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CASE REPORT

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# *Talaromyces marneffei*: A challenging diagnosis in a kidney transplant patient

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## Key Clinical Message

In addition to post-transplant lymphoproliferative disorders, it is necessary to be alert to the drug-resistant bacteria or fungal infection, especially *Talaromyces marneffei*, in kidney transplant patients who have failed antibiotic treatment and whose PET-CT indicates high metabolic mass in the transplanted kidney with a large number of other organs and lymph nodes.

## Abstract

*Talaromyces marneffei* (TM) is a rare pathogenic fungus that primarily affects individuals with compromised immune systems. Post-transplant lymphoproliferative disorders (PTLD) are serious complications that can occur after solid organ and cell transplantation. Both TM infection and PTLD can invade the monocyte–macrophage system and often manifest as extranodal masses. This case report describes a kidney transplant patient who presented with symptoms of frequent, urgent, and painful urination over 6 months. Pulmonary CT scans revealed multiple nodules, and PET-CT demonstrated enlarged lymph nodes in the lungs and the transplanted kidney. The clinical manifestations closely mimicked those of PTLD. The confirmation of TM was achieved through pathogen metagenomic next-generation sequencing and renal biopsy. Unfortunately, despite receiving treatment with antifungal agents, anti-infective therapy, the patient's condition did not respond favorably, ultimately resulting in their unfortunate demise due to COVID-19.

**KEYWORDS**

kidney transplant, metagenomic next-generation sequencing, post-transplant lymphoproliferative disorders, *Talaromyces marneffei*

## 1 | INTRODUCTION

*Talaromyces marneffei* (TM) is a unique thermally dimorphic fungus belonging to the *Penicillium* genus, known as the only temperature bipolar pathogen.[1] This infectious disease primarily affects individuals with compromised immune systems, including those with immune deficiency or immune function suppression.[2] TM predominantly targets the monocyte–macrophage system, leading to its involvement in various organs such as the lungs, liver, intestinal lymphoid tissue, lymph nodes, spleen, bone marrow, kidneys, and tonsils. Among these organs, the lungs and liver are particularly susceptible and can experience severe involvement.[3] TM exhibits a tendency to disseminate throughout the body, resulting in a high case-fatality rate.[2] Common clinical manifestations of TM infection include fever, chills, cough, expectoration, wasting, enlarged liver and spleen, superficial lymph node enlargement, rash, subcutaneous nodules, and abscesses.[1]

Post-transplant lymphoproliferative disorders (PTLD) are characterized by the development of extranodal masses involving various organs, including the gastrointestinal tract, lungs, skin, liver, central nervous system, and even the transplanted graft itself.[4] This case report describes a kidney transplant patient who presented with symptoms of frequent, urgent, and painful urination over 6 months. Pulmonary CT scans revealed multiple nodules, and PET-CT demonstrated enlarged lymph nodes in the lungs and the transplanted kidney. The clinical manifestations closely mimicked those of PTLD leading to potential diagnostic confusion. The confirmation of TM was achieved through pathogen metagenomic next-generation sequencing (mNGS) and renal biopsy. Unfortunately, despite receiving treatment with antifungal agents, anti-infective therapy, the patient's condition did not respond favorably, ultimately died tragically from COVID-19.

## 2 | CASE HISTORY AND EXAMINATION

A 68-year-old male patient was admitted to the hospital with a history of recurring urgent and painful urination over the past 6 months. The patient had previously undergone a living donor kidney transplantation from his mother in January 2001 due to end-stage renal disease caused by IgA nephropathy. The immunosuppressive regimen included mycophenolate mofetil, cyclosporine, and prednisone, and the patient's serum creatinine levels were maintained between 120 and 130 μmol/L. However, in December 2021, the patient's serum creatinine levels increased to 170 μmol/L, leading to a renal allograft biopsy, which revealed acute T-cell-mediated rejection (Banff IA). He underwent methylprednisolone pulse therapy and subsequently switched from cyclosporine to tacrolimus, resulting in the maintenance of serum creatinine levels at 140–165 μmol/L.

