

A Rare Case of Mycobacterium Avium Combined with *Penicillium marneffei* (PM) Infection Involving Multiple Bone Joints throughout the Whole Body: A Case Report

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Abstract

Background: Mycobacterium avium complex (MAC) infection case which involves bones and joints are rare scenarios. Here, we report a rare case of *Penicillium marneffei* (PM), lung infection and systemic multi joint damage reported with positive anti-interferon-gamma at the same time. **Case Presentation:** A 55-year-old woman with fever for 10 days due to repeated multiple joint pain for more than one month was admitted to our hospital on September 19th 2020. During hospitalization, the patient was confirmed with mycobacterium avium combined with *Penicillium marneffei* (PM) infection involving multiple bone joints. Antifungal therapy and immunity regulatory agent were given during hospitalization. Following pharmacol-therapy, symptoms gradually improved, and the patient was discharged. **Conclusions:** The patient was considered disseminated and refractory non-tubercular mycobacterium (NTM) combined with *Penicillium marneffei* infection. In addition, we found that anti IFN- γ autoantibodies are closely related. Although the current incidence of this patient is related to anti IFN- γ , there is a strong correlation between autoantibody-mediated immunodeficiency in adults.

Keywords

Systemic Multiple Osteoarticular, Mycobacterium Avium Complex, *Penicillium marneffei*, Anti IFN- γ Auto-Antibody

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1. Introduction

Penicillium marneffe, also known as *Talaromyces marneffe*, is a facultative intracellular type II fungus that can cause immune dysfunction in hosts, particularly in patients with human immunodeficiency virus (HIV) infection or patients with long-term use of immunosuppressants [1]. Over the recent years, cases of HIV negative patients without significant immunosuppression have also been reported to be infected with *Penicillium marneffe* [2]. *Penicillium marneffe* generally causes disseminated and progressive infection. Typical signs of NTM combined with *Penicillium marneffe* include a range of systemic symptoms such as persistent high fever (38 degrees Celsius and above), which our patient frequently experienced with night sweats, respiratory symptoms such as cough, dyspnea, chest imaging frequently reveals lung consolidation usually involving the upper lobe; joint-related symptoms such as swollen lymph nodes particularly in the neck, axilla and groin; cutaneous signs such as rash on the torso; polyarthralgia, sacroiliitis and gastrointestinal signs such as diarrhea, abdominal pain [3]-[5].

Although theoretically, it is possible to infect both *Penicillium marneffe* and another opportunistic infection, as most *Penicillium marneffe* infections occur in immunocompromised patients, there have been few reports of co infection cases.

Interferon- γ (IFN- γ) pathway plays a crucial role in host defense against intracellular pathogens [4]. Adult-onset immunodeficiency syndrome is characterized by defects in IFN- γ signaling caused by the generation of anti-IFN- γ autoantibodies (autoAbs) or inherited mutations in IFN- γ -signaling-associated factors. Immunocompromised patients are susceptible to various bacterial infections, especially disseminated non tuberculosis mycobacterial disease (NTM) [5]. Adult-onset immunodeficiency syndrome is characterized by defects in IFN- γ signaling caused by the generation of anti-IFN- γ autoantibodies (autoAbs) or inherited mutations in IFN- γ -signaling-associated factors. Immunocompromised patients are susceptible to various bacterial infections, especially disseminated non tuberculosis mycobacterial disease (NTM) [6]. High concentrations of anti IFN- γ Autoantibodies interfere with the natural inflammatory response to infection, including STAT1 phosphorylation, TNF α Signal transduction and IL-12 production. It has been reported that anti IFN- γ Autoantibody mediated adult onset acquired immunodeficiency is the most important factor in severe *Penicillium marneffe* infection in HIV negative patients [4] [7] [8].

In the case of our patient, she has two opportunistic infections of non-tubercular mycobacterium (NTM) and *Penicillium marneffe* at the same time. According to a large number of literature reports reviewed at present, we consider that the disseminated and refractory NTM combined with *Penicillium marneffe* infection and anti IFN- γ Autoantibodies are closely related.

