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Case report

Disseminated histoplasmosis in a kidney liver transplant patient from a non-endemic area: A diagnostic challenge

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ABSTRACT

Disseminated histoplasmosis is a rare opportunistic infection in non-endemic areas, where the disease is often diagnosed late. The spectrum of clinical manifestations is broad and life-threatening complications occur.

We present a detailed case of a kidney liver transplant patient with disseminated histoplasmosis in a non-endemic area. Our case highlights the wide range of pathogens to consider in the immunocompromised patient, the delayed diagnosis of Histoplasmosis Capsulatum in non-endemic areas and the possibility of severe gastrointestinal disease. We also briefly review diagnostic tests and treatment options.

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Introduction

Opportunistic infections are common among transplant patients and often present with nonspecific clinical manifestations. A wide range of potential pathogens should be considered and delayed diagnosis after extensive investigation is frequently observed. We report a case of disseminated histoplasmosis in a kidney liver transplant patient from a non-endemic area.

Case report

A 63-year old woman with a medical history of combined liver and kidney transplantation due to autosomal dominant polycystic

kidney disease in 2016 was referred because of iron deficiency anemia and a persistent cough.

Approximately one year prior to admission, the patient had a colonoscopy because of a positive fecal occult blood test, which showed the presence of diverticulosis and internal hemorrhoids. Approximately 6 months later a control colonoscopy and a gastroscopy were planned because of worsening anemia with iron deficiency. In addition, a few weeks before presentation, the patient developed a non-productive cough and a low-grade fever. A chest X-ray revealed multiple bilateral patchy lung infiltrates. This was confirmed by computed tomography (CT), raising the suspicion of an underlying opportunistic infection or lymphoproliferative disorder (Fig. 1).

Upon admission, the patient reported an ongoing dry cough, fatigue, intermittent fever and night sweats. She had noticed a weight loss of 3 kg in the last 3 months. On examination, body temperature was 37.9 °C, oxygen saturation was 98 % while breathing ambient air, other vital signs were normal. She looked pale but was comfortable. The lungs were clear on auscultation, with no crackles nor rhonchi. There were no lymphadenopathies noted, further clinical examination was unremarkable. Laboratory

Abbreviations: CT, computed tomography; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; H&E, hematoxylin and eosin staining; PCR, polymerase chain reaction; PET/CT, positron emission tomography-CT; PTLD, post-transplant lymphoproliferative disorder; TB, tuberculosis.

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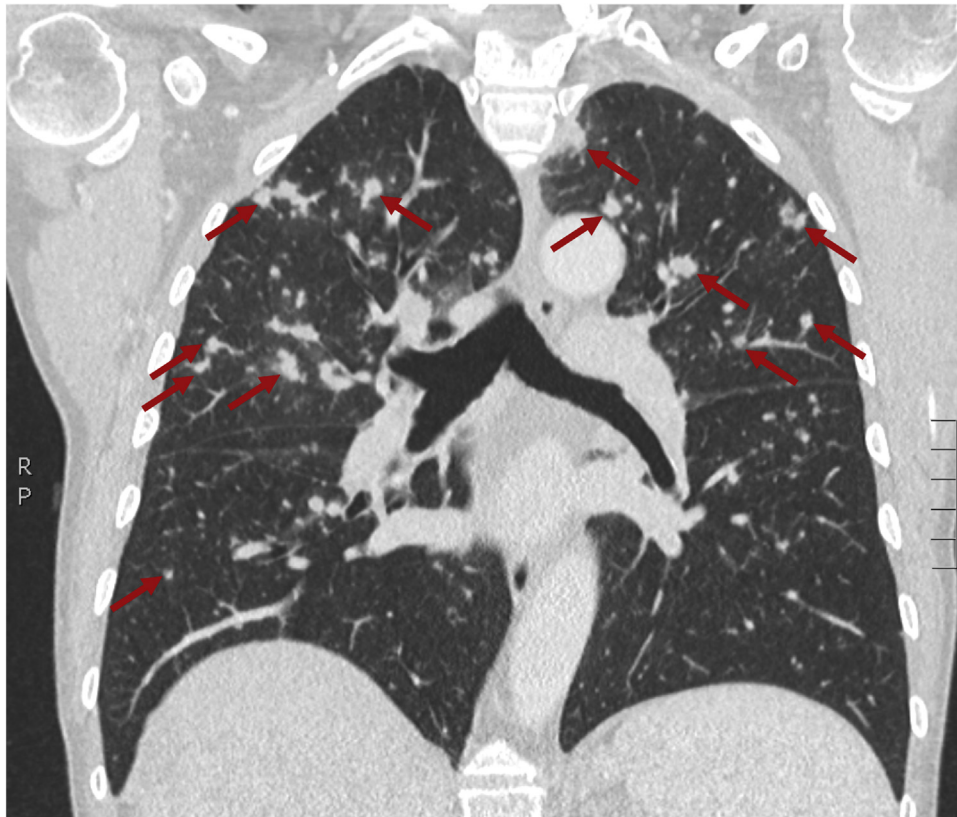