In June 2022, more than 21 years after kidney transplant, the patient began experiencing frequent, urgent, and painful urination, without any accompanying fever. Auxiliary examinations revealed a urine protein level of 0.15 g/L and a white blood cell count of 64.6/μL, with the serum creatinine level recorded as 165 μmol/L. Over the course of the following month, the symptoms worsened, with subsequent review of relevant tests showing a slight increase in the above indicators compared to previous values. Urinary tract infection was considered as a possible cause, and the patient was prescribed levofloxacin. However, the symptoms did not improve, leading to the patient's admission to the hospital. Physical examination revealed depressed edema in both lower limbs. Urine culture results indicated the presence of *Enterobacter cloacae*, and the patient was initiated on meropenem for anti-infection treatment. A renal ultrasound of the transplant kidney revealed multiple heterogeneous echo foci in the left iliac fossa and the transplanted kidney, with the larger area measuring approximately 2.3 × 2.0 cm. Color Doppler flow imaging (CDFI) and color Doppler energy (CDE) showed poor blood perfusion in the affected areas (Figure 1).

A plain CT scan of the lungs (Figure 2) revealed masses in the upper and middle lobes of the right lung,

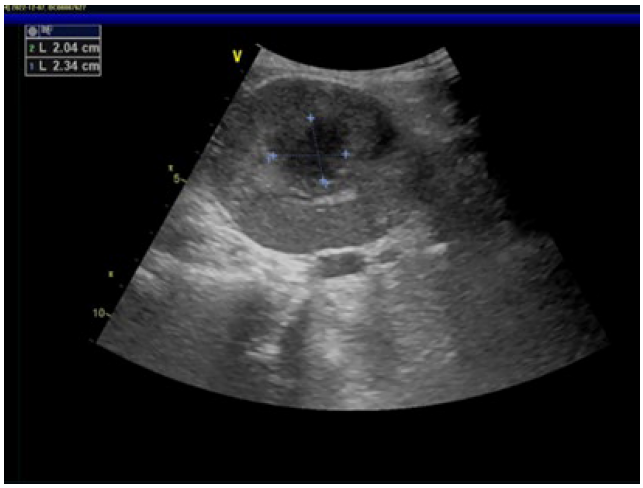


**FIGURE 1** Multiple heterogeneous echo foci and poor blood perfusion in the transplanted kidney. The figure shows multiple heterogeneous echo foci observed in the transplanted kidney. The larger area measures approximately 2.3 cm × 2.0 cm. Color Doppler flow imaging (CDFI) and contrast-enhanced ultrasound (CDE) reveal poor blood perfusion in the affected regions.

