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DONOR-RELATED COCCIDIOIDOMYCOSIS TRANSMITTED THROUGH LEFT-LIVER TRANSPLANT TO A CHILD RECIPIENT IN A NONENDEMIC AREA

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Abstract: This first observation of donor-transmitted coccidioidomycosis in a pediatric liver-transplant recipient underlines a rare condition in transplanted patients in a nonendemic area. This transmission was observed after a liver split, the patient being contaminated by the left liver while the right-liver recipient was not.

Key Words: abdominal coccidioidomycosis, solid organ transplantation, pediatric, liver transplant, transmission

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Coccidioidomycosis is a fungal infection caused by *Coccidioides immitis*/*Coccidioides posadasii* that is endemic in the arid regions of the American continent.[1] The infection, transmitted via the inhalation of arthroconidia, occurs after an environmental exposure or after the reactivation of a latent infection; solid organ recipients have a significant risk of disseminated fungal infection and a lower survival rate.[1] We report a 6-year-old girl who presented with disseminated coccidioidomycosis related to her receiving a left-liver graft from an infected donor.

CASE REPORT

A 6-year-old girl living in France underwent left-liver transplantation for biliary atresia. Because of nonprimary graft function (17-year-old donor), a second transplantation (from a 47-year-old suicide victim) was performed 7 days later. Histologic evaluation of the second graft disclosed no significant lesions, but a donor's chest radiograph and computed tomographic scan revealed a 12-mm calcified pulmonary nodule, which was considered to be the consequence of a past infection and was not removed. The recipient's immunosuppressive regimen consisted of basiliximab (10 mg on days 1 and 4 after first transplantation), corticosteroids (2 mg/kg/d), tacrolimus and mycophenolate mofetil. On day 9 after the second transplantation, the first liver biopsy revealed histologic features of acute rejection, and methylprednisolone was added to the regimen (one 10 mg/kg corticosteroid pulse), associated with increasing targeted tacrolimus blood trough concentrations. On day 13, 3 corticosteroid pulses (10 mg/kg/d) were administered because of persisting acute rejection, followed by a tapering of the oral corticosteroid dosage during subsequent days.

Concerning the second donor, no fungus was found in the conserved graft fluid. On day 7 posttransplantation, mycologic cultures on the lung graft bronchoalveolar lavage fluid had grown a glabrous, greyish white filamentous colony. On day 47, the presence of *Coccidioides* spp. was confirmed by polymerase chain reaction (PCR). On further investigations, donor family revealed that he had visited South America 4 months ago. The donor had visited Peru with certainty; other countries visited are unknown. He also had a cough a few weeks before his death.

Because of the suspicion of sepsis in the recipient, antifungal therapy (caspofungin) was initiated 2 days after the first transplantation in a dosage of 60 mg/m^2 (50 mg) on the first day and then 30 mg/m^2 (25 mg) until 3 days after the second transplant. Seven days after that, in view of the lung graft–positive mycologic cultures on the lung graft bronchoalveolar lavage, intravenous fluconazole (3 mg/kg/d) was introduced for 3 weeks. Oral amphotericin B (50 mg/kg/d) was administered until 3 months posttransplantation as a digestive decontamination. The PCR results were received on day 47, and the recipient's serology was negative. In a context of normal liver function findings, oral corticosteroids were stopped 3 months posttransplantation and amphotericin B 1 week later.

Four months after transplantation, although the patient's liver function remained normal while receiving tacrolimus (blood

