IDCases 31 (2023) e01675

Contents lists available at ScienceDirect

IDCases

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Case report

Atypical presentation of *Mycobacterium xenopi* pulmonary infection in a kidney transplant recipient: A case report and literature review

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ARTICLE INFO

Keywords:
Kidney transplantation
Mycobacterium xenopi
Non-tuberculous mycobacteria

ABSTRACT

Background: Mycobacterium xenopi is one of the most common pathogens responsible for non-tuberculosis mycobacteria (NTM) pulmonary diseases, which are associated with poor prognosis in immunocompromised patients.
Case presentation: We report the unusual case of a 44-year-old kidney transplant recipient with multiple pulmonary nodules revealing *M. xenopi* pulmonary disease with atypical presentation. A three drug-regimen containing moxifloxacin, ethambutol and azithromycin was prescribed, with careful monitoring of the immunosuppressive therapy. The outcome was favorable.
Discussion and conclusion: Although infrequent in kidney transplant recipients, NTM can cause pulmonary infection several years after transplantation. Treatment of *M. xenopi* infection relies on a multidrug regimen with at least 3 antimycobacterial drugs. Drug-drug interactions between immunosuppressive treatments and rifamycins require careful dose adjustment and monitoring to avoid graft rejection.

Introduction

Non-tuberculous mycobacteria (NTM) pulmonary diseases have increased significantly over the past decades with an estimated prevalence of 9.8 cases per 100,000 persons in Northern America in 2010 and up to 33.3 per 100,000 in South Korea in 2016 [1,2]. *Mycobacterium xenopi*, a slow-growing mycobacteria, is one of the most common pathogens causing NTM lung disease after *Mycobacterium avium* complex [1,3]. *M. xenopi* results in infection of preexisting pulmonary cavities among patients with obstructive pulmonary disease and causes diffuse pulmonary infiltrations in immunocompromised hosts, especially in AIDS patients [4]. However, *M. xenopi* pulmonary infections have been rarely described after kidney transplantation [5,6]. Herein, we report the case of a kidney transplant recipient with pulmonary nodules revealing *M. xenopi* pulmonary disease.

Case presentation

A 44-year-old obese black male patient with autosomal dominant polycystic kidney disease was hospitalized in August 2021 to explore pulmonary nodules incidentally discovered on a computed tomography performed while the patient was hospitalized for a renal cyst infection.

The patient was born in Mali but had lived in France for the past 43 years. He received a kidney transplant in February 2018. He had no preexisting lung disease and declared a ten pack-year smoking history. The immunosuppressive regimen consisted of prednisone, mycophenolate mofetil and cyclosporine. Cotrimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia was started after transplantation. Pretransplant screening for latent tuberculosis infection was not performed.

The post transplantation period was marked by a recurrent lymphocele treated by laparoscopic marsupialization. In June 2021, the patient presented with fever and a renal cyst infection was suspected. Despite no bacteriological confirmation, he received a 4-week course of ceftriaxone. Thoracoabdominal CT-scan showed pulmonary nodules that led to subsequent pulmonary explorations. Physical examination including lung auscultation was unremarkable. The body mass index reached 34 kg/m^2. White blood cell count was 4,14 G/L and C-reactive protein level was 7 mg/l. Serum fungal biomarkers (galactomannan and

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https://doi.org/10.1016/j.idcr.2022.e01675
Received 31 August 2022; Received in revised form 28 December 2022; Accepted 28 December 2022
Available online 29 December 2022

B-D-glucan), as well as blood aspergillus PCR assay were negative. Glomerular filtration rate measured by ^{51}Cr-EDTA clearance was 54 ml/min. Computed tomography revealed multiple nodules in both lungs, without interstitial infiltrates (Fig. 1A and 1B). The bronchoalveolar lavage (BAL) fluid contained many cells with macrophage predominance (960,000 cells/ml, 94 % macrophages, 5 % lymphocytes, 1 % neutrophils). Standard bacteriological and fungal cultures were negative and auramine staining did not show any acid-fast bacilli. Whole-body positron emission tomography (PET) depicted moderated hypermetabolism of pulmonary nodules (SUVmax: 3.5) without any other abnormal fixation (Fig. 1C). Trans-thoracic lung biopsy was performed and evidenced non-caseating epithelioid and giant cellular granulomas with a negative Ziehl-Neelsen staining. After 49 days, *Mycobacterium xenopi* grew in the bronchial aspiration culture. No antimicrobial susceptibility testing was performed considering the limited relevance of this test to guide antibiotic treatment [12].

