Infection and Drug Resistance

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CASE REPORT

Anti-Infection of Nasopharyngeal Carcinoma Combined with Non-Tuberculous Mycobacteria: A Case Report and Literature Review

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Background: Patients with nasopharyngeal carcinoma (NPC) combined with non-tuberculous Mycobacteria-pulmonary disease (NTM-PD) are very rare in the clinic, and our case is the first patient with NPC combined with NTM-PD. For oncologists, rapid control of the symptoms of infection is essential to the treatment of the primary disease.

Case Presentation: A 58-year-old man who developed a NTM-PD after chemotherapy for nasopharyngeal carcinoma. Granulocytosis after chemotherapy is a major factor in the development of various infectious diseases. Nasopharyngeal tumor was found on MRI of the patient's head, and nasopharyngeal malignant tumor was considered after pathological examination after endoscopic resection of intranasal lesion, and then nasopharyngeal non-keratonic carcinoma (T4N1M0, stage IV) was confirmed in the department of oncology. The patient developed bone marrow suppression after chemotherapy and was admitted to hospital due to septic shock. Chest CT examination indicated pulmonary infection, and empirical antibiotic treatment was not effective. The NGS results showed that the patient was infected with Mycobacterium abscess. We treated with cefoxitin followed by moxifloxacin to reduce the lung lesions significantly.

Conclusion: NPC with NTM-PD is very rare, and the treatment of NTM-PD is very important for the prognosis of the patient's primary disease. Our study provides experience for anti-infection treatment of patients with immunosuppression.

Keywords: nasopharyngeal carcinoma, immunosuppressed, NTM, anti-infection, cefoxitin, moxifloxacin

Introduction

Mycobacterium abscessus is a rapidly growing non-tuberculous mycobacteria (NTM) ubiquitously found in the environment,[1] which is second only to Mycobacterium avium complex (MAC) species as a cause of NTM pulmonary infections in the United States.[2,3] M abscessus pulmonary disease typically resembles nodular/bronchiectatic MAC disease with gradual symptom onset, including cough and fatigue, high-resolution CT abnormalities, including cylindrical bronchiectasis with multiple small nodules, and indolent disease progression.[4,5] NTM can cause progressive inflammatory lung damage, termed NTM-pulmonary disease (NTM-PD).

Nasopharyngeal carcinoma (NPC) is a rare Epstein-Barr virus (EBV)-associated malignant tumor with a specific geographical distribution within endemic areas (Southern China, Taiwan, the Philippines, Vietnam and Northern Africa). Concerning diseases that are associated with NPC, studies have revealed that connective tissue diseases, such as scleroderma or dermatomyositis, are found in patients suffering from such a malignancy.[6] NPC with NTM-PD has not been reported, only cystic liver metastasis of nasopharyngeal carcinoma has been reported.[7] For patients with nasopharyngeal carcinoma complicated with NTM-PD, the treatment of NTM-PD is a necessary condition for further radiotherapy and chemotherapy. The study provides clinical experience and evidence-based evidence for anti-infective treatment of tumor patients.

Received: 14 May 2024
Accepted: 2 August 2024
Published: 14 August 2024

Case Presentation

On October 8, a 58-year-old man experienced dizziness without obvious causes, accompanied by unsteady standing, nausea, vomiting, and diarrhea for several times, and was admitted to the emergency department for symptomatic treatment.

The patient was diagnosed with nasopharyngeal non-keratonic carcinoma (cT4N1M0 IVB) in our hospital in September. The first cycle of chemotherapy "Docetaxel + Cisplatin + 5-fluorouracil" was performed on October 1 (Figure 1, green box). He was discharged from hospital on October 6 after blood routine examination.

Chest CT (October 9) in the emergency showed that Chronic bronchitis and emphysema. New lesions were found in the lower lobe of the right lung. Laboratory tests showed a WBC count 0.62*10^9/L, PLT count 32*10^9/L, PCT 100ng/mL, Alb 26g/L (Figure 1, blue box), as shown in Tables 1 and 2. After 5 days of empirical anti-infective treatment with meropenem, the patient's body temperature and PCT decreased, and WBC count returned to normal.

