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Case Presentation

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Talaromyces Marneffei Infection in HIV-Negative Patient with Type 2 Diabetes: A Case Report and Literature Review

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Abstract

Background: T. marneffei is an opportunistic fungus that could cause fatal mycosis in immunocompromised patients or even in immunocompetent individuals. Furthermore, the risk of infection including bacterial infections as well as fungal diseases in diabetes is much higher compared with the general population. However, there is very few report of T. marneffei infection in HIV-negative patients with type 2 diabetes (T2DM) so far.

Case presentation: A 58-year-old male, who had a dry cough and lost weight 3 Kg for 2 weeks, was diagnosed with T. marneffei infection and T2DM based on T.marneffei was cultured from Bronchoalveolar lavage fluid (BALF) and elevated glucose level as well as HbA1c. The condition of this patient was improved significantly after receiving Itraconazole 400mg/day for anti-fungal therapy for 3 months as well as insulin Glargine for anti-diabetic treatment followed with Metformin for long-term glucose control.

Conclusion: This case warrants clinicians to pay more attention to the potential hosts of T. marneffei Infection in patients with T2DM. Fungal culture and pathological examination can confirm the diagnosis of T.marneffei infection which requires long-term anti-fungal treatment.

Keywords: Talaromyces Marneffei; Type 2 diabetes; Itraconazole

Abbreviations: Talaromyces Marneffei: T. marneffei; Type 2 Diabetes: T2DM; Bronchoalvelar Lavage Fluid: BALF; glycated hemoglobin A1c: HbA1c; Human Immunodeficiency Virus: HIV; Chronic Obstructive Pulmonary Disease: COPD; Type 1 Diabetes: T1DM; High-Resolution Computed Tomography: HRCT; C-Reactive Protein: CRP; Erythrocyte Sedimentation Rate: ESR; Procalcitonin: PCT; Oral Glucose Tolerance Test: OGTT; Cytokeratin 19 Fragment: CYFRA21-1; Neuron Specific Enolase: NSE; squamous cell carcinoma antigen: SCC; Carcinoembryonic Antigen: CEA; C-peptide: C-P; plasma glucose: PG; white blood cell: WBC; neutrophil: Neu; Eosnophils: EOS; Platelets: PLT; Albumin: ALB; Alanine Transaminase: ALT; Serum

Creatinine: SCr; (1/3)-β-D-Glucan Assay: G assay; Galactomannan Antigen Assay: GM assay; Female: F; Male: M; Amphotericin B: AmB

Background

Diabetes has been a global health problem which is one of the leading causes of morbidity and mortality in the 21th century. Uncontrolled diabetes lead to increased susceptibility to bacterial infections through affecting T cell and B cell function **[1].** Previous studies revealed that the risk of infection in diabetes was much higher compared with the general population including bacterial infections as well as fungal diseases **[2,3],** and recent data showed T2DM patients have much higher incidence for developing severe acute respiratory Syndrome Coronavirus 2 (SARS-COV2) caused by COVID-19 **[4,5].** The high infection risk might attribute to polymorphonuclear neutrophil (PMN) cell performance has been modified in DM patients **[6].** Furthermore, in subjects with T2DM, the immune response is disrupted and natural barrier is damaged due to multiple mechanisms **[7].** Talaromyces marneffei (T. marneffei), also known as Penicillium marneffei, is an important pathogenic, thermally dimorphic fungus that could cause fatal opportunistic systemic mycosis especially in patients with Human Immunodeficiency Virus (HIV) infection or immunocompromised individuals in southeast Asia **[8].** DiSalvo et al. **[3]** reported the first case of a natural T. marneffei infection in humans in 1973. Subsequently, since the 1990s, an ascending number of T. marneffei infections have been reported among non-HIV-infected patients with a history of pulmonary tuberculosis **[9],** Chronic Obstructive Pulmonary Disease (COPD) **[10],** pulmonary sarcoidosis **[11],** papillary thyroid cancer **[12,13],** autoimmune hepatitis **[14],** organ transplant recipients **[15, 16]** or patients who use novel targeted therapies, such as MAPK (Mitogen-Activated Protein Kinases) pathway inhibitors (Sorafenib, Lenvatinib) for thyroid carcinoma and small-molecule kinase inhibitors for breast cancer or hemato-oncology **[17].** Nevertheless, there is very few report of T. marneffei infection in patients with T2DM so far. Hence, we here reported a case of a 58-year-old male who was diagnosed with T. marneffei infection in T2DM, and reviewed the literatures on HIV-negative patients with T. marneffei infection in the past five years.

