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Miliary Tuberculosis due to *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* associated with invasive *aspergillosis* in a renal transplant recipient

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Abstract

Infections in renal transplant recipients (RTRs) carry great risk of morbidity-mortality, and the risk of graft loss. Concomitant infections, although common in immunosuppressed patients, should be highly suspected. The present case involves a RTR with opportunistic pulmonary co-infections caused by *Mycobacterium tuberculosis* (MTb), *Mycobacterium smegmatis* (MSm), and *Aspergillus* spp. While MSm can be a colonizing microorganism, we demonstrate that it can also be pathogenic.

Keywords Renal transplant, *Mycobacterium*, *Aspergillus*

Introduction

Infections in renal transplant recipients (RTRs) are associated with high rates of hospitalization during the first post-transplant year, with reports of 0.33 hospitalizations per person-year [1], and up to 70% of RTRs experience an infectious process by the third year after transplantation [2]. Infections carry a significant risk of morbidity and mortality, increasing the risk of death by 222% and the risk of graft loss by 192% compared to RTRs without infectious events [3]. Concomitant infections can occur in various contexts [4], with RTRs being a particularly susceptible group for presenting with them [5]. In a retrospective cohort study in France involving 74 patients with *Mycobacterium tuberculosis* (MTb) infection, 15% had a concomitant infection: 7 cases of bacterial infections, 5 viral infections, 2 cases of atypical mycobacterial infections, 1 case of cryptococcemia, 1 case of giardiasis; 5 of those patients had 3 simultaneous co-infections [6]. Furthermore, existing reports in the literature describe cases of three or more simultaneous infections in a single RTR with varied pathogen combinations [7, 8]. The present case involves a RTR from a living-related donor with three simultaneous opportunistic pulmonary infections: MTb, *Mycobacterium smegmatis* (MSm), and *Aspergillus*

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spp. To our knowledge, these co-infections have not been reported in the literature until now.

Case-report

A 26-year-old male with a history of chronic kidney disease (CKD) secondary to focal segmental glomerulosclerosis (FSGS) was diagnosed at 10 years of age. The patient underwent a renal transplant in November 2021 from a living donor, classified as low immunological risk. Immunosuppressive therapy included induction with basiliximab (BSL); and maintenance with tacrolimus (TAC) at 0.04 mg/kg, mycophenolic acid (MMF) at 1.5 g every 24 h, and prednisone (PDN) at 5 mg every 24 h. Baseline serum creatinine (SCr) was 0.9 mg/dl prior to the actual onset of the presenting illness. The patient experienced no complications during the first post-transplant year, with no episodes of graft rejection or infections. His body mass index (BMI) at the time of the illness was 21 kg/m^2.

The patient's clinical symptoms began in May 2023 (1 year and 6 months post-transplant) with persistent fever fluctuating between 39°C and 42°C, accompanied by fatigue, dyspnea, nausea, vomiting, and a weight loss of 5 kg over 4 weeks. In the initial diagnostic work-up, sputum cultures and stains were negative for bacteria, fungi, and mycobacteria. The galactomannan antigen (GA) test in sputum was also negative, while the QuantiFERON-TB Gold Plus blood test results were positive. The initial chest X-ray showed no abnormalities, but the chest computed tomography (CT) scan revealed a generalized bilateral micronodular pattern along with a right lung hilar consolidation displaying a ground-glass appearance (Fig. 1).