2. Case Presentation

A 55-year-old woman with fever for 10 days due to repeated multiple joint pain for more than one month was admitted to our hospital on September 19th 2020.

The patient developed sacroiliac joint pain a month ago, which aggravated when squatting with obvious symptom at night, she gradually developed multi joint pain: the limbs, accompanied with lower back pain, the symptoms did not ease after taking a rest. 10 days ago, she developed chill and fever, mostly at night, with a body temperature of about 38 to 39°C, with occasionally night sweats, accompanied by pharyngitis, no cough or sputum, no chest tightness and shortness of breath was noticed. A week ago, she caught fever again which was worse than before, with the highest body temperature of 39.8°C, accompanied by headache and whole-body discomfort. After anti-inflammatory and other symptomatic treatment, her symptoms did not improve.

This patient took a physical examination at our hospital: stable breathing, thick breath sound in both lungs, auscultation: moist rales can be heard in the right lung. Outpatient auxiliary examination was performed at our hospital: routine blood test+ c-reactive protein (CRP): leukocyte $15 \times 10^9/l$, neutrophil% 74.7%, crp163mg/l, out-patient chest CT reveals: consolidation in her right upper lung (**Figure 1(A)**).

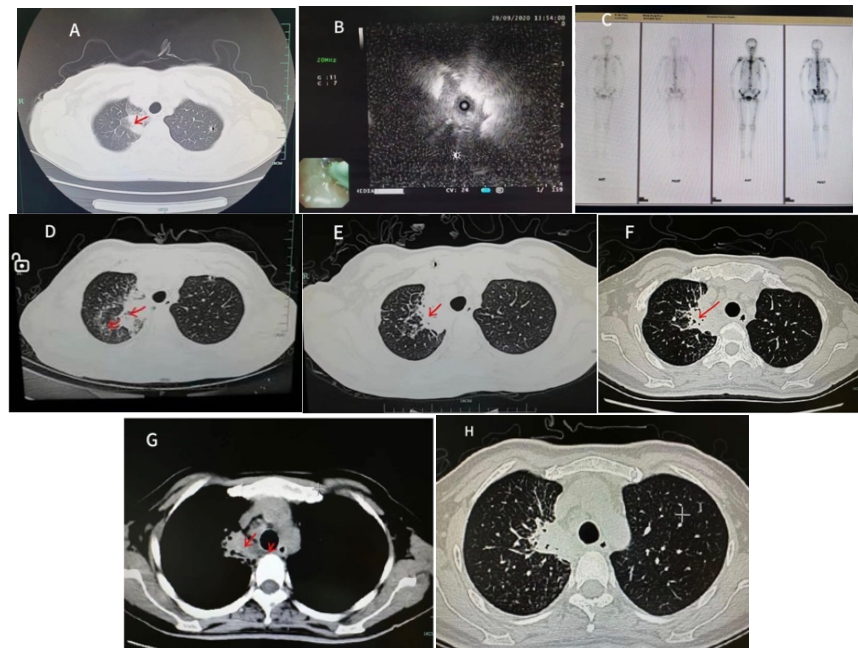


Figure 1. (A) 2020.09.18 chest CT consolidation in the right upper lobe (red arrow); (B) 2020.09.29 Bronchoscopy R-EBUS ultrasonic sheath and probe, hypoechoic lesion in the right upper lobe apical segment; (C) 2020-10-21 Whole body skeletal imaging, multiple abnormal enhancement of bone metabolism throughout the body; (D)-(E) 2020-11-06, 2020-11-17 chest CT, patchy shadow in the right upper lobe (red arrow) roughly opposite to the previous film, new inflammation and small nodules in the right lung (red arrow); (F)-(G) 2020-11-26 Chest CT, mass in the right upper lobe of the lung surrounded by little inflammation better than the 2020-11-06 and 2020-11-17 film (red arrow), mediastinum lymph nodes slightly enlarged (red arrow); (H) 2020-12-05 chest CT, mass in the right upper lobe with a small amount of inflammation better than the 2020-11-26 film.