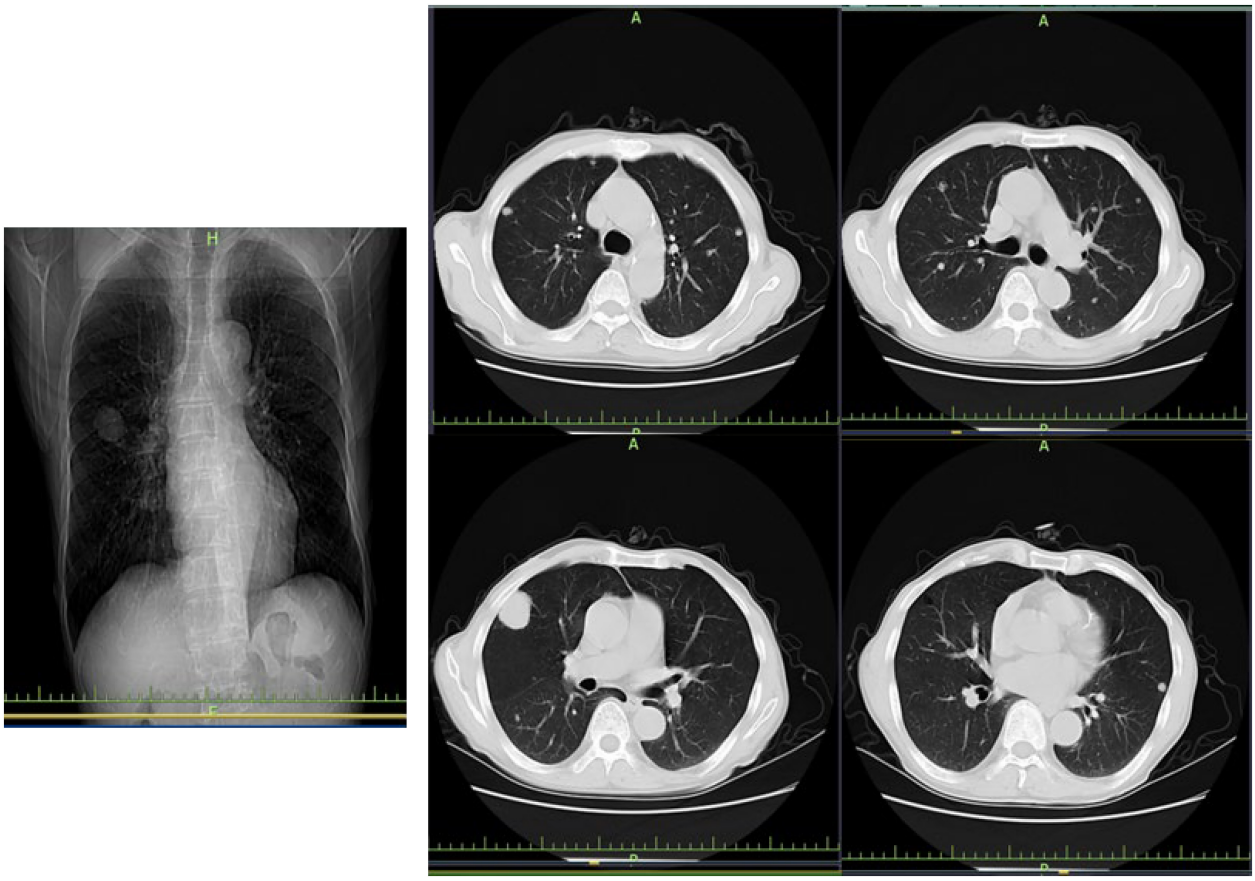

**FIGURE 2** Lung abnormalities and high-density masses in the right lung. The figure illustrates the lung texture, highlighting clear visualizations of both lungs. Within the right lung, high-density masses are observed in the upper and middle lobes, extending across the interlobe fissure, bronchial passage, and surrounded by short burrs. The size of these masses is approximately 32 mm × 27 mm. Additionally, multiple circular nodular dense shadows are visible in both lungs, some of which exhibit eccentric holes. The lesions maintain clear boundaries, with the largest one located in the upper lobe of the right lung, measuring approximately 10 mm × 6 mm. Furthermore, the lower lobe of the left lung displays a high-density shadow.

along with multiple nodules in both lungs. The initial suspicion was focused on malignancies and metastases. Additionally, a plain whole abdominal CT scan showed an increased volume of the transplanted kidney with multiple low-density foci, exudation around the pancreas, and an enlarged lymph node shadow in the retroperitoneal and mesangial regions. To further evaluate the patient's condition, a PET/CT scan (Figure 3) was performed, which revealed abnormal hypermetabolic zones in the lungs, transplanted kidney, sigmoid colon, and multiple lymph nodes. The patient was suspected to have lymphoproliferative disease. Therefore, blood pathogen mNGS was conducted, which indicated the presence of TM. To identify the hypermetabolic foci in the transplanted kidney caused by TM, a kidney allograft needle biopsy was performed, revealing partial degeneration and necrosis of the glomeruli and renal tubules, along with a large number of microorganism colonies (Figure 4). Furthermore, mNGS of the kidney allograft tissue demonstrated a massive number of TM gene reads, surpassing the results obtained from the peripheral blood mNGS analysis. Based on the combined findings of the transplanted kidney biopsy and mNGS, a clear diagnosis of TM infection was established.