Given the high suspicion of miliary tuberculosis and because the clinician considered deferring bronchoscopy due to hemodynamic and respiratory instability with oxygen saturation (Sp02) < 90% at the time of evaluation, the first-line antitubercular treatment (rifampicin, pyrazinamide, ethambutol, and isoniazid) was started empirically. Mycophenolic acid (MMF) was discontinued, and TAC was gradually reduced, resulting in partial symptom improvement. Despite receiving antitubercular treatment for 4 weeks, the fever and symptoms persisted, with the patient developing acute graft dysfunction (SCr 1.7 mg/dl) and severe anemia (hemoglobin 5.9 g/dl), which required a blood transfusion. Due to persistent fever, but with improvement in dyspnea and Sp02 > 90% a bronchoscopy with bronchial lavage was performed, yielding negative cultures for bacteria and fungi; however, the

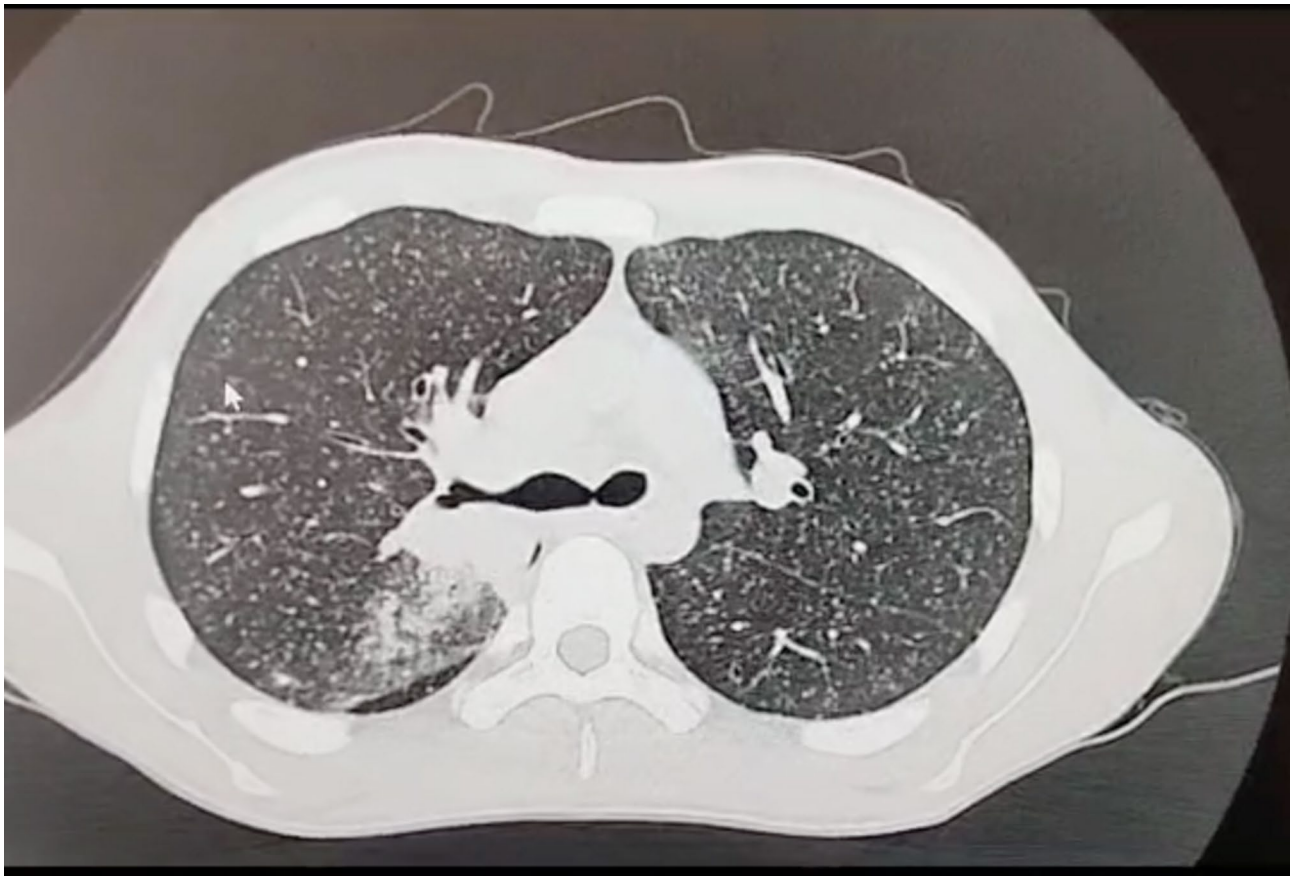

Fig. 1 Thin-slice chest CT scan: bilateral generalized micronodular pattern with right hilar pulmonary consolidation and a ground-glass pattern

Ziehl-Neelsen stain was positive, detecting 13 bacilli per 300 fields (Fig. 2).