She had history of breast prosthesis implantation for 10 years. She underwent

prosthesis removal due to local infection of the right breast six months ago, history of herpes zoster. “Sacroiliac arthritis and lymphangitis of both lower limbs” were diagnosed before April. Anxiety was also diagnosed months ago and she was taking Estazolam tablet half pill QD and Paroxetine 1 pill QD.

Pulmonary infection was first diagnosed after her admission, an empirical anti infection treatment was given to her, at the same time, relevant auxiliary examinations were also done and these are the following results; procalcitonin: 0.76 ng/ml; ESR: 56 mm/h; D2-polymer: 730 ug/l; (Five)immune functions; immunoglobulin:18.3 g/l, TBNK lymphocyte subsets report: helper-T cell cd4: 1174, helper-T cell cd4%: 58.7%, cd4/cd8 ratio: 3.45; Blood light chain: K light chain 15 g/l; Tumor markers, thyroid five, AIDS, syphilis, auto-antibody detection, hla-b27cd3: were all negative, anti-cyclic citrullinated peptide, vasculitis related antibody, stool routine, blood aerobic bacteria culture and identification + (routine drug sensitivity test), sputum smear for acid fast bacteria + (routine drug sensitivity test), respiratory tract infection pathogen IgM antibody test: 1.03, invasive Aspergillus infection GM test, invasive fungal infection G test, EB virus antibody TGM EB virus DNA, adenovirus nucleic acid detection, influenza A virus nucleic acid detection. Previous examination was normal.

After admission, the patients was given meropenem injection 1 g Q12H (8-), moxifloxacin 0.400 g QD (8 AM), this treatment was given to cover common pathogens, Voriconazole injection 200 mg Q12H (8) anti-fungi infection, total Glucosides of whites Paeony Capsules (pavlin) 0.6 g BID to regulate the immunity, Diclofenac Sodium Sustained released tablets (Votalin) 1 pill QD (8 AM) to relief the joint paint, Quetiapine Fumarate Tablets (25 mg Seroquel) 12.5 mg QN, Duloxetine Hydrochloride Enteric Capsule (60 mg Cymbalta) 60 mg QN for anti-anxiety. The patient still had recurrent fever and obvious joint pain, we Consider this patient have an atypical pathogenic bacteria infection, so our hospital repeatedly recommended the patient to undergo through bronchoscopy and blood m-NGS examination to further clarify the cause of the infection, but the patient refused to go through bronchoscopy. On the 28-09-2020 superficial lymph nodes ultrasound of the neck and clavicle was performed and the results showed multiple lymph nodes in bilateral neck and groin were accessible. Once again, the patient was recommended to undergo bronchoscopy and m-NGS detection, this time the patient agreed to do bronchoscopy, but still refused m-NGS. On the 29th of September 2020 Bronchoscopy examination was performed and no obvious abnormality was found under routine microscope, and R-EBUS (**Figure 1(B)**) showed hypoechoic lesions in the right upper lobe tip. Brush examination of the lung at the right upper lobe reveal scattered mucosal epithelium, no cancer cells were found. Alveolar lavage fluid of the right upper lobe results reveals no cancer cells were found. The patient still had recurrent fever, accompanied by muscle and joint pain, and high inflammatory markers. On the 4th of October 2020, the patient was sent for chest CT again and the results reveals a significant development compared to the 18-09-2020, and new inflammation in the lower lobe of the left lung