Fig. 1. Chest CT shows multiple pulmonary patchy infiltrates.

Table 1

Laboratory data.

	Reference range	Admission	Start itraconazole	Discharge	6 months of treatment
Hemoglobin (g/dl)	12.0–16.0	8.1	7.8	9.9	10.5
Hematocrit (%)	37–47	25	24	32	33
White-cell count (per μ l)	4000–10000	5.49	8.98	4.49	4.06
Neutrophils (%)	38.0–77.0	81.5	92.8	84.5	76.7
Eosinophils (%)	<6.0	1.5	0.6	1.1	2.7
Lymphocytes (%)	20.0–50.0	9.7	3.8	9.1	14.0
Monocytes (%)	2.0–10.0	7.3	2.8	5.3	6.2
Basophils (%)	<1.0	0	0	0	0.2
Platelet count (per μ l)	150 000–450 000	318	353	348	272
Sodium (mmol/l)	136–145	138.8	136.5	142	144
Potassium (mmol/l)	3.45–4.45	4.27	4.64	3.95	3.7
Chloride (mmol/l)	98–107	101.6	100.9	101.8	108
Bicarbonate (mmol/l)	22–29	21.9	24.6	26.4	29.0
Calcium (mmol/l)	2.15–2.55	2.44	2.28	2.23	2.61
Phosphate (mmol/l)	0.81–1.45	1.09	1.10	1.07	1.03
Creatinine (mg/dl)	0.51–0.95	1.40	1.48	1.18	0.99
eGFR (MDRD ml/min/1.73m ²)		38	36	46	60
Aspartate aminotransferase (U/l)	<31	15	14	17	18
Alanine aminotransferase (U/l)	<31	8	10	9	11
Gamma-glutamyltransferase (U/l)	<40	21	26	19	18
Alkaline phosphatase (U/l)	35–105	43	39	63	66
Total bilirubin (mg/dl)	<1.18	0.37	0.33	0.53	0.68
C-reactive protein (mg/l)	<5	31.9	87.7	6.7	<5

findings (Table 1) showed a decreased hemoglobin level of 8.1 g/dl (normal value, >12 g/dl), an elevated C-reactive protein level of 32 mg/L (normal value, <5 mg/l), a normal total white blood count with neutrophilic predominance. Electrolytes and liver function were normal. Creatinine level was in line with previous values. Additional medical history included nephrectomy of the right native kidney in 2016 at the time of transplantation and

cytomegalovirus reactivation early after transplantation for which a 3 months course of valganciclovir was administered. Maintenance medication consisted of mycophenolate mofetil 1000 mg daily, tacrolimus 4,5 mg/day and a calcium/vitamin D supplement. The patient was born in Suriname. She lived there until she was 7 years old and then moved to the Netherlands. She moved to Belgium at the age of 11, where she currently resides. There was no

history of recent travels outside Europe. She had never smoked. The donor was a 50 year old male originally from Flanders, Belgium who died from a head trauma in a traffic accident. He had no medical history, took no maintenance medication and had a negative infectious screening at the time of donation except for a positive CMV serology. There were no post-transplant diseases reported in the other organ recipients.

On admission a bronchoscopy was first performed, which was macroscopically normal. Cultures and a respiratory PCR panel of the lavage fluid were obtained. Colonoscopy showed a bulging mass arising from the ileocecal valve, suspicious for a tumoral process from which biopsies were taken (Fig. 2).

Hence, a tentative diagnosis of a colorectal tumor was made. However, given the patient's immunocompromised state and the bilateral patchy lung infiltrates, the suspicion of a concomitant opportunistic lung infection remained.