TABLE 1. Reported Cases of Donor-derived Coccidioidomycosis

Donor (Reference)	Country (Endemic area)	Recipient	Coccidioides	Organ Transplanted	Organ Involved	Steroid Pulses	Antifungal Prophylaxis Before Symptoms (Reason)	Beginning of the Symptoms	Outcome
36 yr male, prior extrapulmonary coccidioidomycosis[4]	US (No)	46 yr male	Yes	Liver	Liver + disseminated	No information	No information	Death on PTD 13	Death on PTD 17
		28 yr male	Yes	1 kidney	Kidney + disseminated	3 steroid pulses PTD 11/12/13	No information	PTD 17	Death on PTD 19
		58 yr female	No	1 kidney	Uninfected	No information	For 3 mo (other recipients infected)	Asymptomatic	Survived
Young female, hiking in desert[5]	US (Yes)	21 yr male	Yes	2 lungs	Lungs	No	No	PTD 6	Survived
		No other recipients known	No information	No information	No information	No information	No information	No information	No information
30 yr female, Mexican visite[6]	US (No)	61 yr male	Yes	2 lungs	Lungs + disseminated	No	No	Immediately	Death on PTM 1
		No other recipients known	No information	No information	No information	No information	No information	No information	
Visited Arizona[7]	France (No)	58 yr male	Yes	1 lung	Lungs	3 steroid pulses at PTM 3 Pulses at PTM 35	For first 6 mo (*Aspergillus*) and PTM 11–23	PTM 40	Survived
		No information	No	1 kidney	Uninfected	No information	No information	Asymptomatic	Survived
		No information	No	1 kidney	Uninfected	No information	No information	Asymptomatic	Survived
		No information	No	Liver	Uninfected	No information	No information	Asymptomatic	Survived
52 yr female, Southern California[8]	US (Yes)	66 yr male	Yes	Heart	Heart + disseminated	No	No information	PTD 16	Death on PTD 22
		40 yr male	Yes	1 kidney	Kidney + disseminated	No	No information	PTD 13	Death on PTD 18
		23 yr male	Yes	1 kidney + liver	Lungs	No	No information	PTD 14	Survived
38 yr female, no information for travelling[9]	Portugal (No)	62 yr male	Yes	1 kidney	Cerebral	3 steroid pulses at PTM 1	No information	PTD 58	Death on PTM 4
		No information	No	1 kidney	Uninfected	No information	No information	Asymptomatic	Survived
		No information	No	1 kidney	Uninfected	No information	No information	Asymptomatic	Survived
		No information	No	1 liver	Uninfected	No information	No information	Asymptomatic	Survived
		No information	No	1 heart	Uninfected	No information	No information	Asymptomatic	Survived
History of living in an endemic area[10]	US (No)	42 yr Nicaraguan female	Yes	Liver	Thyroiditis, lungs	No	No	3–4 mo PT	Survived
		No information	No	No information	Uninfected	No information	No information	Asymptomatic	No information
22 yr male, immigrated in US[11]	US (No)	19 yr African-American male	Yes	1 kidney	Lungs	No	No information	PTD 29	Survived
		45 yr female	Yes	1 kidney + pancreas	Lungs + kidney	No	No information	PTD 26	Death on PTD 36
		62 yr female	Yes	2 lungs	Lungs	No	Yes, PTD 3 (*Aspergillus*)	PTD 50	Survived
		63 yr female	No	Liver	Uninfected	No information	No information	Asymptomatic	Survived
		18 yr male	No	Heart	Uninfected	No information	Yes, PTD 53	Asymptomatic	Death
47 yr male, Peru trip	France (No)	6 yr French girl	Yes	Left liver	Abdominal and lungs	1 steroid pulse at PTD 9 and 3 pulses at PTD 13/14/15	Yes, PTM 3	PTM 4	Survived
		Male	No	Right liver	Uninfected	No	Yes	Asymptomatic	Survived
		Male	Yes	2 lungs	Lungs	No	Yes	Asymptomatic	Death
		No information	No	1 kidney	Uninfected	No	No	Asymptomatic	Survived
		No information	No	1 kidney	Uninfected	No	No	Asymptomatic	Survived
		No information	No	Heart	Uninfected	No	No	Asymptomatic	Survived

PT indicates post transplantation; PTD, posttransplantation day; PTM, posttransplantation month.

trough concentrations: 5–8 µg/L) and mycophenolate mofetil, she developed fever with abdominal pain and vomiting. An abdominal ultrasound was suggestive of appendicitis. Surgical exploration found a 5-cm pseudotumor mass in the terminal portion of the ileum, with thick bowel loops and a preperforation appearance. The appendix was healthy and therefore totally independent of the injury. This mass and the appendix were removed. Histologic examination revealed the presence of spherules containing eosinophilic endospores compatible with the diagnosis of coccidioidomycosis. The final diagnosis was confirmed by a molecular analysis of the ileal resection using a pair of universal fungal primers (NL1/NL4) targeting the D1/D2 domain of 28S DNA. Further analysis of the sequences revealed 99.676% similarity and 99.838% overlap with *C. immitis/C. posadasii* [using the GenBank database (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE_TYPE=BlastSearch) and CBS database CBS-KNAW Fungal Biodiversity Centre, an institute of the Royal Netherlands Academy of Arts and Sciences (http://www.cbs.knaw.nl/Collections/BioloMICSSequences.aspx?file=all)]. Coccidioidomycosis was undetected in any other tests (serology, blood culture and tissue culture).