The patient was treated with meropenem for anti-infection in the early stage, but the intestinal flora was seriously disturbed, repeated diarrhea, and he had no fever. Clinical pharmacists suggested that the patient continued to be treated with ceftazidime for 8 days. On Oct 19, the patient's diarrhea improved. Two days later, the cough of the patient worsened significantly during the night and white phlegm was coughed up occasionally. Physical examination showed that breathing sounds were coarse in both lungs, and wet rales could be heard in the lower right lung. Reexamination showed that the blood routine of the patient was normal and the sputum culture was negative. Chest CT examination was performed on October 22, which showed that the lower lobe of the right lung was infected with multiple new cavities, there were a few new lesions in the posterior and middle lobe of the upper lobe of the right lung (Figure 2A), and the possibility of lung abscess formation was warned. In a prospective study of 46 lung abscesses, 35 (76.09%) were found to be gram-negative and 2 (4.35%) were found to be gram-positive.[8] Accordingly, the patient was switched to anti-infection therapy with latamoxef for 5 days. The patient's symptoms did not improve significantly, and further tests were planned. On October 24, fiberoptic bronchoscopy showed obvious hyperemia of bilateral bronchial mucosa, more white phlegm and bronchial inflammation in the lumen. On October 27, next-generation sequencing technology (NGS) results of fiberoptic lavage fluid of the patient showed Mycobacterium abscess (Figure 1, red box). Considering that the patient had NTM-PD, clinical pharmacists recommended that antibacterial agents were switched to cefoxitin (4g q8h intravenous drop infusion, days 20–54, Figure 1, yellow box). Re-examination of chest CT indicated that the lesions in the lower lobe of the right lung were more absorbed than before, indicating that the treatment was effective. As the patient's cough and sputum were further improved, the reexamination of chest CT on October 31 indicated that the infection in the lower lobe of the right lung was absorbed more than before (Figure 2B) and the right pleural effusion was less.

After anti-infective treatment of cefoxitin, the patient's laboratory indicators showed that the PCT was 0.046 ng/mL and the WBC count was normal. It is suggested that the anti-infective treatment is effective. Subsequent chest CT indicated further improvement of the right inferior lobe (Figure 2C). Mycobacterium abscessus was not found in the second NGS, but DNA virus was found. Clinical pharmacists recommended sequential treatment with moxifloxacin after discharge (0.4g qd orally, days 55–85, Figure 1, yellow box). CT (Figure 2D) showed that significant reduction of the lesions in the lower lobe of the right lung and further reduction of a small amount of fluid in the original right thoracic

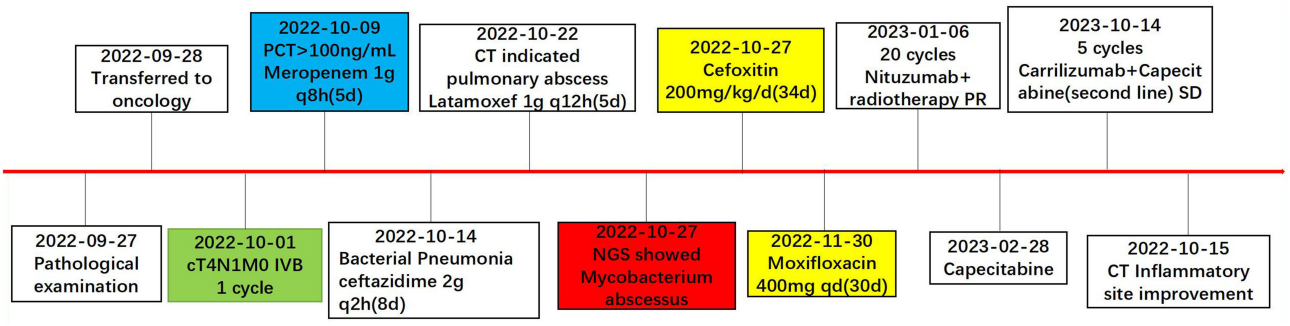

Figure 1 Information of this case report has been organized into a timeline.