Considering the hypothesis of colon cancer, additional abdominal imaging was warranted. A positron emission tomography-CT (PET/CT) with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) was performed to evaluate the lung lesions, and as a staging tool for the putative colon cancer. PET/CT showed multiple mesenteric lymph nodes and a tumoral mass in the terminal ileum at the ileocecal valve and one in the descending colon (Fig. 3). These radiographic findings were highly suspicious for an underlying post-transplant lymphoproliferative disorder (PTLD). In contrast, the diffuse pulmonary nodules and opacities throughout both lungs were rather suspected to be of infectious origin. There were hypermetabolic lymphadenopathies in the right lung hilum and at the right-sided pretracheal level (4R).

During the patient's hospital stay, she developed intermittent high-grade fever (40°C) together with increasing C-reactive protein level (100 mg/L). Otherwise she remained in general good condition, without oxygen need. Repetitive blood cultures were all sterile.

In addition, cultures of the bronchoalveolar lavage came back negative, including auramine staining and culture for acid-fast bacilli, as was aspergillus antigen (galactomannan). The

respiratory panel (polymerase-chain-reaction, PCR) showed only the presence of respiratory syncytial virus (RSV), which was being considered clinically irrelevant. PCR for cytomegalovirus and pneumocystis pneumonia were also negative.

Additional blood tests were negative for Epstein-Barr virus DNA but revealed an increased blood level of 1,3- β -D-glucan (90 pg/mL; <60 pg/mL: negative; >80 pg/mL: positive) and negative galactomannan (index 0.3).

Since there was still no clear diagnosis, the patient was referred to the abdominal surgery department for an exploratory laparoscopy with lymph node excision for pathological examination, culture, panbacterial PCR and panfungal PCR.

While awaiting the results of the lymph node specimen, the pathological examination of the ileocecal mass became available. It showed inflammation with lymphocytes and histiocytes without signs of malignancy. In the cytoplasm of the histiocytes rounded organisms were identified (Fig. 4). Grocott's methenamine silver stain revealed organisms morphologically consistent with *Histoplasma capsulatum*, these results were later reproduced on the lymph node biopsy. Eventually, culture and panfungal PCR of the lymph node confirmed the presence of *Histoplasma capsulatum*.

A diagnosis of disseminated histoplasmosis with pulmonary and intestinal involvement was convincingly made and the patient was started on high dose itraconazole (loading dose of 200 mg three times daily for three days, subsequently twice daily). At that time, we took a thorough lifelong travel history which revealed travels to North America (New York City and Washington D.C.), Suriname and Indonesia more than 20 years prior to transplantation.

The patient remained febrile throughout the first two weeks of antifungal therapy. Itraconazole blood concentrations were within the therapeutic range (1–2 mg/L). Tacrolimus oral dose had to be reduced from 4.5 mg daily to 0.5 mg/day as a result of the known drug-drug interaction between itraconazole and tacrolimus in order to maintain target concentrations. Approximately after one month of treatment, the patient was discharged from the hospital while continuing to have a cough and fatigue, whereas the fever