Case Presentation

A 58-year-old man, native in Jiangxi province of south China, was admitted to our department due to 2-week of dry cough and weight loss (3 kg) without symptoms of fever, pectoralgia, hemoptysis, or dyspnea. This patient was a non-smoker and denied a residential history in any epidemic regions, any medications use as well as surgical history. He was diagnosed with pneumonia in the local hospital by the result of the chest X-ray, which revealed multiple opacities in the bilateral lung, especially the left superior lobe. On admission, his vital signs were largely stable except for high heartbeat (body temperature, 36.7 °C; blood pressure, 129/79 mmHg; and pulse, 101 beats/minute, regular). Physical examination showed coarse breath sounds of the left lung and cervical lymph nodes were not palpable. The High-Resolution Computed Tomography (HRCT) scan (June 07, 2019) showed multiple patchy opacities of the left lung, seriously in the left superior lobe, where a cavity developed suspiciously **(Figure 1A).** Laboratory test results (June 08, 2019) revealed neutrophil, lymphocyte, and eosinophil count were normal **(Table 1).** Both the levels of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) elevated. The plasma Galactomannan (GM) and (1/3) -β-D-Glucan (G) assay was negative which was the same as the serum cryptococcal antigen agglutination test. Microbiology analysis

showed that repeated bacteria and fungus smear tests of sputum, blood, and sputum cultures for bacteria and fungus were negative. But the level of fasting blood sugar was 9.8mmol/L, and glycosylated hemoglobin (HbA1c) was 8.9%. The patient was then diagnosed with T2DM according to the results of Oral Glucose Tolerance Test (OGTT) and elevated level of HbA1c. The detailed laboratory results are shown in **Table 1.**

Table 1: Clinical parameters of the patient on the day of admission.

Parameter	Result (normal range)	Parameter	Result (normal range)
WBC (*10^9 /L)	8.98 (3.50-9.50)	Serum G test	(-)
Neu (*10^9 /L)	6.48 (1.80-6.30) ↑	Serum GM test	(-)
EOS (*10^9 /L)	0.32 (0.02-0.52)		ESAT-6 ↑
Hb (g/L)	138 (130-175)	TB-spot	CPP-10 ↑
PLT (*10^9 /L)	304 (125-350)	Sputum bacteria smear	(-)
CRP (mg/L)	34.55 (0-5) ↑	Sputum fungus smear	(-)
PCT (ng/ml)	0.05 (<0.094)	Sputum acid-fast bacilli smear	(-)
ESR (mm/1h)	74 (0-15) ↑	CYRA21–1(ng/ml)	6.58 (0-3.3) ↑
ALT (U/L)	16.0 (9-50)	NSE (ng/ml)	17.38 (0-16.3) ↑
HbA1C (%)	8.9 (4.0-6.0) ↑	SCC (ng/ml)	1.70 (<1.5) ↑
HIV-Ab	(-)	CEA (ng/ml)	1.70 (0-5)

WBC: White Blood Cell count; Neu: Neutrophil cont; EOS: Eosinophils; HbA1c: Glycated Hemoglobin A1c; PLT: Platelets; CRP: C-Reactive Protein; PCT: Procalcitonin; ESR: Erythrocyte Sedimentation Rate; ALB: Albumin; ALT: Alanine Transaminase; SCr: Serum Creatinine; CYRA21–1: Cytokeratin 19 fragment; NSE: Neuron-Specific Enolase; CEA: Carcinoembryonic Antigen; SCC: Squamous Cell Carcinoma antigen; G test: (1/3) -β-D-Glucan test; GM test: Galactomannan antigen test.