Table 1 Laboratory Data

Variable	Reference Range, Adults	ICU (10–9)	ICU (10–12)	On Admission, Infirmary (10–20)	Day (1–12), Hospital in China
Hematocrit (%)	40–50	36	27	32	38
Hemoglobin (g/dl)	130–175	130	95	106	124
White-cell count (per mm3)	3.5–9.5	0.62	7.24	8.12	2.26
Differential count (%)					
Neutrophils	40–75	59.7	93.0	69.8	56
Lymphocytes	20–50	9.9	2.9	12.7	11
Monocytes	3–10	13.9	3.5	15.5	24
Eosinophils	0.4–8.0	0.0	0.0	0.9	9.0
Basophils	0.0–1.0	1.0	0.6	1.1	0.0
Platelet count (per mm3)	125–350	32	31	472	150

Table 2 Laboratory Data (Other Tests)

Variable	Reference Range, Adults	ICU (10–9)	ICU (10–12)	On Admission, Infirmary (10–20)	Day (1–12), Hospital in China
Smear description					
C-reactive protein (mg/dl)	0.046	>100	44.0	0.263	–
Erythrocyte sedimentation rate (mm/hr)					
Fibrinogen (mg/dl)	1.8–3.5	8.5	8.1	–	5.0
d-Dimer (mg/liter)	0–0.55	1.02	1.86	–	0.17
Prothrombin time (sec)	9.8–12.1	17.3	11.2	–	12.2
Prothrombin-time international normalized ratio	0.86–1.15	1.65	1.03		1.13
Potassium (mmol/liter)					
Urea nitrogen (mg/dl)	3.1–8.0	11.8	5.6	3.8	3.6
Creatinine (mg/dl)	57–97	131	58	60	63
Glucose (mg/dl)					
Bilirubin (mg/dl)					
Total	0.0–26.0	–	13.1	10.9	7.3
Direct	0.0–6.8	–	6.0	3.9	2.2
Protein (g/dl)					
Total	65–85	47	42	60	70
Albumin	35–55	26	24	30	41
Aspartate aminotransferase (U/liter)	15–40	27	60	25	27
Alanine aminotransferase (U/liter)	9–50	19	56	18	22
Alkaline phosphatase (U/liter)	45–125	38	58	60	85
γ-Glutamyl transferase (U/liter)	10–60	19	21	19	15
Lipase (U/liter)	13–63	13	–	–	–
Amylase (U/liter)	35–135	20	–	–	–
Lactate (mmol/liter)					
Carcinoembryonic antigen (ng/mL)					1.25

cavity. Subsequent CT (Figure 2E and F) results indicated that the lesions were further reduced and the treatment of infection was successful.

Computed tomography (CT) and magnetic resonance imaging (MRI) are useful imaging tools.[9] Therefore, when the infection was controlled, head and neck MRI (plain scan + enhancement) of the patient were immediately performed, and no significant thickening of the nasopharyngeal mucosa was observed. The tumor area was reduced. The original lymph nodes in the neck have largely disappeared (Figure 3). After one cycle of chemotherapy, reexamination of the head and neck MRI showed that the local lesions were significantly receded, and the disease was evaluated as PR.