## 3 | METHODS

Combined with the patient's history, clinical manifestations, lung CT and PET-CT results, the patient was suspected to have lymphoproliferative disease, although ruling out infection was challenging. It was subsequently confirmed as TM infection by NGS. The patient was initially treated with voriconazole, which was subsequently switched to isavuconazole due to liver injury. Unfortunately, 1 month later, the patient contracted COVID-19, resulting in severe pneumonia and respiratory failure. Despite signs of improvement on pulmonary CT scans, multiple cavities remained. Tragically, the patient succumbed to the complications of COVID-19 infection.

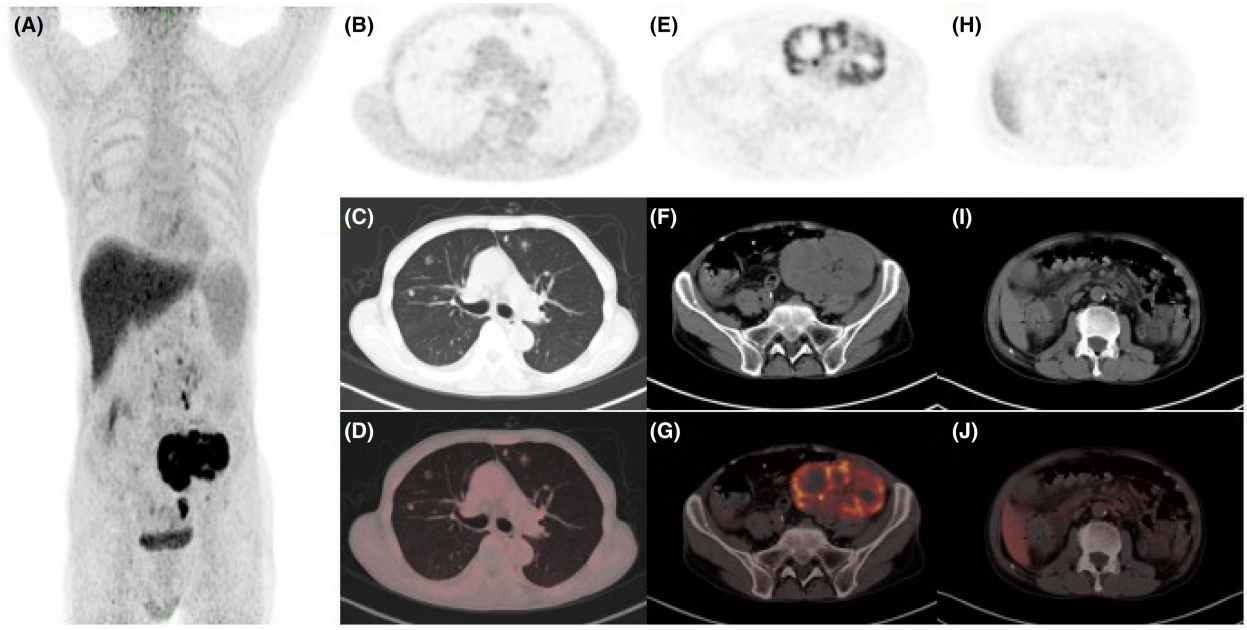


**FIGURE 3** The 18FDG (fluorodeoxyglucose)-PET-CT scans revealed the presence of slightly high-density nodules in the upper lobe of the right lung (B-–D). These nodules exhibited slightly increased FDG metabolism. Additionally, scattered high-density nodules of various forms were observed, with accompanying small hollow shadows. These nodules also displayed increased FDG metabolism. Furthermore, several lymph nodes (E–G) were identified in the posterior peritoneal parapal aorta, abdominal mesenteric, mesenteric space, iliac vessel bifurcation, left iliac vessel, and left iliac fossa. These lymph nodes exhibited mild increases in FDG metabolism. Notably, the density of the middle abdominal mesentery appeared indistinct with slightly increased FDG metabolism. These findings led to a consideration of the possibility of post-transplant lymphoproliferative disorders (PTLD). The transplanted kidney (H–J), located in the left iliac fossa, exhibited an enlarged appearance and noticeable cortical thickening. Multiple patchy areas were observed within the renal parenchyma, along with increased FDG metabolism at the edge of the lesion.

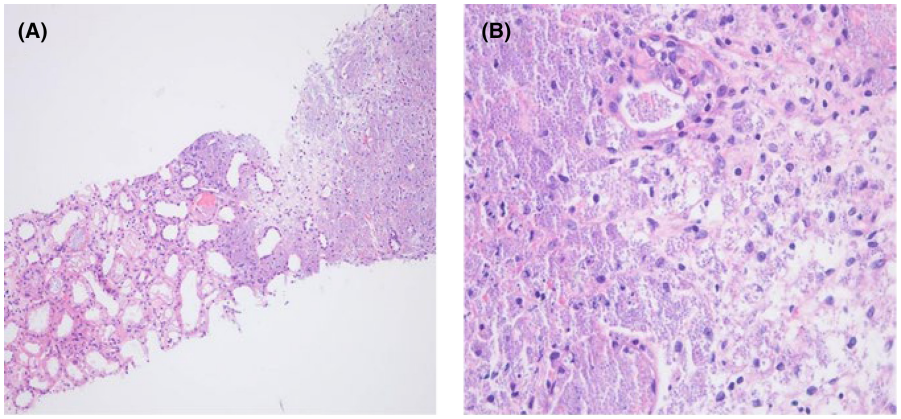