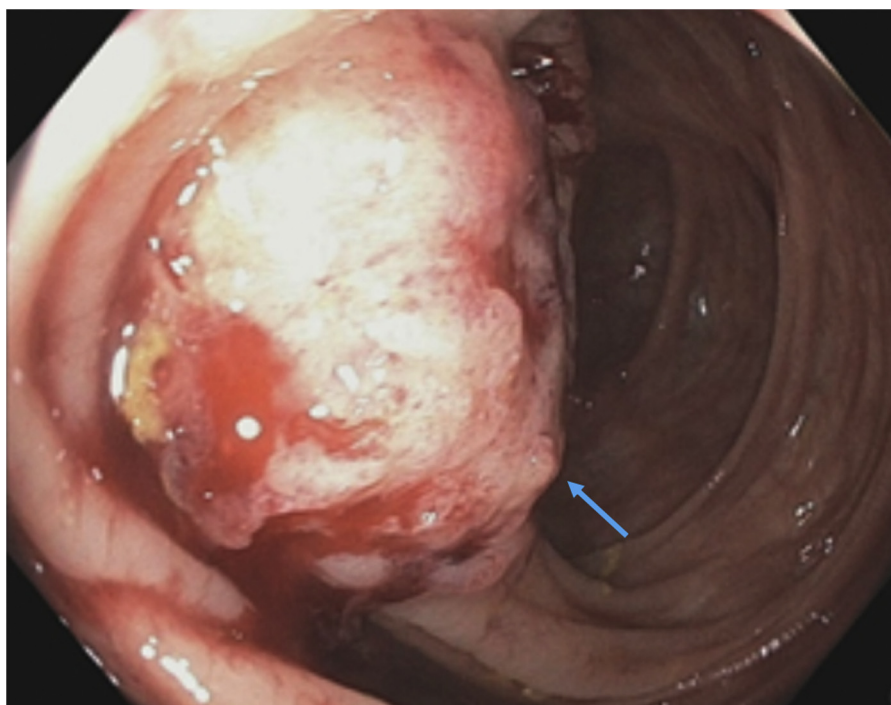


Fig. 2. Colonoscopy shows a bulging mass at the ileocecal valve.

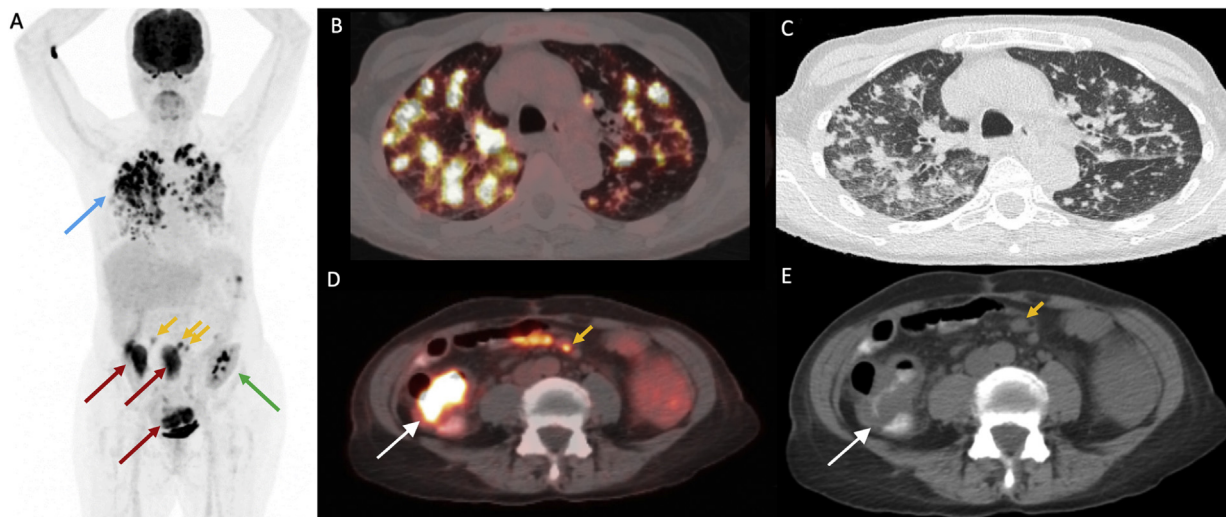


Fig. 3. ¹⁸F-FDG PET/CT scan. (A) Maximum intensity projection (MIP) image. (B, C) multiple highly hypermetabolic pulmonary infiltrates. (D, E) hypermetabolic tumoral mass (arrow) at the ileocecal valve and hypermetabolic abdominal adenopathies.