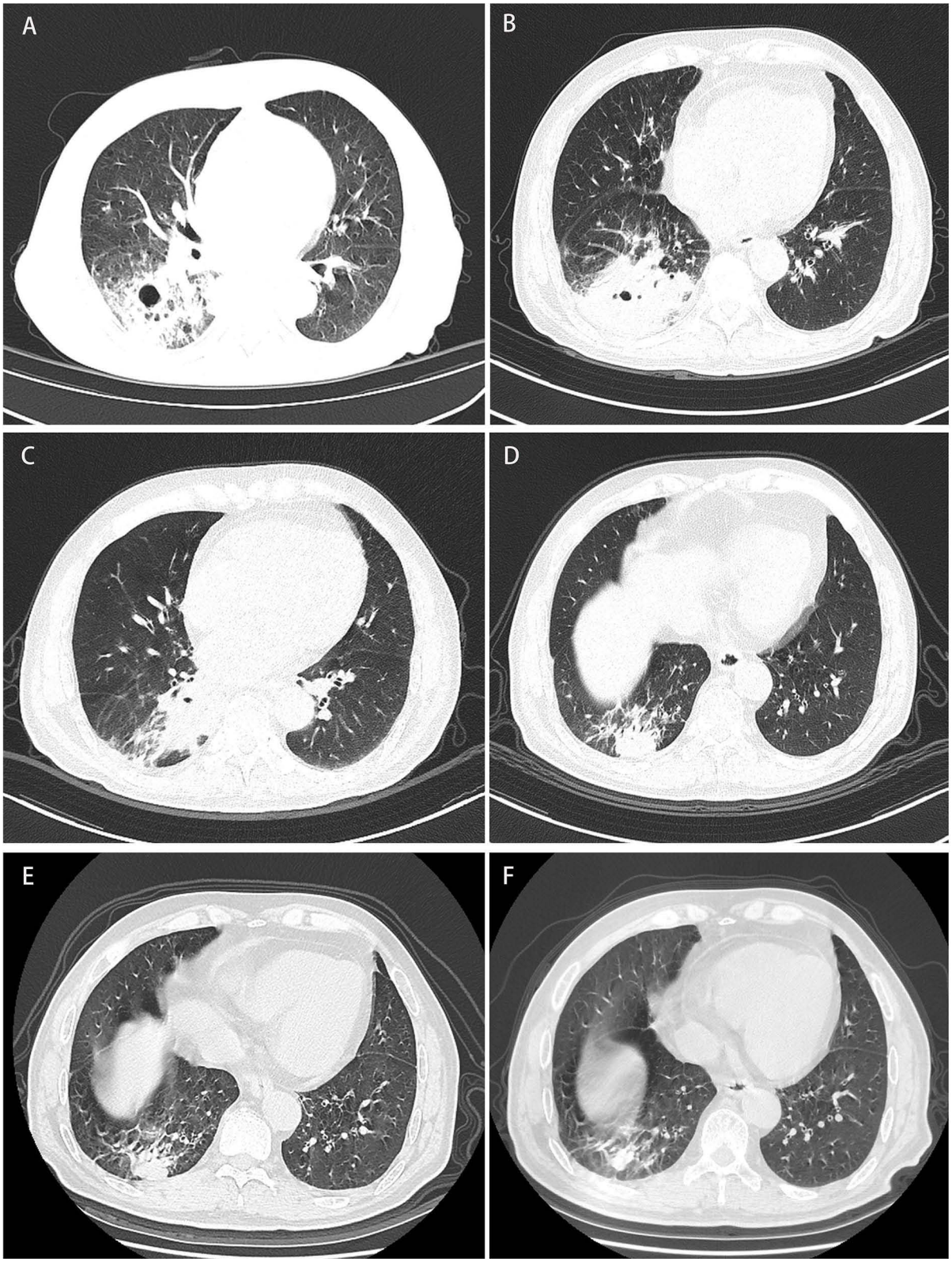

Figure 2 (**A** and **B**) Multiple new voids, alert for lung abscesses. (**C**) and (**D**). Compared with (**A** and **B**), the cavity disappeared and the lesion shrank, but not fully absorbed. (**E**) and (**F**). The lesion site of the lower lobe of the right lung was significantly reduce.