Blood and urine cultures were negative for mycobacteria. Pulmonary nodules increased in size at one-month follow-up CT scan, despite the patient remaining afebrile without any respiratory symptoms. Mycophenolate mofetil dosing was lowered and an antimycobacterial treatment containing rifabutin, ethambutol and azithromycin was initiated. Immunosuppressive drugs were carefully monitored, and doses were adapted for interaction with rifabutin: prednisone and cyclosporine doses were increased by 50 % and 100 % respectively. Several days later, the patient discontinued treatment because of asthenia, fever and myalgias. Adverse events related to rifabutin were suspected and the treatment was switched off for moxifloxacin. The patient's condition improved, and he quickly became afebrile after rifabutin discontinuation. Two months later, computed tomography showed that pulmonary nodules decreased in size. Graft function remained stable. A 12-month treatment was planned.

Discussion

We report a rare case of *M. xenopi* pulmonary infection revealed by multiple pulmonary nodules in a kidney transplant recipient occurring 3.5 years post-transplantation. In two large European retrospective studies assessing mycobacterial infections after kidney transplantation, NTM infections were rarely documented (12 NTM out of 3763 kidney recipients). Only one case of *M. xenopi* bone infection was reported in these studies [5,6] and we found 5 additional cases of *M. xenopi* pulmonary infections among kidney recipient (Table 1) [7–10]. These cases occurred late after transplantation with a median time of 70 months. Out of 5 patients, four were symptomatic and most of them exhibited pulmonary infiltrates (Table 1).

Diagnosis of NTM pulmonary infection requires differentiating colonization from invasive infection. In a retrospective nationwide Dutch study, isolation of *M. xenopi* was considered clinically relevant in only 51 % of patients [11]. In the present case, the diagnosis was based on the association of lung nodules, the presence of non-caseating granuloma at lung biopsy, and a positive culture of bronchial aspiration. Our patient did not have any clinical symptoms, and therefore did not meet the diagnosis criteria of the current guidelines [12]. However, given the underlying immunosuppression and the progressive worsening of pulmonary nodules, an antibiotic treatment against *M. xenopi* was begun. Lung nodules size significantly decreased after antimycobacterial treatment administration, which supported the diagnosis of *M. xenopi* pulmonary infection. This case highlights that decision to initiate antimicrobial therapy for NTM disease should be individualized [12]. An expert opinion is required for complex cases.

In severely immunocompromised patients, other opportunistic infections must be ruled out, especially tuberculosis as for this patient with an African origin. Andrejak et al. described clinical and radiological