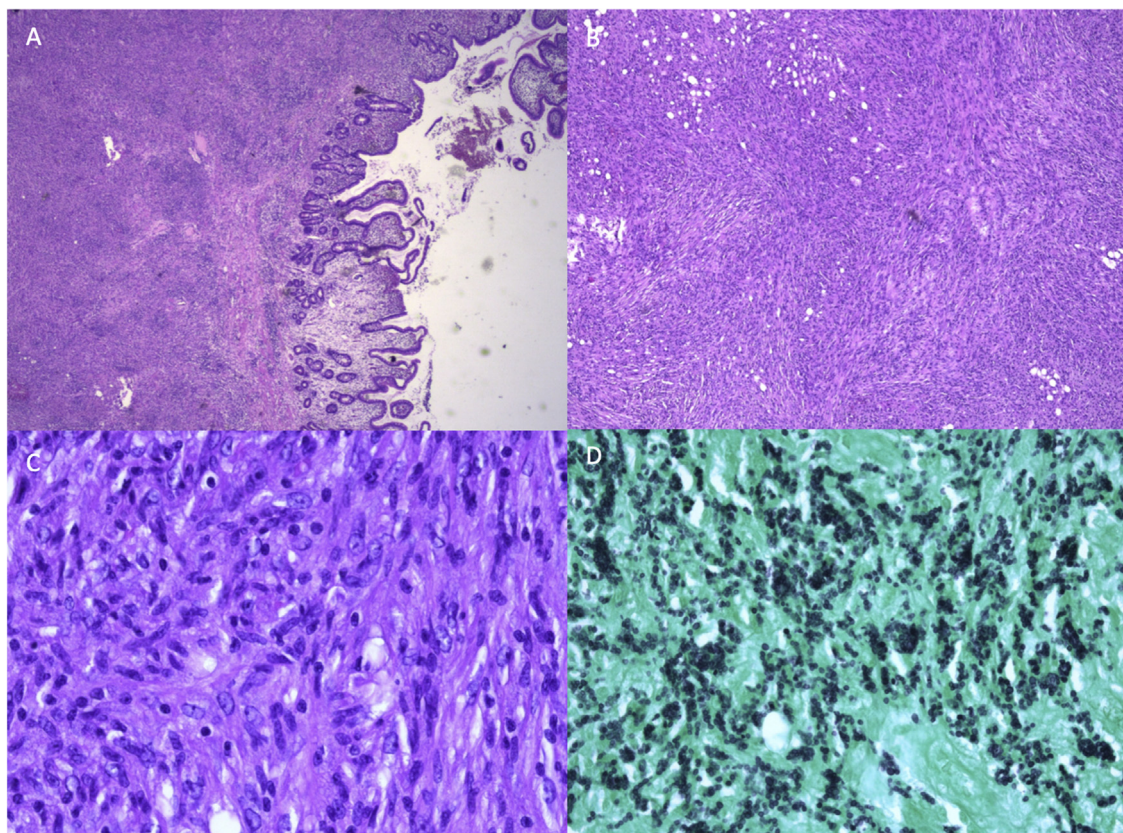


Fig. 4. Biopsy specimens of the ileocecal mass. (A-C) Hematoxylin and eosin staining shows inflammation with lymphocytes and histiocytes. (A: 25 x H&E, B: 100 x H&E, C: 400 x H&E. (D) Grocott's methenamine silver stain shows yeast-like forms.

resolved, and her C-reactive protein level decreased to near normal.

Ten days after discharge the patient was readmitted with diffuse abdominal pain, nausea and vomiting. She reported absence of stool for 5 days. On clinical examination the abdomen was distended, no muscle resistance observed, and bowel sounds were reduced. CT revealed a small bowel obstruction secondary to thickening of an ileal intestinal segment. The patient was

conservatively managed with intravenous fluid, a nasogastric tube in suction and she was put on IV posaconazole as IV itraconazole is not available in Belgium. While this strategy initially seemed successful, one-week later symptoms recurred and a decision for surgery was made. Laparoscopic resection of two small bowel segments was performed. Histological examination of both specimens confirmed active histoplasmosis infection as the underlying cause of obstruction. Six out of 10 resected lymph

nodes also showed signs of active infection. After regaining intestinal transit, oral itraconazole was restarted with a 3-day loading dose and continued at a maintenance dose of 2×200 mg/day for a planned duration of 12 months. Five weeks after discharge from the hospital the patient started to have improved appetite and regained weight. Fever and cough had disappeared. A plain chest x-ray demonstrated partial regression of the lung lesions. Itraconazole blood concentration remained within the therapeutic range.

Discussion

This patient presented with anemia, persistent cough and pulmonary infiltrates, a low-grade fever, weight loss and night sweats.

Because the patient was on maintenance immunosuppressive drug therapy since July 2016 for her combined liver-kidney transplantation, the first diagnosis to consider was an opportunistic pulmonary infection. Cytomegalovirus disease was considered, especially given the medical history of CMV reactivation in the immediate post-transplantation period. However, late CMV disease reactivation is rare in the absence of increased immunosuppression. Given the wide variety of presentations of (atypical) tuberculosis, auramine staining and culture for acid-fast bacilli were routinely performed. Pneumocystis jiroveci pneumonia remains common in transplant patients, however because our patient did not require oxygen supplementation at any stage of her disease, the former was less likely the case. Nocardiosis was also withheld in the differential diagnosis as it can present as a pulmonary and/or abdominal infection with lymphadenopathies. More frequently observed, especially among neutropenic patients, is pulmonary aspergillosis which was excluded [1].