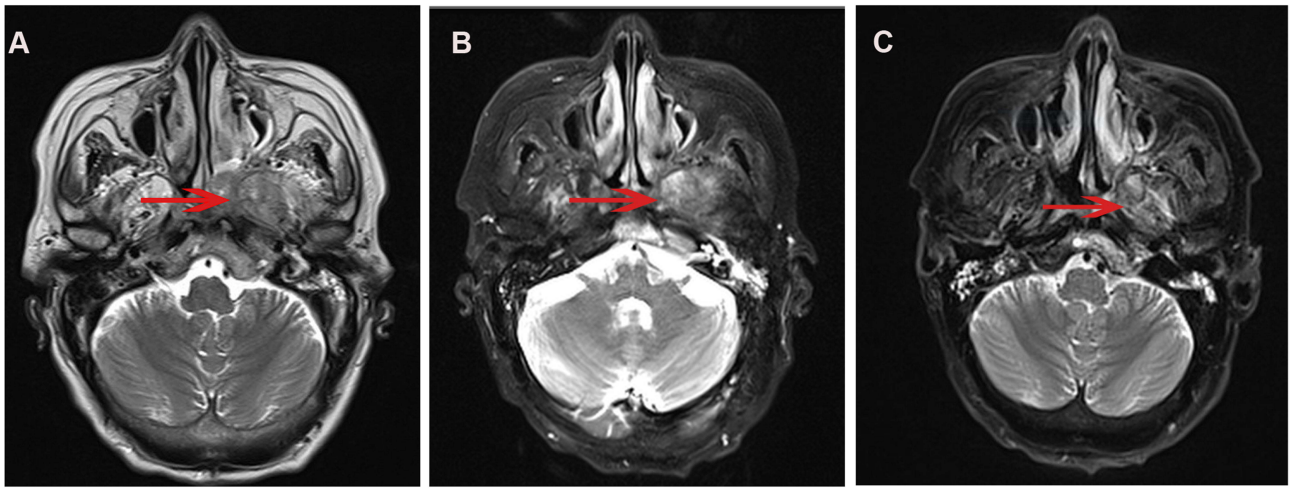

Figure 3 Compared with (**A**), the above bones and surrounding soft tissues at the skull base of (**B**) were changed and the tumor invasion was smaller than before; Compared with (**B**), the mucosa of the left lateral wall of the nasopharynx in (**C**) was significantly thickened.
Note: The lesion site of nasopharyngeal carcinoma was indicated by the red arrow.

Since systemic chemotherapy is not suitable with anti-infective therapy, local radiotherapy is used to control the lesions, and clinical pharmacists suggested the targeted therapy of nituzumab with the patient. The combination of nituzumab and concurrent chemoradiotherapy is an important treatment strategy for local advanced nasopharyngeal carcinoma.[10] A patient with acute myelogenous leukemia combined with right calcaneal osteomyelitis also required prolonged interruption of leukemia therapy in the treatment of mycobacterium osteomyelitis. Diagnosis and treatment involving doctors and pharmacists and multidisciplinary cooperation are crucial in patient management.[11]

Discussion

In our case, the patients had no pulmonary disease when NPC was diagnosed, mainly due to secondary infection by decreased immunity after chemotherapy. NTM is a conditional pathogen, some types of NTM will colonize the respiratory tract of healthy people. When the body's local or systemic immunity is reduced, it can cause disease, invade the human lungs, lymph nodes, bones, joints, skin soft tissue and other parts of the body, and may even cause systemic disease. Serine protease inhibitor kazal-type 6 (SPINK-6) is the main gene involved in the proliferation and metastasis development of NPC.[12] Thus, no direct association was found between NTM-PD and NPC in our study. What's more, anyone with lower immunity is likely to be infected by NTM, not just patients with NPC. As long as the patient is in a state of low immunity, it is possible to be infected by NTM at or before the NPC diagnosis.

Mycobacterium tuberculosis is an air-borne bacteria transmitted via Pflügge's droplets during coughing, talking, or sneezing.[13] Wu et al reported a patient of NPC with secondary pulmonary tuberculosis. Anti-tuberculosis treatment of the patient was according to the regimen: Once-daily (q.d). administration of 300 mg isoniazid, twice a week administration of 600 mg rifapentine, and q.d. administration of 750 mg ethambutol, which was continued for 6 months.[14]

NTM-PD has similar clinical manifestations with pulmonary tuberculosis, including systemic poisoning symptoms and local damage, but systemic poisoning symptoms are less severe than tuberculosis, others with the clinical manifestations of the underlying diseases of itself overlap. However, its treatment regimen is different from that of pulmonary tuberculosis, cefoxitin 200 $mg \cdot kg^{-1} \cdot d^{-1}$ was administered in three doses and administered intravenously to a maximum amount of 12 g in a day. Primary stage should be at least 1 month, and it is recommended to be extended to 3 to 6 months. Moxifloxacin, 400 mg/d, was administered orally in continued phase.

The patient developed grade IV myelosuppression, fever, neutropenia and other symptoms after the first chemotherapy. All patients with febrile neutropenia should be promptly initiated with broad spectrum antibiotics to reduce the risk of serious complications and death.[15,16] The initial selection of antimicrobial regimens should be based on the patient's underlying disease, allergy status, symptoms, signs, recent or concurrent antibiotic and bacterial culture results, and the

susceptibility pattern of pathogens in the corresponding healthcare facility.[17] Although gram-positive bacteria are the most common pathogen in neutropenic fever episodes, antibiotic treatment should cover aerobic gram-negative pathogens extensively because the virulence of aerobic gram-negative pathogens is associated with severe sepsis syndrome.[18] In addition, gram-negative bacteria continue to cause infection in most sites outside the bloodstream (respiratory tract, biliary tract, gastrointestinal tract, urinary tract, and skin), and the patient was at high risk, so clinical pharmacists recommended empirical treatment with pseudomonas covered meropenem.[19–22] The patient had no clear source of infection and the blood culture results were negative. The formulation of antibiotic regimen usually depends on the patient's infection markers and bone marrow hematopoietic function. If the patient has no fever for at least 2 days, and ANC≥500/μL continues to rise, broad-spectrum antibiotics are usually discontinued to avoid drug resistance. This method is consistent with IDSA guidelines.[23] The ANC of the patient was 5.9*10^9/L after 4 days of use of meropenem and no fever was found. Clinical pharmacists considered using ceftazidime for anti-infection.