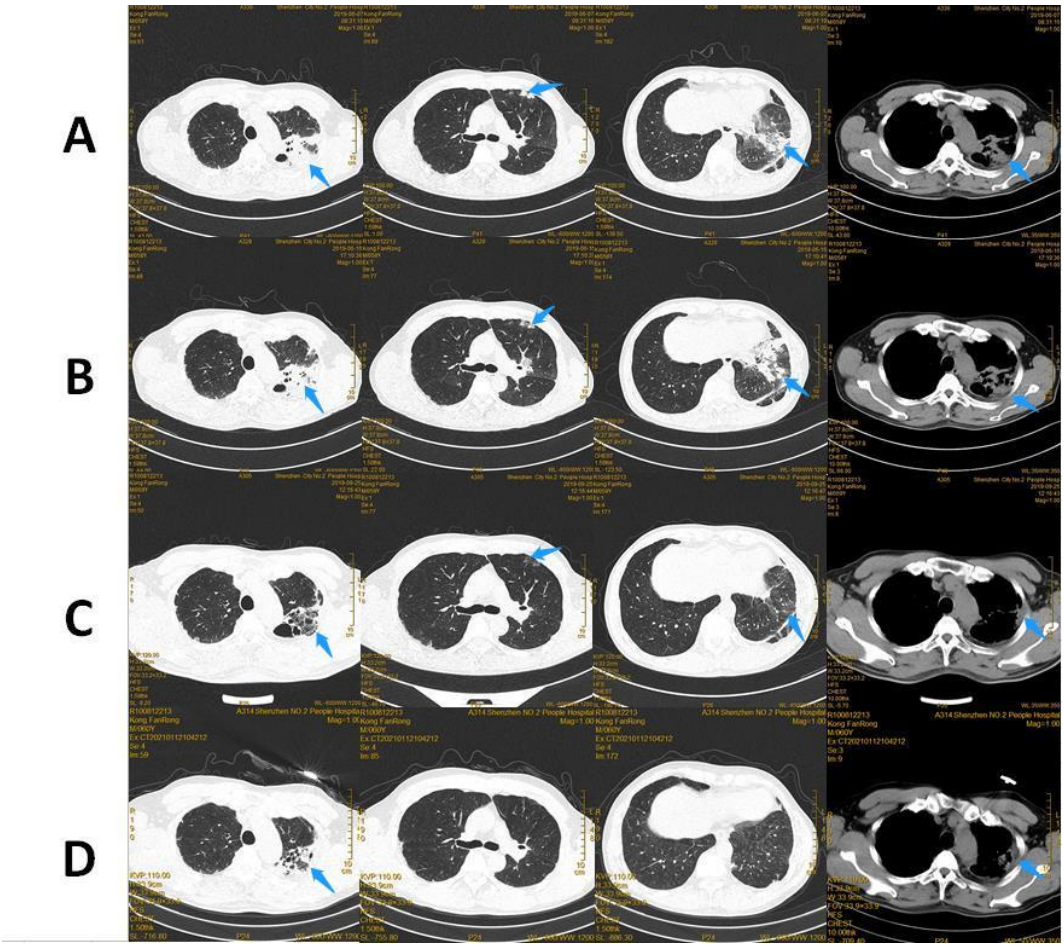

Figure 1: (A) Chest CT on the first day of admission (June 07, 2019) showed multiple patchy exudative shadows of the left lung, seriously in left superior lobe, where occurred cavity suspiciously (blue arrows); (B) Chest CT on day 8 of admission (June 15, 2019) showed shadows progress in the left lung, and an air bronchogram in right lower lobe; (C) Chest CT after 3 months treatment (September 21, 2019) showed the left lung shadows were markedly absorbed ; (D) Chest CT after discontinuation of anti-fungal therapy for more than 1 year (January 12, 2021) showed the left upper shadow was further reduced and the left lower lung lesion was almost absorbed.