A GeneXpert test returned positive for MTb, sensitive to rifampicin, and a positive polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) test for atypical mycobacteria showed a pattern compatible with MSm. This technique amplifies the hsp65 gene and subsequently examines restriction fragment polymorphism utilizing two restriction enzymes (BstEII and HaeIII), enabling the rapid and precise identification of DNA fragment patterns that match with MSm and differ from those of other mycobacteria.

Aspergillus was also identified through direct visualization of its characteristic hyphae (Fig. 3), and a GA test was positive so voriconazole was initiated; but even after 14 days of initiation, the patient only improved partially. Antitubercular treatment was continued (2 months of intensive phase and 6 months as maintenance phase), and voriconazole was continued for 12 weeks at a dose of 200 mg BID.

In addition to antituberculous drugs and voriconazole, the patient received 14 days of empirical antimicrobial treatment with Imipenem adjusted to renal function for bacterial coverage. Finally, the patient achieved remission of symptoms and normalization of laboratory parameters (SCr 1 mg/dl) with discharge the hospital. During antituberculous and antifungal pharmacological therapy and the reduction of immunosuppression, we always considered the risk of acute graft rejection. However, given the patient's severe condition, we believed that the benefit of suspending and/or reducing immunosuppression outweighed the risk. The patient was continuously