was considered. We consider the disease is progressing so we thought bacterial infection should be considered first, at the same time, the tests of alveolar lavage fluid bacteria, fungal culture, Mycobacterium tuberculosis culture, Mycobacterium tuberculosis DNA: were all negative. The hospital recommended the patients to take an infection sequencing, bone puncture and other examinations to determine the cause of the infection, the patients once again refused. The patient still has temperature fluctuations under the anti-infection treatment covering positive bacteria, negative bacteria and conventional atypical bacteria, and still has pain with discomfort in the lumbar back and bilateral inguinal areas, which intensifies when walking. Physical examination: no obvious tenderness near the lumbar spine, and the Fabere test was negative. The patient's pain and discomfort in the lumbar back and groin area gradually increased. Combine with the patient's multiple lymphadenopathy, we consulted doctors from the orthopedics department, hematology department and rheumatology department for consultation. Considering the fact that we might not rule out the possibility of having "reactive arthritis", she might be transferred to the rheumatology and Immunology Department for further treatment.

The rheumatology department recommended a total glycoside of peony capsule 0.6 g BID to regulate immunity and Votalin 1 pill QD (8 AM) to relieve joint pain, the patient's joint pain did not ease, and gradually aggravated with whole body continuous multi-joint pain. On October 21st 2020, whole body skeletal imaging was recommended. The results revealed an abnormal enhancement of multiple bone metabolism in the whole body (**Figure 1(c)**). Considering the possibility of bone malignant lesions (bone tumor metastasis to be considered), therefore, consider hematologic tumors are to be excluded as well, so we consulted the hematology department and completed bone marrow puncture.

On October 25th 2020, the patient developed chest tightness, shortness of breath, dizziness, edema of both lower limbs, and orthopnea. Physical examination; heart rate: 103 times/minute, breathing: 23 times/minute, blood pressure: 168/92 mmhg, the oxygen saturation: 95%, auscultation of the lungs: wheezing from both lungs. Considering the aggravation of the patient's primary disease and the occurrence of acute heart failure. The emergency blood examination: D-2 polymer: 11030 ug/l, leukocyte 30.3*10⁹/l, neutrophil count%: 88.9%, crp: 255 mg/l, N-terminal B-type natriuretic peptide precursor: 4280 pg/ml, Pct: 0.55 ng/ml, we gave oxygen inhalation, ECG monitoring, report critical illness, methylprednisolone 40mg intravenous injection, rescue once. High inflammatory indicators even after reexamination. On the 26th of October 2020 we performed a bedside chest X-ray and the results revealed: an extensive exudative lesions in both lungs, a mass on the right upper lobe (cannot rule out space occupying lesions diseases), the patient was recommended to further do a CT scan and the results reveal: Pleural effusion on both sides. The pleural effusion was drained and sent to have an examination. The patient complained about her muscles: thigh, abdomen, chest and other parts, sacroiliac joints and other joints were also painful and she could not

turn over automatically. The patient's condition was not easing, after a multi-disciplinary consultation we consider the possibility of hematological tumors, pulmonary vascular embolism and other factors might not be ruled, it was recommended to continue symptomatic treatment such as chest cavity drainage, and improve pulmonary vascular CTA, pleural effusion test, PET-CT, bone biopsy and other examinations. On the 27th October 2020, Bone marrow puncture was performed and the results showed: 1) Absence of marrow particles in smear; 2) Nucleated cells proliferate actively; 3) Granulocyte hyperplasia is significant, toxic changes can be seen; 4) Siphon ratio decreased, mainly in the middle and late; 5) Lymphocytes accounted for 5%, mainly mature cells; 6) A total of 86 megakaryocytes and platelet clusters were seen in the whole film; 7) Macrophages can be seen in the film. Bone marrow morphology suggests: proliferation is active, bone marrow image, granulocyte proliferation is significant, toxic changes can be seen, these should be combined with other relevant examinations. On the October 29th 2020, PET-CT results suggests that the glucose metabolism of bones in many parts of the body within the scanning field is severe, with some corresponding bone destruction and/or soft tissue mass formation. Considering the possibility of patients having hematological diseases, we transferred her to the hematology department for further treatment.