The patient had no underlying lung disease and was previously hospitalized in the ICU. Aspiration is highly suspected and the possibility of primary pulmonary abscess is considered before NGS examination of alveolar lavage fluid is performed. The pharmacists selected the broad-spectrum antimicrobial drug latamoxef to treat the patient (covering most G-, some G+, enzyme-producing resistant bacteria and some anaerobic bacteria). It has also been reported that latamoxef treated a case of lung cancer secondary lung abscess.[24] Patients with aspiration lung abscess usually show clinical improvement within 3–4 days of starting antibiotic therapy, manifested as reduced fever and the return of white blood cells to normal, and fever resolution is expected within 7–10 days.[25] After 5 days of use latamoxef, the patient did not show significant improvement, and further examinations were considered to identify the pathogen.

After the detection of Mycobacterium abscess by NGS, clinical pharmacists recommended cefoxitin (4 g q8h Intravenous drop infusion, days 20–54) for anti-infection treatment. Reexamination chest CT showed that the lesions in the lower lobe of the right lung were more absorbed than before, indicating that the treatment was effective. The above treatment further indicated that the patient's diagnosis with infection of Mycobacterium abscess was further supported. Resistance updates reveal that macrolides and most beta-lactam drugs have begun to be resistant, with only cefoxitin and imipenem are useful.[26] According to guidelines for the diagnosis and treatment of non-tuberculous mycobacteriosis, cefoxitin has strong antibacterial activity in a M. abscessus complex (MABC). For the initial phase of MABC treatment, this phase lasts at least 1 month and can be extended to 3–6 months.[27] And moxifloxacin (0.4g qd orally, 30 days) for sequential therapy after discharge. For this patient, clinical pharmacists and clinicians suggested that antimicrobial therapy should be continued until chest CT showed that the lesions disappeared or only stable small lesions remained. At subsequent follow-up, CT of the patient (Figure 4) indicated significant reduction in the extent of the lesion.

A high index of suspicion for mycobacterial infection is required for immunocompromised patients with prolonged fever or unusual presentation, Nontuberculous mycobacterial pulmonary disease (NTM-PD) often develops in patients

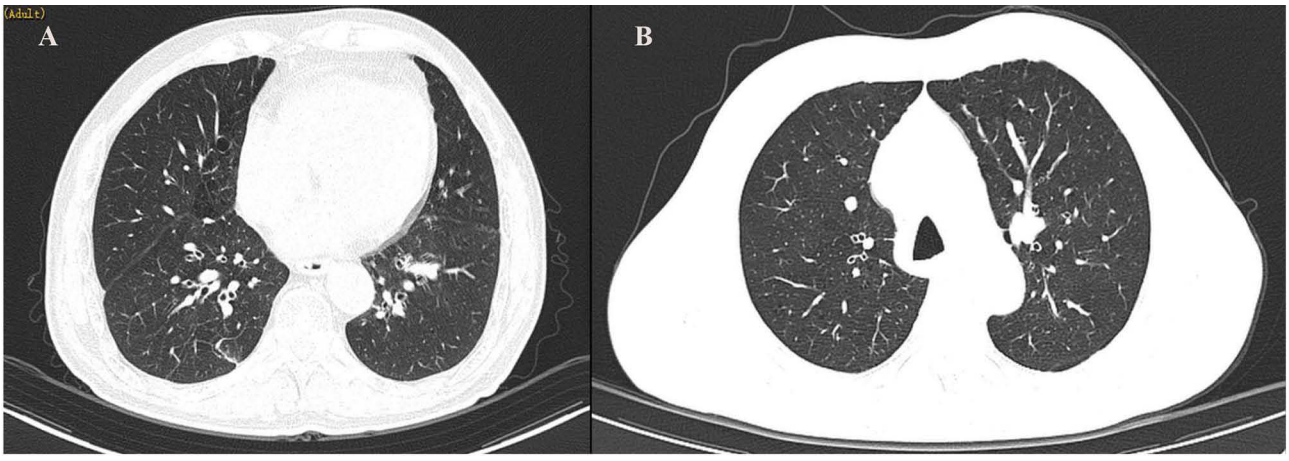

Figure 4 (**A**) Follow-up chest CT of the patient after 10 months. (**B**) Follow-up chest CT of the patient after 12 months.