A colonoscopy -performed because of overt anemia- revealed the presence of a tumoral mass at the ileocecal valve, further complicating the diagnosis. The patient could have had two concomitant pathologies, however certain types of infections like CMV, TB or nocardiosis may explain both pulmonary and gastrointestinal disease. When the ^{18}F -FDG PET/CT scan showed multiple abdominal lymphadenopathies, another differential diagnosis at that time was post-transplant lymphoproliferative disorder (PTLD). PTLD, in which the EBV virus is a major risk factor, occurs in 3–10 % of the solid-organ recipients [2]. Our patient initially reported weight loss, night sweats and low-grade fever, making PTLD a likely diagnosis. Moreover, the ileocecal mass could perfectly be explained by an underlying lymphoproliferative disease as this is a frequent location of PTLD [2].

Since all microbial cultures and respiratory PCR panels came back negative while the panfungal 1,3- β -D-glucan test was positive, a biopsy for tissue diagnosis was obtained which unexpectedly revealed histoplasmosis in a non-endemic area.

Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum*, is endemic in certain areas in the Americas as well as in parts of Africa and Southeast Asia. However, the highest prevalence is found in the Ohio and Mississippi river valleys. Although rare, autochthonous cases -with no prior history of travel to endemic areas- have been reported, even in Europe. Infection occurs by the inhalation of *H. capsulatum*'s microconidia, which are found in soil contaminated with bird droppings [3–5].

Whereas the infection in an immunocompetent host usually remains asymptomatic, infection of the immunocompromised patient frequently results in disseminated and life-threatening disease [3,4]. Despite the high prevalence of *H. capsulatum* in endemic areas, post-transplant histoplasmosis is uncommon with an incidence of less than 1% [4,6]. In solid organ transplant patients, active histoplasmosis may be acquired by *de novo* infection, reactivation of latent infection acquired prior to

transplantation and by transmission through an infected allograft [3,7,8]. Reactivation most often occurs in the first 2 years post transplantation during maximal immunosuppression. Nonetheless, delayed manifestations -even many years after transplantation- have been reported [3,4,9]. Transmission of histoplasmosis directly by the transplanted organ is rare and often difficult to prove [4,7]. Interestingly, the use of mycophenolate mofetil as immunosuppressive agent has been reported as an independent risk factor for severe disease [4,8].

Our patient probably acquired the infection during her stay in Northern-America, Suriname or Indonesia many years prior to transplantation with reactivation 3 years after transplantation. However, neither donor-derived nor autochthonous infection could be definitely excluded as route for transmission.

The presentation of histoplasmosis varies widely depending on the severity of the disease and the involved organs. It most commonly presents with fever, cough, dyspnea, diaphoresis and weight loss. The most frequently affected organs are the lungs, followed by the bone marrow, liver, spleen, gastrointestinal tract, central nervous system and the skin [4]. Our case accentuates the challenging presentation and the potential severity of gastrointestinal histoplasmosis. Whereas gastrointestinal involvement is commonly reported on autopsy reviews in disseminated histoplasmosis, gastrointestinal disease is rather rare with a prevalence of 3–12 %. Its manifestation is very protean and misleading as it can mimic malignancy, inflammatory bowel disease or other intestinal diseases. Furthermore, it may present with life threatening complications like bowel obstruction, perforation or bleeding [10,11]. The anemia present in our case was not further investigated by bone marrow examination which can lead to rapid diagnosis of histoplasmosis in some situations [12].

In our patient, histoplasmosis was diagnosed by histopathological examination followed by fungal PCR and a positive fungal culture. However, these procedures are time consuming and therefore may delay start of treatment. Newer techniques like antigen detection are more rapid and easier to perform. Antigenuria has the highest sensitivity for histoplasmosis, being positive in 93 % of patients, whereas antigenemia is positive in 86 % of cases [8]. Antigen detection can be used to evaluate therapy response; The Infectious Diseases Society of America (IDSA)-guidelines propose that antigen concentration should be <2 ng/mL before therapy can be stopped [8]. Nonetheless, as in our case, antigen detection assays are not universally available and while the test itself is not very expensive, the international shipment of contaminated human tissue is. The use of antibody tests is less reliable since they are often false-negative in immunocompromised patients with disseminated infection because of an inadequate immune response [4,13,14].