So far, after repeatedly adjustment of the patient's antibiotics including antibiotics which cover Gram-positive/negative, and fungal antibacterial, the patient still has repeated high fever (highest body temperature 39 degree Celsius), and joint pain in the whole body is also obvious. We re-check the patient's chest CT and laboratory exams, we noticed there is a development in the patient's disease. First of all, we consider the possibility of having malignant tumors, special infections are to be ruled out. In order to further clarify the diagnosis, we repeatedly talk with the patient and her family, and on the 2nd of November 2020, the patient agreed to complete ultrasound-guided lymph node puncture and bone marrow puncture again, but no cancer cells were found in the pathology. On the 6th of November 2020, we reexamine the chest CT (**Figure 1(D)**), and the film showed a mass shadow in the right upper lobe (apical segment) and was accompanied by multiple lymph node metastasis in the right hilum and the mediastinum of the lung. Considering the possibility of neoplastic lesions. Compared to the previous film (20-10-2020) there is a progression in the right upper lobe apical segment with atelectasis and peripheral inflammation.

On the 11th of November 2020 left supraclavicular lymph node puncture was completed and the results showed: multiple epithelioid cell nodules were seen, with mixed neutrophils infiltration inside. Immunohistochemistry showed active T lymphocyte proliferation consistent with granulomatous inflammation accompanied by active lymphocyte proliferation with some interstitial fibrous tissue hyperplasia, bone marrow examination showed active hematopoietic tissue proliferation, granulocytes, hyperplasia mainly in the middle and late myeloid hyperplasia. The m-NGS sequencing of the lung puncture tissue submitted for testing

showed: 6 sequencing of mycobacterium avium infection and 30 sequences of staphylococcus aureus. Whole -body PET-CT indicates extensive hypermetabolic lesions in bones, lymph nodes, lungs, liver, spleen, and other parts of the body. No tumor cells were found under bronchoscopy puncture, Supraclavicular lymph node puncture and CT-guided lung mass puncture. Lymphoma basically was not considered; infections were considered from the pathological morphology. During hospitalization, the patient developed scattered red rash on her abdomen and back, without pain or itching, with difficulty breathing, and with orthopnea so she was diagnosed with “cardiogenic asthma”. She was given 25 mg Seroquel QN, Oxapin 40 mg BID for anti-anxiety, 2.5 mg of Diapazam QN, and 2 mg of Clonazepam QW for sleep, Celecoxib capsule Pregabalin Capsule 75 mg BID, and Fentanyl Transdermal patches 4.2 ng Q72 for topical pain relief, Sulprazon 2 g 08H d5+ Azithromycin 0.5 g QD d2 was used as an empiric anti-infection, but it was ineffective after a certain course of treatment, so Moxifloxacin Hydrochloride tablets (Baifulex) 0.4 g QD d8. Later, because the patient's intestinal CRE was positive, Micafenin sodium “Ying” needle 150 mg QD d5, lung puncture tissue NGS detected Staphylococcus aureus and mycobacterium infection so azithromycin 0.5 g QD + Rifampicin capsules 0.6 g QD + Ethambutol 0.75 g QD was added to treat mycobacterium infection, Tigecycline injection “Tige” 50 mg Q12 was also used to fight infection. The patient still had fever with multiple joint pains throughout her body. On the 17th of November 2020, a chest CT was performed to access the patient's condition (**Figure 1(E)**), and the film showed no absorption compared to the previous film.

Later, due to patient's personal reasons she was discharged and transferred to the First Hospital of Zhejiang Province for further treatment. After admission, the patient still had fever (high body temperature: 38 degree Celsius) accompanied by generalized polyarthralgia, fatigue and anorexia for 1 month. The patient had red rashes on her abdomen, and back, without itching or pain, she had difficulties in breathing and was forced to “sit up right breathing”, she was later on diagnosed with “cardiogenic asthma”.