with rheumatoid arthritis (RA), especially during immunosuppressive treatment.[28,29] The abscess mycobacterium was detected in the lung sample of this patient, which is the second most common nontuberculous mycobacterial lung disease pathogen and comprises three subspecies: abscessus, massiliense, and bolletii. Subspecies identification is critical for disease management, as subspecies abscessus and bolletii have an inducible macrolide resistance gene [erm (41)] that results in clinical macrolide resistance. The drug susceptibility characteristics of M. abscessus subspecies and Bolei subspecies isolates are usually as follows: Clofazimine (90%), amikacin (90%), cefoxitin (70%), imipenem (50%), Linezolid (23%), tigecycline (sensitivity threshold not yet determined, but MIC<1μg/mL for most isolates), clarithromycin (sensitivity 100% in initial in vitro susceptibility test); However, many of these isolates have active inducible macrolide resistance genes, so they may be resistant in vivo even if the initial in vitro susceptibility test shows sensitivity. The characteristics of drug susceptibility of M. abscessus Masai subspecies were similar to those of M. abscessus subspecies, but most of the isolates did not have active inducible macrolide resistance genes.

NTM-PD is the most common NTM disease, accounting for about 70% to 80% in foreign countries, but there is no specific data in this regard in China.[30] The clinical manifestations of NTM-PD vary greatly. Some patients may have no obvious symptoms for a long time or only cough and sputum by physical examination. Chest CT lesions may remain unchanged for a long period of time or may vary from time to time. In some patients, the disease progresses rapidly, including cough, phlegm, hemoptysis, chest pain, chest tightness, asthma, night sweats, low fever, fatigue, emaciation and malaise, etc. The chest CT lesions may progress, spread and form voidage in the short run, and the clinical condition is relatively serious. It can also invade the pleura and pericardium, causing pleural effusion and pericardial effusion.[31–34]

The clinical significance of NTM strains isolated from different clinical specimens varies, and NTM isolates from specimens from blood, lymph nodes, bone marrow, liver, kidney and spleen often indicate pathogenic bacteria. In addition, the NTM of sputum, induced sputum, bronchial flushing fluid, bronchoalveolar lavage fluid and other respiratory specimens should exclude the possibility of specimen contamination or respiratory tract colonization.[35,36] The limitation of our study was that the specimens were obtained from the alveolar lavage fluid, but the patient's clinical symptoms and imaging both showed improvement after the administration of Mycobacterium abscess, so we did not verified whether the specimens were contaminated or colonized. Secondly, there is only one case by far, and more cases are needed to support our views in the future.

After the NTM-PD was improved, clinicians and clinical pharmacists suggested that anti-tumor therapy should be continued in the patient. For NTM lung disease patients with underlying diseases (such as malignant tumors and immunosuppression), active treatment of the primary disease is also conducive to the prognosis of lung lesions.[37]

Conclusions

Our study used NGS to detect pulmonary infection with Mycobacterium abscess in nasopharyngeal carcinoma patients, which is relatively rare. Our team applied the actively anti-infection regimen in time, and continued the treatment of the primary cancer after infection was controlled. It provides some references for the treatment of NTM-PD in clinical immunodeficient patients.

Abbreviations

CT, computed tomography; MRI, magnetic resonance imaging; WBC, white blood cell; PCT, procalcitonin; Alb, albumin; PL, platelet; NGS, Next-generation sequencing technology; PR, Partial Response; NTM, non-tuberculous Mycobacteria.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee and Institutional Review Board of the Chengdu Second People's Hospital, China

Consent to Publish

The patient provided written informed consent to publish the case details and any accompanying images.

Acknowledgments

All authors would like to thank Professor Chen for the funding support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Key Research and Development Program of China (2020YFC2005500), the Pharmaceutical Scientific Research Foundation of the Chengdu Pharmaceutical Association (Grant No.Cdyxky5021) and Individualized drug therapy Sichuan Province key laboratory development project (2021YB02). The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing this manuscript.

Disclosure

The authors have no conflicts of interest to disclose in this work.

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