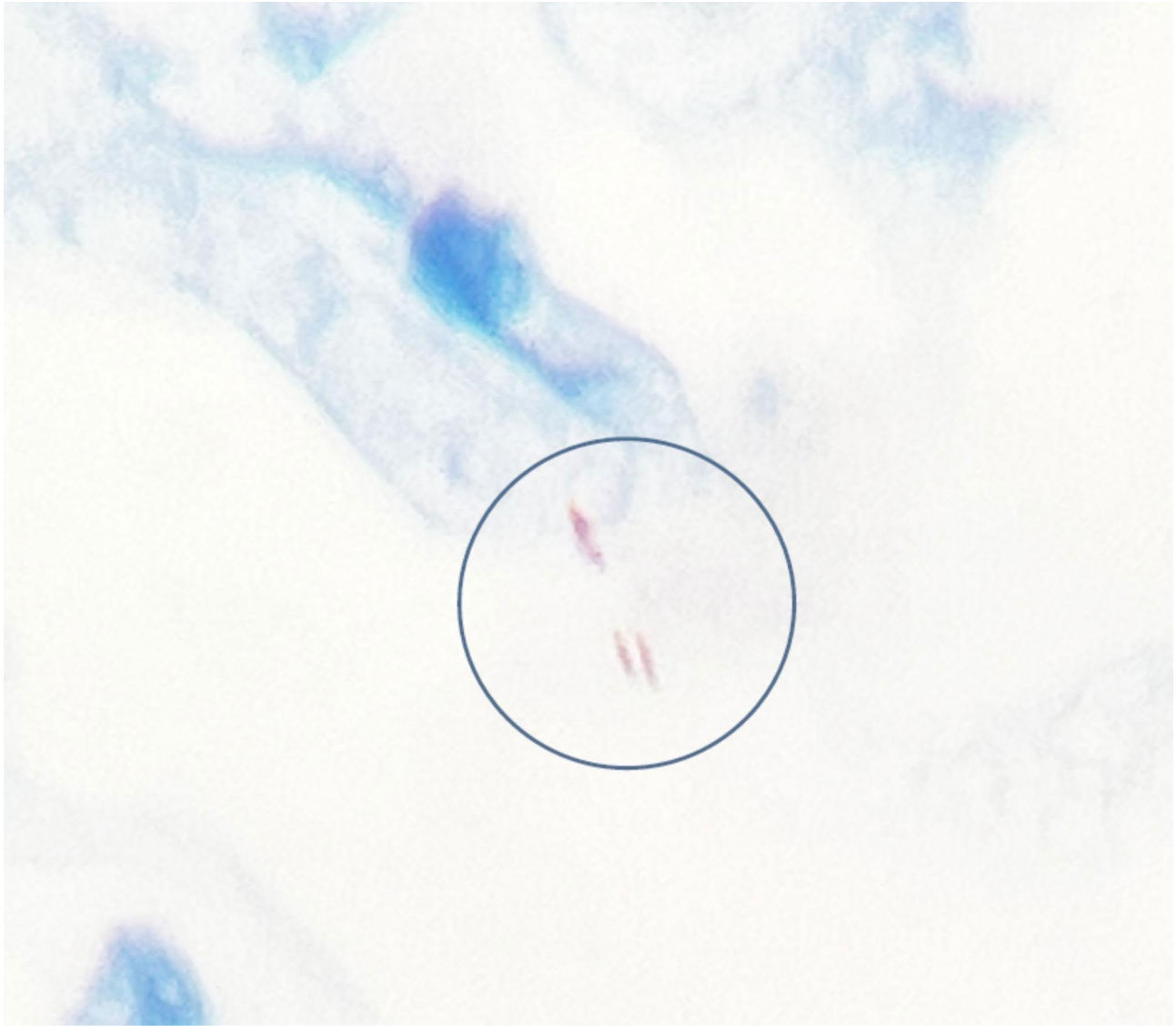

Fig. 2 A cytological smear at 40x magnification, Ziehl-Neelsen stain shows the presence of three acid-fast bacilli (circled)