Then intravenous Cefperazone-sulbactam (3.0g Q12H) was used empirically for antibiotic therapy. Meanwhile, subcutaneous injection of insulin Glargine was started immediately and the dosage was adjusted depending on the glucose levels to maintain euglycemia. However, his cough persisted after 5 days of antibiotic treatment. Then the blood T-spot returned with a weakly positive result (June 12, 2019), so the diagnosis of Tuberculosis could not be excluded completely. However, intracutaneous tuberculin tests (PPD) and repeated acid-fast bacilli

smears of sputum revealed negative results, and mycobacterium culture of sputum was inspected (the result turned out negative after 6 weeks culture). Furthermore, the diagnosis of lung cancer was suspected because of multiple tumor markers including Cytokeratin 19 fragments (CYFRA21-1), Neuron-Specific Enolase (NSE), Squamous Cell Carcinoma antigen (SCC) slightly elevated. Therefore, the patient underwent whole-body Positron Emission Tomography and CT (18F-FDG PET/CT) scan which showed a lump with thick wall hollow which intensely increased 18F-fluorodeoxyglucose uptake in the posterior apical segment of left upper lobe, as well as subcentrimetric hypermetabolic lesions in lingular segment of the left upper lobe and basal segment of the left lower lobe, considered the primary focus of infection **(Figure 3).**

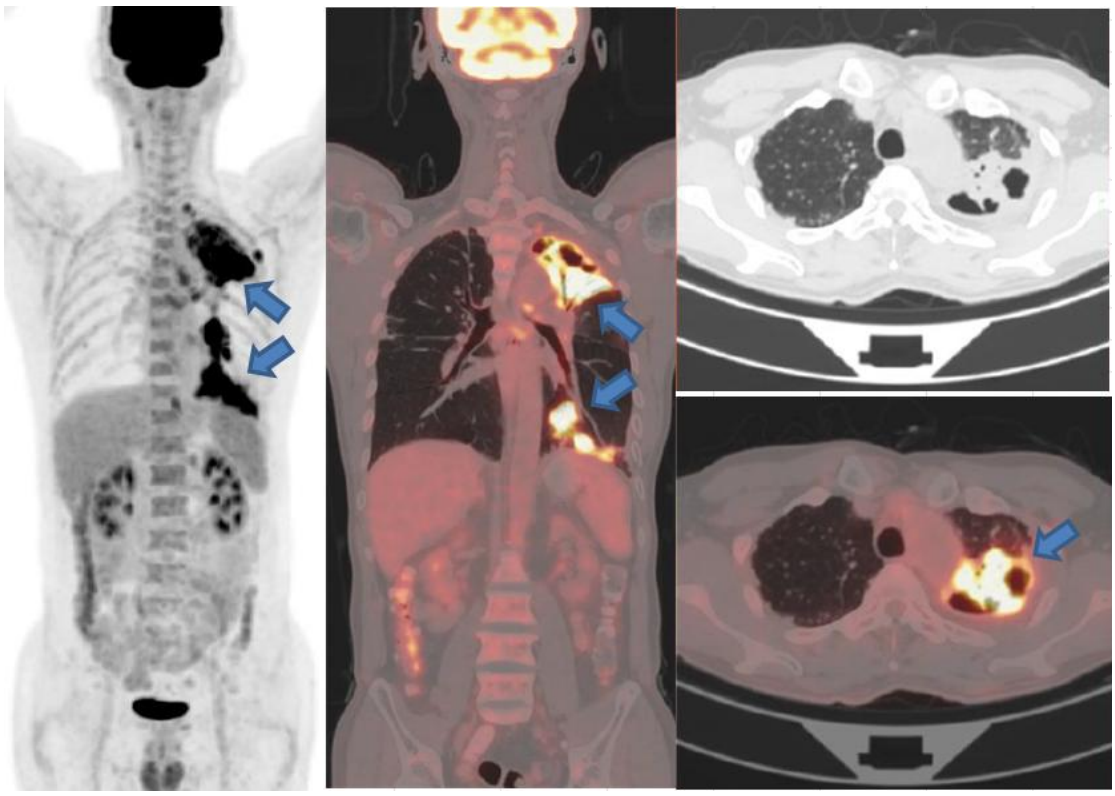

Figure 3: Coronal attenuation-corrected image and axial Positron Emission Tomography and Computed Tomography (PET–CT) fusion image demonstrating increased metabolic activity (18F-fluorodeoxyglucose uptake) of left upper lobe and basal segment of left lower lobe (blue arrows).