On 20th of November 2020, the patient still had fever (high body temperature 38 degree Celsius) and whole-body multiple joints pain, blood routine test showed WBC count: $23.5 \times 10^9/L$, neutrophils (%): 86.2%, lymphocytes (%): 6.5%, hemoglobin: 105 g/L TSPOT was negative. 2020-11-21 procalcitonin exam was done: 0.65 ng/ml, ESR: blood sedimentation: 25 mm/h, the following day on the 22nd, tumor markers + CA125 + ferretin + CA153 was done and it reveals; ferretin: 1362.0 ng/ML Carbohydrate Antigen 125 57.oUL, A30 + RF + high-sensitivity C-reactive protein + CCP; high-sensitivity C-reactive protein: 126.0 mg/L. CD3/4/8/16/19/45/46 shows; B cells (CD19+): 4.6%, B cells (CD19+) 56 each/ul. ON the 25th of November 2020, the levels of TNF + IL2/4/6/10/17 + INF- γ were tested: IL-6: 781.42 pg/ml; IL-10: 36.20 pg/ml, TNF- α : 0.94, IFN- γ : 0.10 pg/ml.

A lumbar puncture was performed on November 24th 2020 and the pressure was 90mH20, the cryptococcus neoformans smear test (cerebrospinal fluid) was

negative; cerebrospinal fluid routine: clear clarity; Paneth test: +, nucleated cells: 98/WBC (GeneXpert). On the 26th November 2020, the clinicians recommended a high resonance chest CT (view **Figure 1(F)**, **Figure 1(G)**) and the results revealed: The mass in the right upper lobe of the lung with a small amount of surrounding inflammation, and the mediastinal lymph nodes are slightly enlarged, better than the previous film, small nodules in both lungs, which is similar to the previous films. Mycobacterium tuberculosis was not detected and cerebrospinal fluid was 9.592 g/L; a bone marrow aspiration + biopsy was performed on 2020-12-03, the biopsy showed an extremely active proliferation of bone marrow, hematopoietic tissue accompanied by granuloma formation? Immunohistochemistry reveals: anti-acid (+), silver amine (-), PAS (negative), TB(FISH) (+), Fungus (FISH) (-).

The diagnosis was: 1-sepsis, 2-disseminated non-tuberculous mycobacterial disease (mycobacterium leucocephalus clavicle skull) increased intracranial pressure, 3-atopic dermatitis, 4-anxiety state, 5-hypoglycemia, 6-amenia.

The patient was given Azithromycin 0.5 g QD, moxifloxacin 0.4 g QD, faropenem tablets 200 mg TID, Linezolid tablets 0.6 g Q12H anti-mycobacterial infection, Rabeprazole capsules were also used to protect the stomach and supportive treatment such as lipid emulsion amino acid injections and potassium supplements. After few days of observation, the patient condition was getting better so she was discharge.

Later, on the 5th December 2020 the patient completed a High resonance CT (**Figure 1(H)**) and the results revealed mass in the right upper lobe of the lung with a small amount of surrounding inflammation, and the mediastinal lymph nodes are slightly enlarged, similar to the 2020-11-26 CT, small nodules in both lungs, which is similar to the previous films.

3. Discussion

Mycobacterium avium is usually called *Mycobacterium avium* complex (MAC). It is an opportunistic pathogen and a common type of non-tuberculous *Mycobacterium*. It mainly causes disease in patients with impaired immune function caused by HIV infection or other reasons [9]. The main way for it to enter the body is through the bronchus or intestinal mucosa [10] [11]. In most cases, Non tuberculous mycobacteria are associated with pulmonary infections in adults, cervical lymphadenitis in children, and disseminated infections of children and adults [12] [13]. Joint involvement is most common in patients with low immune function [14], such as HIV infected patients, patients receiving immunosuppressive drugs in the affected joints or patients receiving joint endothelium steroids injection in advance, while hosts with normal immune function are rarely affected.