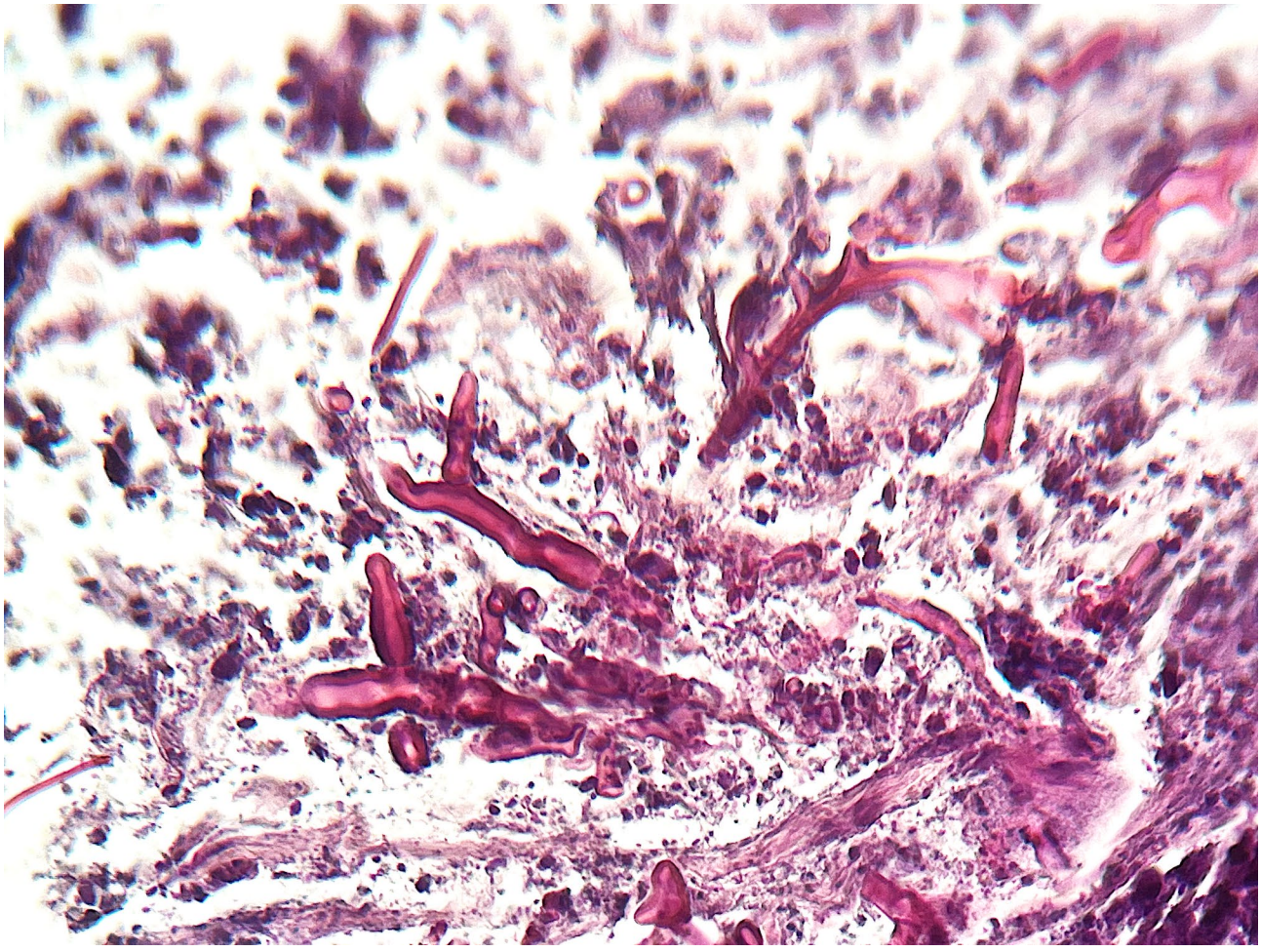

Fig. 3 Cytological smear. PAS stain at 40x magnification. The presence of septate and branched hyphae with acute angles of 90 and 45º, with well-defined walls on a necrotic background is identified

monitored for TAC levels, and dosage adjustments were made to avoid major adverse effects due to the pharmacological interactions with voriconazole, which increases levels, and rifampicin, which reduces levels. Currently, the patient is asymptomatic with a normofunctional renal graft (SCr 0.9 mg/dL). After completing their antitubercular and antifungal treatment; immunosuppression was gradually restored and the dose of immunosuppression maintained corresponds to TAC 1 mg of extended release every 24 h, MMF 1 g per day, and PDN 5 mg per day.

Discussion

Mycobacterium tuberculosis (MTb) infection occurs with a frequency of 0.45-3.2% in RTRs [6, 9], while the incidence of invasive aspergillosis varies between 0.4 and 2.3% depending on the geographical region [10]. In contrast, the incidence of infection by atypical mycobacteria is less than half of that reported for MTb [11]. In addition to the low incidence, there are more than 150 species of atypical mycobacteria. The one most strongly associated with disease is the Mycobacterium avium complex, followed, at a significant distance, by M. chelonae, M. abscessus, and M. fortuitum [12]. In the case of MSm, a study in North America involving 933 patients with positive cultures for atypical mycobacteria over a period of two years isolated MSm in only one culture, but it was not attributed as the cause of the disease [12]. Considering the afore mentioned, we can demonstrate that the combination of pathogens presented by our patient is extremely rare.