Subsequently, the patient underwent bronchoscopy after signed informed consent, which revealed inflammatory changes of bilateral bronchial mucosal, and no nodular projection or evident mucosa damage in the bronchus (June 11, 2019) **(Figure 2B).** Bronchoscopic vision and the pathology of the posterior apical segment of the left upper lobe mucosa revealed no malignancy. The bacteria and acid-fast bacilli smear of BALF were negative, the DNA of acid-fast bacilli in BALF was not present, and mycobacterium culture was inspected (the result was also negative after 6 weeks). But the smear was positive for fungus (aspergillus suspiciously) in the BALF. With this finding, there was no clinical and imaging improvement after antibacterial therapy; he was advised to receive anti-fungal therapy after our suspicious consideration of fungal infection. However, the patient was unwilling to accept empirical treatment due to personal perspectives. After 8 days of continuously antibacterial

treatment, he was examined with the other chest CT (June 15, 2019) **(Figure 1B),** which showed increased shadows of the left lung compared with the initial one.

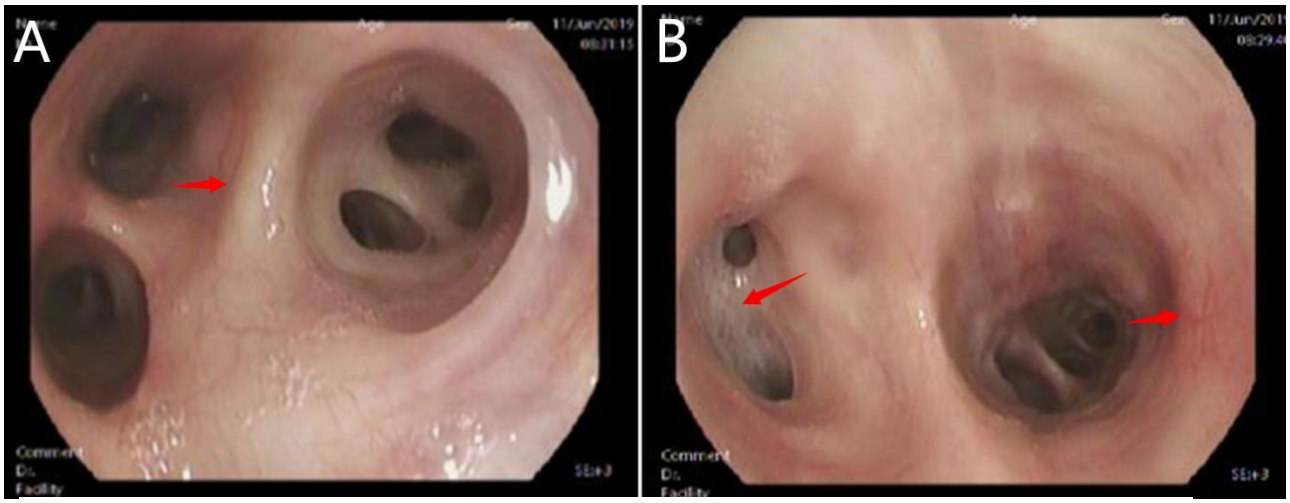

Figure 2: Bronchoscopic examinations revealed bilateral bronchial mucosa were smooth but hyperaemia. (A) The posterior apical segment of left upper lobe; (B) Lower left lobe with white viscous secretion.