Meanwhile, Anti interferon- γ Auto-antibodies (anti IFN- γ Auto-Abs) were first reported in patients with mycobacterial infection [15]. The first case of disseminated *Trypanosoma marneffi* infection, including the lungs, lymph nodes, and chest wall, was successfully treated with antifungal therapy [16]. Given that

recurrent opportunistic infections have no potential for immune dysfunction, we conducted an IFN- γ Autoantibody test on the patient, and the result was positive. Therefore, she is considered to have adult immunodeficiency syndrome. The elevated serum levels of anti-IFN- γ Auto-antibodies, which later inhibited the phosphorylation of signal transduction and activators of the transcription 1 (STAT1) and the high titer of interleukin-12 production, leading to serious impairment of Th1 response and increased risk of infection with a variety of intracellular pathogens, including *non-tuberculous Mycobacterium* (NTM), *ankle bacterium marn- effei*, *Cryptococcus neoformans* [15]. Although several studies have shown that patients with normal and low immune function can be infected with NTM [17] [18], the cases of disseminated NTM infection usually occur in patients with low immune function, such as people using immunosuppressants for a long time or patients infected with human immunodeficiency virus (HIV), especially in patients with CD4 counting less than 50 cells, in which NK and INF- γ secreted by T cells [6]. In addition, it plays a key role in resisting cellular immunity. In addition, we can detect that other opportunistic infections, such as *penicillium marneffeii* infection, have also happened to patients with NTM infection and anti-IFN- γ auto-antibodies [19].

The triggering factors of IFN- γ autoantibodies are not yet clear. As is well known, strong local HLA DRB and DQB are associated with *Mycobacterium avium* infection. These genes encode proteins that are expressed on the surface of antigen-presenting cells (APCs) and recognized by Th cell receptors. The interaction between APC and Th cells may promote the development of anti-IFN- γ auto-antibodies [20]. In addition, environmental stimuli may trigger disease induction, including infections and toxins. Therefore, anti IFN- γ High titer anti IFN- γ Autoantibodies are the main cause of disseminated NTM infection [21]. Although the current incidence of this patient is related to anti IFN- γ , there is a great correlation between auto-antibody mediated adult acquired immunodeficiency). The patient once had her breast prosthesis removed after infection, which may also be one of the reasons for her infection. We noticed that Surgery can also lead to opportunistic disease, and there had been reports of *Mycobacterium avium* infection after breast augmentation surgery in the past [22] [23].

The treatment of intracellular *Penicillium marneffeii* infection in conjunction with disseminated and refractory non-tuberculous mycobacterium (NTM) is challenging [24], because it is easy to produce resistance to antibiotics, never the less treatment plan includes involves immunological modulation in addition to a mix of antifungal and antibacterial drugs [16]. Clarithromycin, rifampicin, capreomycin, ethambutol, linezolid, amikacin, moxifloxacin and other drugs were considered to be effective in reports of different cases, among which clarithromycin, rifampicin and capreomycin showed better antibacterial activity against intracellular mycobacteria [25] [26]. Voriconazole was shown to have better efficacy for anti-fungal treatment. *Mycobacterium avium* complex (MAC) infection has also been described in conjunction with other serious illnesses, such as thyroid cancer

and concomitant pulmonary mycobacterium avium infection indicating the prevalence of mycobacterium avium infection in complex clinical settings [27]. Furthermore, the identification of mycobacterium avium paratuberculosis (MAP) in individuals suffering from long-term immune-related conditions like Crohn's disease highlights the impaired immune systems that these infections grow in [28].