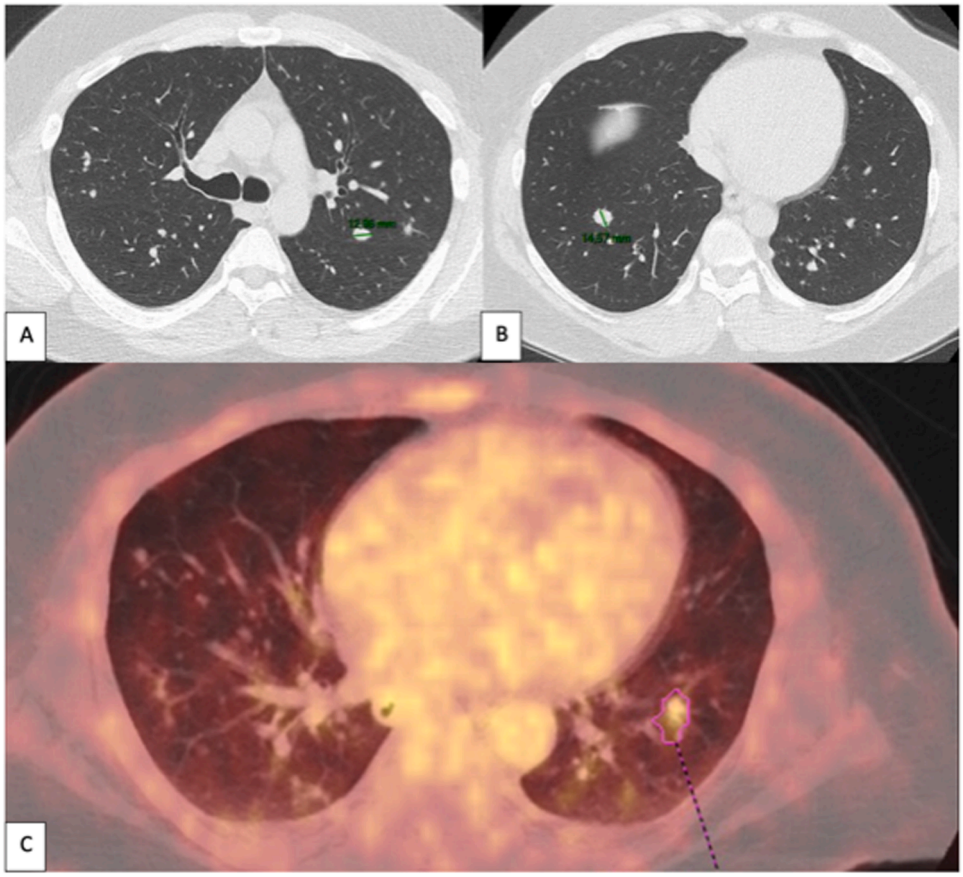

Fig. 1. Transverse computed tomography images showing multiple pulmonary nodules (A, B), hypermetabolic on PET scan (C).

Table 1
Characteristics and outcomes of reported *M. xenopi* pulmonary infection in renal transplant recipients.

	Renal disease	Immuno-suppression	Onset after transplantation	Clinical presentation	Radiologic presentation	Treatment	Main events during treatment	Outcome
Case 1 (1980) 40-year-old woman (10)	End-stage renal failure after post-partum hemorrhage	AZA + PRED	60 months	Asymptomatic	Alveolar interstitial infiltrates	RIF + INH + ETH Duration: Unknown	None	Favorable
Case 2 (1989) 39-year-old man (9)	GN of unknown origin	AZA + PRED + CYS	70 months	Weakness, weight loss	Alveolar interstitial infiltrates	RIF + INH + ETH Duration: 12 months	None	Favorable
Case 3 (2004) 34-year-old woman (8)	Urinary malformation	AZA + PRED + SIRO	74 months	Fever, dyspnea, cough	Alveolar interstitial infiltrates + unique nodule	RBT + CLARI + ETH + OFLO Duration: 8 months	- RBT-induced uveitis - switch from SIRO to TACRO	Favorable
Case 4 (2004) 44-year-old male (8)	GN of unknown origin	PRED + SIRO	40 months	Fever, weight loss, dyspnea, chest pain	Alveolar interstitial infiltrates	RBT + CLARI + ETH + OFLO Duration: 12 months	- OFLO-induced tendinopathy - Major drug interactions (SIRO and RBT)	Favorable
Case 5 (2009) 63-year-old male (7)	GN of unknown origin	SIRO + MMF	99 months	Fever, cough	Unique pulmonary cavitation	RIF + INH + LEVO Duration: 12 months	- Major drug interactions (SIRO and RIF)	Favorable
Case 6 (Present case) 44-year-old male	Autosomal dominant polycystic kidney disease	CYS + PRED + MMF	42 months	Asymptomatic	Multiple pulmonary nodules	AZI + ETH + MOX Duration: on going	- RBT induced flu-like syndrome	Treatment on going

GN: glomerulonephritis, SIRO: sirolimus, MMF: mycophenolate mofetil, TACRO: tacrolimus, AZA: azathioprine, CYS: ciclosporin, PRED: prednisone, RIF: rifampicin, RBT: rifabutin, INH: isoniazid, ETH: ethambutol, CLARI: clarithromycin, AZI: azithromycin,LEVO: levofloxacin, OFLO: ofloxacin.