Ultimately, the fungal culture of BAL confirmed the diagnosis of T. marneffei infection on June 17, 2019 **(Figure 4).** Then Itraconazole (200mg po) at every 12 hours was initiated and his condition improved after a week of treatment, Metformin was prescribed to improve insulin resistance after control of infection. Then he was discharged home on daily Itraconazole and Metformin three times a day. The result of the chest CT (September 21, 2019**) (Figure 1C)** re-examination showed that the left lung shadows were markedly absorbed after 3 months. Itraconazole treatment was withdrawn on September 21 after three-month course of antifungal treatment. This patient came back to our hospital for follow-up after the discontinuation of Itraconazole for 1 year, chest CT (January 12, 2021) showed the left upper shadow was further reduced and the left lower lung lesion was almost absorbed **(Figure 1D)**, he had no respiratory symptoms and the level of blood glucose was under control with Metformin.

Figure 4: (A) Fungal hyphae were found in Bronchoalveolar lavage fluid(BLFA) of the patient by gram stain**;** (B) The Talaromyces marneffei from BLA grew on Blood agar medium (after 48 hours incubation at 35 °C)**;** (C) Colony morphology of T.marneffei. Left: yeast phase with yeast-like colonies (after 7 days incubation at 37 °C, PDA agar). Right: mould phase with diffusible red pigment (after 7 days incubation at 25 °C, Sabouraud agar).

Discussion

T. marneffei infections are most often described in patients with advanced HIV, but sporadic cases of T. marneffei infection have been reported in non-HIV-infected patients or even immunocompetent individuals **[18].** The incidence of T. marneffei infections in patients with diabetes may increase due to glucose is an ideal medium for kinds of bacteria and fungi. But there are rare reports of T. marneffei infection in patients with T2DM. Hence, we reported one case with T. marneffei infection in T2DM male who had a good response to Itraconazole. Meanwhile, we summarized clinical characteristics of 28 HIV-negative cases of T. marneffei infection with different comorbidities over the past five years **(Table 2).** 23 of 28 cases were reported in China which is consistent with previous studies suggesting that the incidence rate of T. marneffei infection markedly increased after the HIV/AIDS epidemic commenced in Southeast Asia in 1988 **[19],** and only one child who was 5 year-old was reported very recently **[20].** Since T. marneffei is a highly lethal but potentially therapeutic fungal infection, a high index of suspicion is required to identify the possibility of T. marneffei infection, which requires proper microbiological testing and the prescription of appropriate anti-fungal agents. Overall, 12/28 (42%) patients died despite receiving antifungal treatment, such as Itraconazole, Amphotericin B, or Voriconazole, although not all of them died of T. marneffei infection directly. Castro-Lainez in the USA even added Micafungin empirically after Amphotericin B and Voriconazole combination therapy had failed **[21].** Chan et al have demonstrated the mortality of HIV-negative patients with T. marneffei infection is 27.7% which is higher than in HIV-positive counterparts (20.7%) **[8,22].** The most likely reason for this is some HIV-negative patients with T. marneffei infection have been initially misdiagnosed and empirically treated as tuberculosis because both infections are endemic in Southeast Asia, have similar predisposing factors and overlapping clinical manifestations **[9].** There are new reports about new gene mutations (i.e. Y287N mutation in the coiled-coiled domain of STAT1 and CARD9 mutations) which were identified using whole-exome sequencing with in patients with T. marneffei infection **[23,24]**. In our literature review, those infected patients embraced different clinical manifestations which might delay diagnosis of T. marneffei infection due to the lack of clinical suspicion in the early stage. These factors remind doctors it's necessary to consider whether patients are associated with T. marneffei infection if they don't improve accordingly after empirical anti-tuberculosis treatment has been implemented in patients who are diagnosed with pulmonary tuberculosis. Familiarity with the non-HIV conditions associated with T. marneffei infection would facilitate clinicians to improve the clinical management of the infection among these at-risk patients **[8].** The case we referred here whose T-spot revealed weakly positive although Tuberculosis was excluded eventually.

Table 2: Summary of clinical characteristics of HIV-negative cases of T. marneffei infection between the years of 2017-2022.