Combined with the clinical characteristics and NGS examination of the patient, furthermore the diagnosis of intracellular Mycobacterium avium infection was clear [29]. However, during the treatment of our case patient, there were repeated conditions and poor effect. We think that it may be related to the drug resistance of Mycobacterium, and we also believe that it is closely related to the patient's positive anti IFN- γ auto-antibodies [30]. Literature reports that anti IFN- γ patients and disseminated NTM infection with positive auto-antibodies are more likely to have failed treatment and recurrent disease [31]. Anti IFN- γ Compared to PM infected patients with negative auto-antibodies, anti IFN- γ , patients with positive auto-antibodies have no potential respiratory diseases, but it is more frequently for them to embody show the spread of systemic infection with severe pleural effusion. Despite the standardized antibacterial treatment, most patients still show unsatisfying effect for treatment [32]. Therefore, we consider that the above is the main possible reasons for the recurrence of the disease and difficult treatment of this patient after standardized treatment. Firstly, Non-tuberculous Mycobacterium infection occurs in the bone and joint of the whole body, which is a rare part of the performance. Due to lack of consciousness or unclear performance, it is often misdiagnosed as inflammatory arthritis at the initial stage, which is easy to mislead doctors in using anti-rheumatic drugs to treat the disease Our patients showed multi-joint pain in the whole body during the treatment, with obvious pain in and the knee and lumbar joints [33]. PET-CT and bone whole-body imaging showed that bone metabolism was vigorous and bone destruction, which misled us to suspect that the patients might have rheumatic diseases and hematological malignancies. All these highlight the importance of a detailed medical history. Thus eliminating inflammatory arthritis and avoid immunosuppressive therapy which may lead to disastrous consequences. Secondly disseminated, refractory and recurrent NTM, *Penicillium marneffe*i infection are closely related and anti IFN- γ Autoantibodies [34]. We should pay attention to the relevant examination of immune deficiency caused by anti-IFN- γ autoantibodies in the process of the treatment of infection such as NTM. Lastly, anti-IFN- γ patients with positive autoantibodies still show the characteristics of refractory and recurrent non-tuberculous Mycobacterium infection. At present, according to some reports, rituximab may be an alternative or salvage treatment for disseminated NTM infection in patients with anti-IFN- γ autoantibodies, but there is still a lack of relevant basis and institutional research, suggesting the development of production defects of human cytokine in special infectious diseases and in more effective treatment methods [35].

In summary, the patient presented here was considered disseminated and

refractory nontubercular mycobacterium (NTM) combined with *Penicillium marneffei* infection. In addition, we found that anti IFN- γ autoantibodies are closely related. Although the current incidence of this patient is related to anti IFN- γ , there is a great correlation between auto-antibody mediated adult acquired immunodeficiency.

Authors' Contributions

EFY & XXZ: Wrote the original draft, writing-review and editing; both should be considered as first co-authors; **CHY & YTZ:** Data curation; **LJD:** Formal analysis; **EJ:** Super-vision, conceptualization.

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Conflicts of Interest

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviation

PM	<i>Penicillium marneffe</i>
MAC	Mycobacterium Avium Complex
IFN- γ	Interferon- γ
AIDS	Acquired Immune Deficiency Syndrome
HIV	Human Immunodeficiency Virus
Mmhg	Millimeter of Mercury
CRP	C-Reactive Protein
g/l	Gram per liter
CT	Computerized Tomography
PET-CT	Positron Emission Tomography and Computed Tomography
TBNK	T and B Natural Killer Cells Panel
Hla-b27	Human Leukocyte antigen 27
cd3	cluster of differentiation 3
igM	immunoglobulin M
GM	Galactomannan
G	Globulin
EB	Epstein-Bar
DNA	Deoxyribonucleic Acid
mNGS	metagenomic Next-Generation Sequencing
ESR	Erythrocyte Sedimentation Rate
Mg/l	Milligrams per liter
Pg/ml	Picograms per milliliter
Mg	Milligrams
Mg/ml	Milligrams per milliliter
Ng/ml	Monograms per milliliter
Ug/l	Micrograms per liter
Mm/hr	Millimeters per hours
BID	Twice in a Day
TID	Three Times in a Day
QD	Once in a Day
Q12H	Take Every 12 Hours
R-EBUS	Radial Endobronchial Ultrasound
ECG	Electrocardiogram
CTA	Computed Tomography Angiography
Pct	Procalcitonin
Mg	Milligram
STAT1	Signal Transducer and Activator of Transcription 1
CD4	Cluster of Differentiation 4
NTM	Non Tuberculous Mycobacterium