infections by *Sc/Lp* within this population (incidence 3.04%), and all of them underwent bilateral LT, except for patient #6. Among these episodes, seven affected the lungs, three involved skin and soft tissue, and two were disseminated infections. All of them were caused by *Scedosporium apiospermum* complex, except for two pulmonary infections which were caused by *L. prolificans*. Clinical features, treatment and outcome are summarized in Table 1.

Pretransplant colonization by *Sc/Lp* has been related to early infection (first month post-transplantation) with poor outcome, despite antifungal prophylaxis.[8,11] There were eight patients colonized by *Sc/Lp* before transplantation, three of them developed IS in the early post-operative period (less than 15 days after surgery), and one of them (#1) died after a thoracic dissemination in the context of increased immunosuppression due to acute rejection. Based on our experience, aggressive pretransplant antifungal prophylaxis with a triazole and intensive preemptive antifungal therapy after surgery are crucial to having a good outcome and should be implemented in pretransplant colonized receptors.

Interestingly, the isolation of *Sc/Lp* in the respiratory tract of LTR does not necessarily mean invasive disease in the late post-transplant period.[17] In our study, 9 LTR in whom *S. apiospermum* complex (4 patients) or *L. prolificans* (5 patients) were isolated in respiratory samples (sputum, bronchoaspirate or bronchoalveolar lavage) never developed IS (42.8%). *Sc/Lp* were found from 3 to 50 months after LT, and only two of these patients received a preemptive antifungal treatment. Thus, microbiological findings should be interpreted always in conjunction with patient risk factors, clinical signs and imaging techniques.

There were eight infections in patients suffering either chronic lung allograft dysfunction (4 patients), or acute rejection (4 patients); interestingly, three out of four late infections (more than six months after LT had passed), occurred during chronic (2/4), or acute rejection episodes (1/4). Intensification of immunosuppression was the main risk factor for the fungal infection, as shown in a previous study.[8] Cutaneous infection by *Sc/Lp* usually occurs by traumatic inoculation or by hematogenous dissemination. In our study, the three cutaneous infections found were caused by *S. apiospermum* complex more than two months after transplantation. These patients were receiving intensive immunosuppressive therapy due to graft rejection episodes. All of them recovered very slowly despite prolonged antifungal treatment (from six months to years of treatment), possibly because the initial focus could not be controlled or a more extensive surgical debridement could not be performed. In absence of previous trauma, a hematogenous dissemination from an undetected respiratory tract colonization was considered the origin of these three episodes.

Breakthrough infections were found in 8 of 12 patients (66.7%), six by *S. apiospermum* complex and two pulmonary infections by *L. prolificans*; all but one LTR had received prophylaxis with inhaled amphotericin B lipid complex. This is very similar to what is described in the literature, where 67–100% of IS in LTR are breakthrough infections.[2,15,19]

Table 1
Clinical characteristics of lung transplant recipients with scedosporiosis/lomentosporiosis.

Patient	Cause of LT	Age/sex	Species	Time from LT[a]	Colonization before LT	Organ rejection	Sample (*n*)	Treatment	MIC (mg/l)	Type of infection	BI/antifungal	Alive at 30 days	One-year evolution
1	CF	24/F	*S. apiospermum* complex	4 d	Yes	Acute	Pericardial tissue (1) Bronchial biopsy (1) BAL (3) Pleural liquid (1)	VOR (IV, INH) TER (O)	0.5 NA	Proven disseminated IS	Yes/CAS, AMB (INH)	Yes	Dead [d]*(48 days)
2	CF	20/F	*S. apiospermum* complex	14 d	Yes	No	Surgical wound exudate (2) BAL (5) BAS (4)	VOR (O)	NA	Disseminated IS	Yes/AMB (INH)	Yes	Favorable
3	CF	37/F	*S. apiospermum* complex	15 d	Yes	No	Bronchial suture (1) BAL (3) BAS (5) Sputum (3)	AMB (INH) POS (IV/endobronchial/INH) TER (O) Surgical debridement	>8 0.25 NA	Proven pulmonary + tracheobronchitis IS	Yes/MICA (IV)	Yes	Favorable
4	COPD	59/M	*S. apiospermum* complex	20 d	No	Acute	Bronchial biopsy (1) BAL (6)	AMB (INH, IV) POS (IV, INH, O) TER (O)	4 0.5 NA	Proven pulmonary IS	Yes/AMB (INH)	Yes	Dead[c]
5	CF	31/M	*S. apiospermum* complex	29 d	No[d]	Acute	BAL (1) Sputum (1) Bronchial biopsy (2)	AMB (INH) POS (O, INH) TER (O)	NA NA	Proven pulmonary IS	Yes/AMB (INH), MICA (IV)	Yes	Favorable
6	COPD	66/F	*S. apiospermum* complex	8 m	No	No	BAL (1)	POS (O)	NA	Probable pulmonary IS	Yes/AMB (INH)	Yes	Dead
7	BRQ	47/F	*S. apiospermum* complex	18 yr	No	CLAD	BAL (2) Sputum (3)	AMB (INH) POS (IV) TER (O)	NA NA NA	Possible pulmonary IS	No	Yes	Favorable
8	CF	21/F	*L. prolificans*	12 d	No[e]	No	BAL (1) Sputum (1) BAS (1)	AMB (IV) VOR (IV)	NA NA	Probable pulmonary IS	Yes/AMB (IV)	Yes	Favorable
9	CF	34/M	*L. prolificans*	15 yr	No	CLAD	BAL (1)	AMB (IV, INH) VOR (O)	NA NA	Possible pulmonary IS	Yes/AMB (INH), POS (IV), CAS (IV)	No[f]	Dead
10	COPD	61/M	*S. apiospermum* complex	4 m	No	CLAD	Skin biopsy (1) Wound exudate (3)	→ AMB (IV) VOR (O), TER (O, T) AMB (IV) POS (O) MICA/CAS (IV) Surgical debridement		Cutaneous + osteomyelitis	No	Yes	Chronicity Skin healing >5 years
11	COPD	57/M	*S. apiospermum* complex	2 m	No	CLAD	Skin biopsy (1) Wound exudate (2)	VOR (O, IV), TER (O, T), → + MICA (IV)	0.25 NA NA	Cutaneous	No	Yes	Relapse
12	COPD	59/M	*S. apiospermum* complex	20 m	No	Acute	Wound exudate (1)	VOR (O, IV) TER (O, T)	NA NA	Cutaneous	No	Yes	Favorable