The day after surgery, the abdominal symptoms and fever were persisting, and the patient developed bilateral pulmonary infiltrates with nodules. Neurologic investigations were normal. Voriconazole (15 mg/kg/d intravenous) was initiated for 72 hours, followed by intravenous amphotericin B (3 mg/kg/d) for 55 days. The patient was subsequently advised as to the need for lifelong oral fluconazole treatment (7 mg/kg/d). The tacrolimus dose was reduced (2–4 µg/L) and mycophenolate mofetil withdrawn. At 2 years posttransplantation, the patient is asymptomatic and continues to receive combination therapy with tacrolimus (0.2 mg twice-daily) and fluconazole (100 mg twice-daily or 8.5 mg/kg/d). Her liver function parameters are normal.

Five adult patients were transplanted with organs from the same donor (both lungs, right liver, both kidneys and heart). The patients who received the lungs and right liver were treated with fluconazole for 8 days after transplantation. The lung recipient's bronchoalveolar lavage had *Coccidioides* on day 50 after transplantation. He was treated with amphotericin B but died 9 months after transplantation; fungal infection was still present. The heart and 2 kidney recipients did not receive any antifungal prophylaxis. After 2 years of follow-up, these 4 remaining patients are all doing well, and none have received any corticosteroid pulses or presented with fungal infection.

DISCUSSION

Endemic in the arid regions of the American continent, coccidioidomycosis is not observed elsewhere.[1,2] Necessary conditions for growth are arid climate, little altitude, extremely hot summers, mild winters and alkaline, sandy, silty soil. The journey in South America was considered as the only exposure to *Coccidioides* spp. The donor visited Peru with certainty but this country is not know as an endemic area. Because of the lack of information obtained from the family, we couldn't know if other countries were visited.

In immunocompetent patients, infection is usually asymptomatic or associated with influenza-like illness or pneumonia.[1,2] In most cases, coccidioidomycosis occurs after an environmental exposure or the reactivation of a previous latent infection. In patients transplanted in endemic areas, the principal problem is de novo coccidioidomycosis, with an incidence ranging from 1.4% to 6.9%.[2] After inhalation, the lungs are the first organ to be affected by the spores, but infection disseminates to other organs as well, the most common being the skin, skeleton and central nervous system.[3]

The first important finding from our case was that donor organs can be a source of a transmissible agent. As shown here, a maximum amount of information about the background of donors, and particularly whether they have lived in or travelled to endemic areas, is of crucial importance to diagnosing cases of coccidioidomycosis.[2] To the best of our knowledge, only 8 cases of coccidioidomycosis linked to solid organ transplant donors have so far been reported (Table 1).[4–11] Our observation was unusual because it was the first case reported in a child. Moreover, only 2 of the 8 contaminated donors were European,[7,9] and in both cases, the transplant teams in Europe were not initially aware of the fact that the donor had stayed in an endemic area and might be infected.

Our case report also suggests that the location of the infection may unnecessarily be linked to the transplanted organ (Table 1).[4–11] Our patient received a contaminated liver and presented with an abdominal mass and secondarily with severe lung disease. We strongly suspected a peritoneal cavity contamination during transplantation rather than spores contained in the liver, which pass through the intestine and secondarily in the peritoneum. Another case reported coccidioidal pneumonia in a lung-transplant recipient after positive findings in the donor's lymph node.[5] It should be noted that the donor's calcified pulmonary nodule was not attributed to coccidioidomycosis as it is an unusual presentation (generally these are uncalcified).

Our observation also emphasizes the fact that abdominal coccidioidomycosis is a rare and highly misleading condition.[3] Indeed, after transplantation, there has been few reported cases of abdominal coccidioidomycosis in adult heart-transplant[3] or liver-transplant recipients. In our patient, coccidioidomycosis first presented as an intestinal infection mimicking appendicitis and was linked to a mass in the ileum. Moreover, in transplanted children, this presentation was suggestive of lymphoma induced by immunosuppressive therapy, which was indeed the primary diagnosis and underlined the crucial role of the pathologist in such cases.