The recommended treatment for severe histoplasmosis (disseminated and CNS involvement) is a lipid formulation of amphotericin B during the first weeks of treatment, followed by oral itraconazole. In mild to moderate disease, itraconazole is the first line therapy [14,15]. The use of newer azole agents like posaconazole is less well studied, although in some case reports it appears to be an effective alternative to itraconazole [16]. In conclusion, this case highlights the challenging aspect of diagnosing histoplasmosis after solid organ transplantation in non-endemic areas where this disease is rarely taken into consideration. Establishing the diagnosis is further complicated by the heterogeneous presentation and the potential mimicry of other diseases. Additionally, this case illustrates the possibility of important gastrointestinal involvement with the risk of serious complications.

Author contribution

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Participated in the diagnostic process.
Participated in the writing of the paper.

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Van Wijngaerden Erik

Participated in the diagnostic process.
Critically reviewed the paper.

Kuypers Dirk

Participated in the diagnostic process.
Participated in the writing of the paper.

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Consent

Written informed consent was obtained.

Statement

We don't know the travel history of the donor but it concerns a man from a non-endemic area.

Declaration of Competing Interest

The authors report no declarations of interest.

References

- [1] Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357(25):2601–14.
- [2] Dierickx D, Tousseyn T, Sagaert X, Fieuws S, Wlodarska I, Morscio J, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. *Leuk Lymphoma* 2013;54(11):2433–40.
- [3] Ashbee HR, Evans EG, Viviani MA, Dupont B, Chrystanthou E, Surmont I, et al. Histoplasmosis in Europe: report on an epidemiological survey from the European confederation of medical mycology working group. *Med Mycol* 2008;46(1):57–65.
- [4] Gajurel K, Dhakal R, Deresinski S. Histoplasmosis in transplant recipients. *Clin Transplant* 2017;31(10).
- [5] Syed TA, Salem G, Kastens DJ. Lower gastrointestinal bleeding secondary to intestinal histoplasmosis in a renal transplant patient. *ACG Case Rep J* 2017;4:e93.
- [6] Brahmandam S, Brahmandam S, Pradhan S. Disseminated histoplasmosis in a solid organ transplant patient with rapid CNS involvement. *Chest* 2019;156(4):A250–A250.
- [7] Limaye AP, Connolly PA, Sagar M, Fritsche TR, Cookson BT, Wheat LJ, et al. Transmission of *Histoplasma capsulatum* by organ transplantation. *N Engl J Med* 2000;343(16):1163–6.
- [8] Assi M, Martin S, Wheat LJ, Hage C, Freifeld A, Avery R, et al. Histoplasmosis after solid organ transplant. *Clin Infect Dis* 2013;57(11):1542–9.
- [9] Majeed A, Kapoor V, Latif A, Zangeneh T. A 30-year delayed presentation of disseminated histoplasmosis in a heart transplant recipient: diagnostic challenges in a non-endemic area. *BMJ Case Rep* 2017;2017:.
- [10] Anderson BR, Marriott J, Bulathsinghala C, Anjum H, Surani S. Gastrointestinal histoplasmosis presenting as an acute abdomen with jejunal perforation. *Case Rep Med* 2018;2018:8923972.
- [11] Kahi CJ, Wheat LJ, Allen SD, Sarosi GA. Gastrointestinal histoplasmosis. *Am J Gastroenterol* 2005;100(1):220–31.
- [12] Fakhfakh N, Abdelmlak R, Aissa S, Kallel A, Boudawara Y, Bel Hadj S, et al. Disseminated histoplasmosis diagnosed in the bone marrow of an HIV-infected patient: first case imported in Tunisia. *J de Mycologie Médicale* 2018;28(1):211–4.
- [13] Guimarães AJ, Nosanchuk JD, Zancopé-Oliveira RM. Diagnosis of histoplasmosis. *Braz J Microbiol* 2006;37(1):1–13.
- [14] Gajurel K, Dhakal R, Deresinski S. Diagnosis and treatment of histoplasmosis in solid organ transplant patients. *Curr Opin Infect Dis* 2018;31(4):301–8.
- [15] Kabir V, Maertens J, Kuypers D. Fungal infections in solid organ transplantation: an update on diagnosis and treatment. *Transplant Rev* 2019;33(2):77–86.
- [16] Kauffman C. Treatment of the midwestern endemic mycoses, blastomycosis and histoplasmosis. *Curr Fungal Infect Rep* 2017;11(3):67–74.