**FIGURE 4** The needle biopsy of the transplanted kidney was subjected to hematoxylin and eosin staining (A: original magnification, ×100; B: original magnification, ×400). The staining revealed partial degeneration and necrosis of the glomeruli and renal tubules. Importantly, a significant number of microorganism colonies were observed within the kidney tissue.

## 4 | CONCLUSION AND RESULTS

In this case report, we presented the clinical details of a kidney transplant patient who experienced frequent, urgent, and painful urination over 6 months. The patient's chest CT scan revealed multiple pulmonary nodules, and PET-CT indicated enlarged lymph nodes. After initial suspicion of PTLD, the diagnosis was later confirmed as TM with multisystem involvement, including the transplanted kidney which based on blood and tissue mNGS as well as pathology findings from the transplanted kidney biopsy.

## 5 | DISCUSSION

The confirmation of TM in this case was achieved through comprehensive evaluation using blood and tissue mNGS, as well as pathological analysis. Although the patient presented with symptomatic urinary tract

infection lasting for an extended period, the treatment response to antibiotics, such as *Enterobacter cloacae*, was unsatisfactory. During the diagnostic process, we did not conduct fungal culture or mNGS to explore the possibility of a fungal infection causing the urinary tract symptoms. This was a limitation in our diagnostic approach. Conventional culture methods tend to prioritize bacterial growth over fungal growth, potentially inhibiting the detection of fungi in samples. Therefore, in cases where urinary tract infections are unresponsive to treatment, particularly in immunocompromised patients, it is crucial to consider and investigate the presence ofuberculosis,[5,6] fungal,[6] trichomonas[7] and other pathogenic bacterial infections. Additional monitoring methods, including fungal culture and urine mNGS,[8–10] should be employed to achieve a definitive diagnosis whenever possible.