features of *M. xenopi* pulmonary infections in a retrospective analysis of 136 cases. They found that 96 % of the patients had respiratory symptoms, often combined with general signs (89 %). Three radiologic patterns were individualized [4]. The cavitary forms are observed among patients with chronic obstructive pulmonary disease, while nodular lesions are mainly associated to *Aspergillus sp.* co-infections. Diffuse pulmonary infiltrations can be found in immunocompromised hosts, especially in AIDS-patients. Data regarding the best antimycobacterial regimen for *M. xenopi* infections remains limited. As the value of in vitro antibiotic susceptibility testing is uncertain, clinical practice guidelines do not recommend routine drug susceptibility testing of clinical isolates for first-line treatment [11,12]. In a retrospective study, patients receiving a rifamycin-containing regimen experienced a significantly better outcome [4]. Two randomized clinical trials with a limited number of patients compared several 24 month-regimens. The first trial, including 42 patients, showed that there were less treatment failures and relapses with a combinations of rifampicin, ethambutol, and isoniazid (5 %) than with rifampicin and ethambutol (18 %), but the difference was not statistically significant and global 5-year mortality was 57 % [13]. In the second trial, 34 patients receiving rifampicin and ethambutol (RE) were randomized to receive ciprofloxacin or clarithromycin [14]. Clinical outcome did not differ significantly between the two groups, and 38 % of study participants died within 5 years after inclusion in the study. A third larger randomized trial is still ongoing, comparing a RE-based regimen associated with moxifloxacin or clarithromycin [15]. An intermediate analysis highlighted that 21 of the 24 patients achieved culture conversion after 6 months of treatment, whatever the treatment group. Currently, the 2020 Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline recommend a regimen including at least 3 drugs: rifampicin, ethambutol, and either a macrolide or a fluoroquinolone and treatment should last at least 12 months after culture conversion [12].

NTM infection treatment in solid organ transplant recipients remains challenging due to significant drug-drug interactions, which require close monitoring of drug levels. As rifampicin strongly induces CYP450 3A4, the interactions with calcineurin inhibitor agents (cyclosporine and tacrolimus) and corticosteroids are the most problematic. Calcineurins inhibitors and glucocorticoids doses should be increased by 100 % and 50 %, respectively [16]. Rifabutin might have less effect on the serum concentrations of calcineurin inhibitors due to a lower induction of human cytochrome P450. Conversely, macrolides inhibit cytochrome P450 3A4 and raise serum levels of calcineurin inhibitors, but no dose adjustment is recommended. When using macrolides, azithromycin might be safer than clarithromycin with less risk of drug-drug interactions [12]. Dosages also need to be adjusted in patients with a creatinine clearance below 50 ml/min [17].

For this case, we started a 3-drugs regimen with rifabutin, ethambutol and azithromycin and ideal body weight was used to adapt doses of antimycobacterial drugs, as the patient had a BMI over 34 [18]. Drug-related adverse events leading to antimycobacterial treatment discontinuation are significantly more frequent in transplant recipients (risk ratio: 5.66) [19]. In this case, rifabutin was replaced by moxifloxacin for a flu-like syndrome, a well-described dose-dependent side effect of rifamycins [20]. Finally, immunosuppressive therapy reduction remains of paramount importance in the management of opportunistic infections, although this is not always possible in those patients. While *M. xenopi* pulmonary infection results in a high mortality rate in most individuals, our review of the literature shows that cases reported among kidney transplant recipient had a good prognosis without treatment failure or deaths reported (Table 1). This might be explained by a younger age and a preserved respiratory function compared to patients with chronic obstructive pulmonary diseases, who are mainly infected by this pathogen.

Conclusion

We present a rare case of multinodular pulmonary *M. xenopi* infection in a kidney transplant recipient. This report highlights the difficulties in terms of diagnosis, management of drug-drug interactions and tolerance issues in such population, although our literature review indicates that the prognosis is usually favorable under treatment. The latest guidelines recommend a 3-drugs regimen for at least one year after culture conversion but the optimal treatment remains uncertain. Clinicians should be aware of the risk of late pulmonary non-tuberculosis mycobacteria infections among kidney transplant recipient and their potentially atypical clinical presentations.

CRediT authorship contribution statement

Conceptualization: Antoine Hamon, Geoffroy Liegeon, Nathalie De Castro. Writing – original draft: Antoine Hamon. Writing – review & editing: Geoffroy Liegeon, Kévin Louis, Emmanuelle Cambau, Nathalie De Castro. Supervision: Geoffroy Liegeon, Nathalie De Castro.

Sources of funding

No financial support was received for this work.

Ethical approval

All procedures performed were in accordance with the declaration of the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Consent

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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