Disseminated infections have been associated with several risk factors, which include male gender, pregnancy, blood group B, children and the elderly, African and Asian ancestries and immunocompromised patients.[1] As in our case, the treatment of acute rejection (eg, high-dose corticosteroids or antilymphocyte therapy) can be considered as a risk factor for coccidioidomycosis after solid organ transplantation. Our patient had received high-dose corticosteroids to treat rejection, but this type of treatment was noted in only 3 of the 13 adults with donor-derived infection,[3,6,8] and it was not recognized as a risk factor by all authors.[2] Interestingly, only the recipient of lungs was infected. The other organs from the same donor (right liver, heart and kidneys) were transplanted successfully without any contamination. Donor to recipient transmission can be spotty, and coccidioidomycosis is not always transmitted in every organ transplanted from an infected donor. Approximately, 70% of posttransplant cases of coccidioidomycosis occur during the first year after surgery, and this includes de novo infections in patients remaining in an endemic area.[2] In the entire series of 8 donors reported as being infected, 13 infected and 11 noninfected recipients were observed (Table 1). In addition, 11 of the 13 infected patients had not received prophylactic antifungal therapy, and the infection started between the sixth and ninetieth days after transplantation. Our patient received oral fluconazole as prophylaxis for 3 weeks. She presented the symptomatic infection 3 weeks after the discontinuation of digestive decontamination with amphotericin B (and 3 months after the discontinuation of oral fluconazole). It is important to note that oral amphotericin is not the expected prophylaxis against the cocci infection, neither

would caspofungin. Like our patient, 2 adults received early antifungal prophylaxis (lung transplantation and an initial suspicion of aspergillosis).[7,11] One patient was treated with itraconazole for 23 months and presented with pulmonary symptoms 17 months after stopping the prophylaxis and 5 months after corticosteroid pulses for acute rejection.[7] The other patient was treated with voriconazole and was asymptomatic at 5 months of follow-up.[11] The mechanism for the transmission of *Coccidioides* to recipients remains unclear but could be linked to a latent infection in the donated organs and the immunologic status of the recipient.

In conclusion, the case of this child highlights the point that coccidioidomycosis in recipients transplanted with organs from a suspected donor requires an exhaustive evaluation of the donor that includes serologic testing, chest imaging and, as in our case, PCR or mycologic culture at 25°C (up to 40°C on Sabouraud) of respiratory samples and in particular, whenever possible, histologic examination of the graft.[12]

At present, primary donor-transmission prophylaxis with fluconazole (400 mg daily) or itraconazole (200 mg twice-daily) is recommended. If recipient lives in an endemic area, its duration should be adapted to the risk of de novo infection.[2,12] If at risk for donor-derived coccidioidomycosis and receiving antifungal prophylaxis with echinocandin or inhaled aerosolized or oral amphotericin B, additional prophylaxis with an azole should be added.[12] The treatment undertaken for the patient may have not been the one recommended by guidelines, but they are American and adapted to the epidemiologic situation of the US. It seems that there are no similar guidelines for French or even European.

First-line therapy for coccidioidomycosis is fluconazole (400–800 mg daily). Intravenous amphotericin B (5 mg/kg/d) or voriconazole can be used in the event of severe infection or as salvage therapy, respectively. Lifelong secondary prophylaxis with fluconazole is also recommended.[12]

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CLINICAL PROFILES OF RESPIRATORY SYNCYTIAL VIRUS SUBTYPES A AND B AMONG CHILDREN HOSPITALIZED WITH BRONCHIOLITIS

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Abstract: In this analysis of a prospective, multicenter study of children hospitalized with bronchiolitis, 925 had respiratory syncytial virus (RSV)-A and 649 had RSV-B. Overall, bronchiolitis severity did not differ by RSV subtype. However, among children with RSV-only bronchiolitis, those children with RSV-A had higher risk of intensive care treatment (odds ratio, 1.31; 95% confidence interval, 1.00–1.71; $P = 0.048$) when compared with those having RSV-B.

Key Words: RSV, subtype, bronchiolitis, severity

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Bronchiolitis is the leading cause of hospitalization in young children, and occurs commonly during the winter months due to respiratory viral infections.[1] Of the multiple viral etiologies, the most frequent is respiratory syncytial virus (RSV). Two antigenically different RSV subtypes exist, A and B. These 2 subtypes co-circulate during the same season, but in general, 1 predominates.[2] Although, some studies have shown that RSV-A is associated with an increased disease severity,[2–4] others have shown that either RSV-B is more severe[5] or that the 2 subtypes have equivalent severity.[6,7] Most of these studies included 1 winter season or had small sample sizes, and in general used nonpolymerase chain reaction (PCR) diagnostics which in most may have omitted the confounding effects of viral coinfections or led to ascertainment bias. Therefore, our objective was to determine whether RSV subtype is independently associated with increased disease severity in a multicenter, multiyear sample of children hospitalized for bronchiolitis that utilized PCR diagnostics.

MATERIALS AND METHODS

Study Design

This is a secondary analysis of the 30th Multicenter Airway Research Collaboration prospective cohort study of children hospitalized with bronchiolitis. Study design and data collection