LT: lung transplantation; MIC: minimal inhibitory concentration; BI: breakthrough infection; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis; BRQ: bronchiectasis; M: male; F: female; d: days; m: months; yr: years; CLAD: chronic lung allograft dysfunction; BAL: bronchoalveolar lavage; BAS: bronchoaspirate; AMB: amphotericin B; POS: posaconazole; TER: terbinafine; VOR: voriconazole; MICA: micafungin; CAS: caspofungin; INH: inhaled therapy; IV: intravenous therapy; O: oral therapy; T: topic therapy; NA: not available; IS: invasive scedosporiosis; CMV: cytomegalovirus. → Arrows indicate changes in treatment.

[a] Time elapsed from transplantation to IS diagnosis (d: days; m: months; yr: years).

[c] Attributable dead with acute organ rejection, growth of *S. apiospermum* complex in bronchial biopsy and coinfection with CMV.

[d] Chronic colonization with *S. apiospermum* complex three years before transplantation, with no isolates ever after.

[e] One single isolate of *L. prolificans* two years before transplantation, with no isolates ever after.

[f] Not attributable dead with intestinal CMV with massive digestive bleeding. Co-infection with *Fusarium oxysporum*.

[b] Attributable dead in 48 days.

Although *L. prolificans* has been associated with sepsis and positive blood cultures in neutropenic patients, we did not find this species in blood or causing disseminated infection. Therefore, neutropenia appears to have more impact on the incidence and severity of disseminated *Sc/Lp* infections than solid organ transplant immunosuppression regimens.[6]

The *Sc/Lp* infection was treated in all our patients, except for patients #2 and #6, with combined antifungal therapy, being the most frequent combination liposomal amphotericin B plus a triazole (with or without terbinafine). Furthermore, in patients #1, #3, #4 and #5, aerosolized and/or endobronchial instillation of posaconazole was added to the conventional treatment, as we have reported before.[18]

One year after the *Sc/Lp* infection 4 of the 12 patients (33.3%) had died (Table 1). In two of these four patients (#1 and #4) the death was related to the fungal infection, both by *S. apiospermum* complex. Patient #1 died after developing a disseminated infection on the 48th day of the immediate postoperative period in spite of salvage therapy administered with posaconazole local instillations. During the first month post-diagnosis only one patient died (#9), but her dead was not related to IS.

In most studies, the *Sc/Lp* crude mortality rate reported is very high, ranging 30–70%, even 100% for *L. prolificans;* mortality is usually associated to dissemination, central nervous system infection, fungemia, and lack of recovery of neutrophils.[4,8,10] To our knowledge, the global mortality observed in our study (33.3%) is one of the lowest ever reported. This low mortality could be explained by the lack of central nervous system infections, the few *L. prolificans* infections and the use of the combination of triazoles (systemic and local) and lipidic amphotericin B (nebulized or intravenous) in an attempt to reproduce the synergy reported in vitro.[3] Based on this experience, combination therapy including voriconazole plus lipidic amphotericin B, terbinafine, and local therapy with triazoles should be considered to treat refractory cases of tracheobronquial or lung infections by *Sc/Lp* species, although this proposal must be confirmed in further studies.

The present study had some limitations. The observational and retrospective design, together with the small sample size, did not allow to identify the risk factors for *Sc/Lp* infection nor the clinical aspects associated to a favorable outcome. Furthermore, the morphological identification of the species could not be confirmed by molecular techniques since most of the isolates were not stored.

Despite the limitations of the study, our case series is the largest invasive Sc/*Lp* infection in LTR case series ever published in Europe, and we present the lowest attributable mortality ever reported. This low mortality could be related to the aggressive antifungal therapy used post-lung transplant as preemptive and targeted therapy. The incidence of IS in LTR in our setting is 3.04%, with an increase in the risk of breakthrough infections for patients with allograft dysfunction and prolonged prophylaxis with nebulized lipidic amphotericin B. Finally, based on our experience, we highly recommend the implementation of combined antifungal therapy in IS as well as regular monitorization in *Sc/Lp* colonized LTR with acute or chronic lung dysfunction.

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