M. Smegmatis is an unusual pathogen due to the strong innate immune response it generates [13]. However, it may be an opportunistic pathogen when the immune system fails and is associated with infections of the skin and soft tissues [14, 15], as well as atypical pneumonias [13, 16–19]. Furthermore, evidence of MSm persistence in pulmonary epithelial cells for longer periods (latent infection) is convincing [20] and should lead us to consider atypical mycobacteria as infectious agents. The diagnosis of MSm infection in the present case was made

through visualization with Ziehl-Neelsen staining in a bronchoalveolar lavage sample. Although this method cannot distinguish MSm from MTb, it was also identified through PCR-RFLP. In the context of immunosuppression, as in the present case, the identification of the pathogen through PCR-RFLP in bronchoalveolar lavage samples appears to support its role as a pathogen. Some authors have reported false positives for atypical mycobacteria in the presence of MTb [21], but with the new PCR tests, it has been shown that the test is very specific and does not generate cross-reactivity between MTb and MSm [22]. The persistence of symptoms despite 4 weeks of anti-tuberculosis treatment led us to consider two options: resistance to first-line treatment and the search for pathogens concomitant with MTb. The first option was ruled out with GeneXpert, which showed no resistance to rifampicin and, consequently, no resistance to isoniazid. The second option was confirmed through bronchoscopy with sample collection for PCR testing for atypical mycobacteria, a second galactomannan determination, and the detection of non-septate hyphae with divisions compatible with Aspergillus in lung tissue samples. Although the probability of contamination may be significant, the role of MSm as a pathogen in our patient is possible. We believe that the lack of symptom remission, despite several weeks of anti-tuberculosis treatment and at least 14 days of voriconazole treatment for invasive aspergillosis, in conjunction with the discovery of MSm using PCR-RFLP in bronchoalveolar lavage samples, provides sufficient reasons to assume that the patient had a lung infection caused by MSm. We consider that the suspension and/or reduction of immunosuppression, the use of ethambutol, and Imipenem therapy could have influenced the clinical improvement, given that mSM usually shows susceptibility to these antimicrobials [23].

Our main limitation is that MSm is ubiquitous in the environment and has rapid growth and may plausibly have a non-pathogenic role. Although in the present case, we cannot categorically rule out contamination by environmental mycobacteria, we believe that, in the context of severe immunosuppression and miliary tuberculosis, with inadequate response to treatment, we must maintain a high index of suspicion for infections caused by atypical mycobacteria, including SMm, in order to develop effective prevention and management strategies that will consequently reduce mortality.

In conclusion; In RTRs with persisting symptoms of miliary tuberculosis, must rule out resistance to drugs and opportunistic infections.

Abbreviation

RTRs	Renal transplant recipients
MTb	*Mycobacterium tuberculosis*
MSm	*Mycobacterium smegmatis*
CKD	Chronic kidney disease
FSGS	Focal segmental glomerulosclerosis
BSL	Basiliximab
TAC	Tacrolimus
MMF	Mycophenolic acid
PDN	Prednisone
SCr	Serum Creatinine
BMI	Body mass index
GA	Galactomannan antigen
CT	Chest computed tomography
PCR-RFLP	Polymerase chain reaction-restriction fragment length polymorphism

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None.

Author contributions
JAS: Contributed to the study's development, conceptualization and critical review.MCV: Contributed to the study's development, conceptualization and critical review.AJAO: Contributed to the study's development, conceptualization and critical review.JAO: Contributed to the study's development, conceptualization and critical review.JICG: Contributed to the study's development, conceptualization and critical review.LAF: Contributed to the study's development, conceptualization and critical review.AABH: Contributed to the study's development, conceptualization and critical review. ACC: Contributed to the study's development, conceptualization and critical review.

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Data availability
All data generated or analyzed in this case are included in this manuscript and do not compromise patient confidentiality.

Declarations

Ethics approval and consent to participate
This study was conducted according to the guidelines laid down in the Declaration of Helsinki 1964. The name of the ethics committee that approved the study and the committee's reference number if appropriate; Not applicable.

Consent for publication
The patient has provided written informed permission for for publication of this case report, as well as any identifiable images.

Competing interests
The authors declare no competing interests.

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