When managing urinary tract infections in kidney transplant patients, it is important not only to consider bacterial infections but also to remain vigilant for fungal infections.[11] Kidney transplant recipients have compromised immune systems due to long-term immunosuppressive drug therapy, making them more susceptible to fungal infections upon exposure to environmental fungi. Refractory fungal infections are challenging to treat clinically and are associated with high mortality rates. Therefore, clinicians should maintain a high level of suspicion for fungal infections in this population and prioritize early diagnosis and treatment.

In cases involving hypermetabolic space-occupying lesions affecting transplanted kidney parenchyma, tumors, particularly PTLD, are typically considered as the primary differential diagnosis. This patient also had enlarged lymph nodes in the lung and abdominal cavity, further raising suspicion of PTLD. However, it is crucial to clinically exclude infectious lesions such as TM in cases presenting with space-occupying lesions involving multiple organs and exhibiting high metabolic activity. Our unpublished data suggests that TM may also involve the gastrointestinal tract, presenting with lymphomatoid manifestations. Obtaining pathological tissue samples and assessing characteristic pathological changes are valuable for making a definitive diagnosis. TM, being a bidirectional bacterium, is challenging to culture, and the use of mNGS,[12,13] which is widely employed in clinical practice, can significantly enhance detection capabilities.

The most common clinical manifestations of PTLD include fever and lymph node enlargement. These findings were consistent with the symptoms and imaging results observed in this patient. However, it is important to note that PTLD is more commonly observed in pediatric patients, particularly those who have undergone lung or small intestinal transplantation. In adults, the incidence of PTLD is higher in lung transplant recipients (4%–6%) and intestinal transplant recipients (up to 20%), compared to kidney transplant recipients (1%–3%).[14,15] PTLD is more likely to occur within the first year after transplantation, and its incidence decreases gradually with increasing time since transplantation, with rates of 224 per 100,000 in the first year, 54 per 100,000 in the second year, and 31 per 100,000 in the sixth year.[16] In addition, Epstein–Barr virus (EBV) infection is a significant contributing factor to the development of PTLD, and measuring EBV viral content can serve as an auxiliary diagnostic test.[17,18] These factors, along with pathological and mNGS analyses, can aid in the identification and differentiation of PTLD and TM infection.

TM is usually asymptomatic and can be divided into localized type and disseminated type. When the patient develops fever, chills, cough, sputum, wasting, fatigue, liver and spleen and superficial lymph node enlargement, rash, subcutaneous nodules or abscesses,[1,2] TM infection should be vigilant. Clinically, the diagnosis is generally made by culture (such as blood culture, urine culture, alveolar lavage fluid culture), mNGS, and pathological biopsy.[2,3] In this case, TM infection was diagnosed by blood and tissue mNGS. Currently conventional recognized as effective treatment of TM infection is amphotericin B, azole drugs (itraconazole, esaxonazole, etc.).[8] TM has a high fatality rate, and early recognition, diagnosis and treatment are key to this disease.

In summary, we reported a case of TM involving multiple organs, including the transplanted kidney, which mimicked PTLD. Clinicians should be cautious in ruling out infectious lesions in immunocompromised patients, and the use of mNGS and biopsy procedures can be helpful in achieving an accurate diagnosis.

## AUTHOR CONTRIBUTIONS

**Sulin Luo:** Writing – original draft. **Pengpeng Yan:** Project administration. **Xingxia Wang:** Investigation. **Xue Ren:** Validation. **Ke Sun:** Software. **Luying Guo:** Conceptualization. **Junhao Lv:** Data curation. **Xinhui Su:** Formal analysis. **Kui Zhao:** Visualization. **Jianghua Chen:** Resources. **Rending Wang:** Funding acquisition.

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Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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## CONFLICT OF INTEREST STATEMENT

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

## DATA AVAILABILITY STATEMENT

Research data are available through corresponding authors for legitimate reasons.

## CONSENT

We've obtained a signed informed consent from the patient's wife according to the journal's patient consent policy.

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