Ref	Age/ Sex	Area of report	Underlying disease	Medications	Clinical presentations	Involved organ or tissue(diagnostic methods)	Treatment/maintenance	Outcome
He et al. (2019)	57/F	China	Hemolytic anemia	Dexamethasone	Fever; Cough;	Supraclavicular	Voriconazole	Cured

[26]					Pharyngalgia	lymph nodes		
Lin et al. (2019) [27]	50/F	China	primary pulmonary lymphoepithelioma-like carcinoma (LELC) Obstructive pneumonia	Combination of docetaxel and carboplatin / Docetaxel	Sputum-coughing; Fever; Weight loss	Endobronchial nodule	Voriconazole/Itraconazole	Tumor recurrence
Wongkamhla et al. (2019) [28]	52/F	Thailand	Anti-IFN-ɣ autoantibodies	None	Sore throat; Pharynx pain; Odynophagia; Hoarseness; Fever; Weight loss	Right tonsillar biopsy	AmB/ Itraconazole	Cured
Castro-Lainez et al. (2018) [21]	75/M	United States	Chronic obstructive pulmonary diseases (COPD)	Not stated	Productive cough (purulent sputum); Night sweats; Malaise; Hemoptysis	BALF	AmB/ Isavuconazole/ Micafungin	Died
Yu et al. (2018) [11]	41/M	China	Pulmonary sarcoidosis	Corticosteroid (irregularly)	Hyperpyrexia; Sputum-cough; Skin lesions	BALF	Voriconazole	Improved
Zhang et al. (2017) [12]	45/F	China	Papillary thyroid cancer	Thyroidectomy with radical neck	Arthralgia; Fever; Productive cough	BALF Skin lesions secretion	AmB/ Traconazole	Not stated

				dissection				
Peng et al. (2017) [15]	51/ M	China	Renal transplant twice in 1998 and 2014	MMF, Tac, Methylprednisolone	Fever; Progressive renal impairment	Kidney biopsy Blood culture	AmB/ Itraconazole	Renal transpant
Wong et al. (2017) [14]	65/F	China (Hong kong)	Autoimmune hepatitis Prednisolone for acute hepatitis flare	MMF,	Fever; Mild dysuria	Blood culture	Not stated	Died
Wang et al. (2017) [18]	59/ M	China	Schistosomal liver disease	Not stated	Fever; recurrent cough; headache; chest tightness; hoarseness; hard masses in right neck and	Bone marrow+ Purulence from hard mass	Voriconazole/ Corticosteroid	Cured
Darma et al. (2017) [13]	58/F	Indonesia	Papillary thyroid carcinoma	Total Thyroidectomy	Non-purulent cough; dyspnea; hemoptysis; mild fever	Sputum culture	Micafungin	Died of cancer
Qu et al. (2017) [29]	45/F	China	Multiple erythematous	Not stated	Disseminated granulomatous lesions of face, arms and trunk	Skin tissue culture	AmB	Improved

Hermans et al. (2017) [16]	61/M	Belgium	Bilateral lung transplantation	Tac, MMF, Methylprednisolone	Fatigue; fever; oral ulcers; anorexia; diarrhea	Lymph nodes biopsy	AmB /Voriconazole	Improved
Qiu et al. (2016) [30]	64/F	China	Tuberculosis?	Standard antituberculous therapy (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol)	Productive cough; shoulder pain; weight loss; fever; anemia	Pus from the left shoulder	AmB /Voriconazole	Died
Hermans et al. (2017) [16]	61/M	Belgium	Bilateral lung transplantation	Tac, MMF, Methylprednisolone	Fatigue; fever; oral Ulcers; anorexia; diarrhea	Lymph nodes biopsy	AmB /Voriconazole	Improved
	64/F	China	Tuberculosis?	Standard antituberculous therapy (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol)	Productive cough; shoulder pain; weight loss; fever; anemia	Pus from the left shoulder	AmB /Voriconazole	Died
You et al. (2021) [24]	5/M	China	No diseases history	intravenous cephalosporin, Antituberculosis therapy (ethambuto	Fever; dry cough	Bone marrow smear + ascites culture	Empirical antituberculosis treatment / AmB+ Voriconazole	Died of multiple organ failure

				l, linezolid, isoniazid, and levofloxacin)				
Lin et al. (2021) [31]	63/M	China	Lung adenocarcinoma Patients with Positive AIGAs; family history of cancer	Not stated	Recurrent fever; productive cough; persistent right chest Pain; shortness of breath	Lung biopsy tissue	mipenem-cilastatin, Voriconazole, compounded sulfamethoxazole and linezolid	Died (due to lung cancer)
	57/M	China	Family history of cancer	None	Fever	TBNA tissues	AmB (discontinued due to the development of renal impairment) /Voriconazole	Died
Yang et al. (2021) [32]	51/M	China	Diabetes and previous lung surgery; Nodular Sclerosing Hodgkin Lymphoma	Insulin injection	Cough; expectoration, intermittent fever; fatigue; night sweats; shortness of breath	Lymph node biopsy + Lung culture	Diagnostic anti-tuberculosis treatment / AmB	Improved but unfortunately, he died of Salmonella sepsis later
Chen et al. (2021) [23]	20/M	China	Candida dermatitis	Not stated	Chills; Cough with white sticky sputum	Peripheral Blood+bone marrow+sputum	Voriconazole	Improved

Chen et al. (2021) [33]	68/M	China	No	None	Recurrent fever; cough; lymphadenectasis; renal dysfunction	BALF (mNGS)	AmB + Voriconazole	Died
	43/F	China	Erythema nodules	Glucocorticoid	Fever; Lymphadenopathy; cough	BALF (mNGS)+ subcarinal lymph node sample	Antituberculotic / Voriconazole	Cured
	49/M	China	No	None	Recurrent fever; thoracalgia; cough	Blood culture	Diagnostic anti-tuberculosis/ AmB+ Voriconazole (was replaced with itraconazole)	Cured
	45/F	China	Exposure history to mice	None	Cough; hemoptysis; night sweats;	Sputum BALF (culture) + BALF (mNGS)	AmB	Cured
	54/M	China	No	None	Recurrent cough; night sweats; lymphadenopathy	BALF (mNGS)	AmB + Voriconazole	Cured
Lin et al. (2022) [20]	5/F	China	Recurrent lower respiratory tract infection	none	Persistent cough; gasping	BALF	AmB + Itraconazole	Cured
Xing et al. (2022)	61/M	China	Hypertensive	MMF, PED, Tac	Repeated cough;	BALF (NGS)	Voriconazole + caspofungin	Died

[34]			nephropathy, kidney transplantation		expectoration; intermittent fever; shortness of breath			
	55/M	China	Hypertension, uraemia and chronic Type B viral hepatitis, kidney transplantation	MMF, PED, Tac	Repeated fever; shortness of breath	Peripheral blood (NGS)	Voriconazole + methylprednisolone	Died

In addition, T. marneffei is a thermally dimorphic fungus, normally appearing as a mold at temperatures of 25-30°C and as yeast at a temperature of 37°C [25]. Well-experienced microbiologists are essential to the process of the fungal culture of specimens such as sputum, blood, BLAF, and so on. Otherwise missing the diagnosis is frequent to happen.

Conclusion

Herein, we presented a rare case of T. marneffei infection in T2DM. The diagnosis of T. marneffei is largely based on microbiological culture, which requires cooperation with well-experienced microbiologists in the laboratory to improve the diagnostic rate. The limitation of this case is that further follow-up and chest CT review are necessary after discontinuation of itraconazole to determine further absorption of the exudate. Unfortunately, the patient failed to re-examine due to the outbreak of the COVID-19 pandemic. Recently we are told that the patient has no clinical manifestations with telephone follow-up.

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Author's Contributions

Y. Z and H. H were responsible for the patient and carried out the clinical follow up. Z. H and JD. Z made substantial contributions to the conception and design of the Study and drafting of the manuscript. H. A provided microbiological data including fungal identification. All authors read and approved the manuscript.

Ethics Approval and Consent to Participate

This case report has been granted an exemption from requiring ethics approval according to Shenzhen Second People's Hospital.

Consent for Publication

Written informed consent was obtained from the participating patient for publication of this case report and any accompanying images.

Conflict Interests

The authors declare that they have no conflict interests.

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