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CASE REPORT

Talaromyces marneffei and *Burkholderia cepacia* Co-Infection in a HIV-Uninfected Patient with Anti-Interferon-γ Autoantibodies

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Abstract: A high titer of neutralizing anti-interferon-γ autoantibodies can cause immunodeficiency associated with severe or disseminated infections caused by *Talaromyces marneffei* in human immunodeficiency virus-negative patients. Herein, we reported a rare case of disseminated *Talaromyces marneffei* and *Burkholderia cepacia* infection. The patient's lungs, lymph nodes, and bronchi were involved, and he had neck abscesses and osteomyelitis. We measured the neutralizing anti-interferon-γ autoantibodies in the peripheral blood and found that the patient had a persistently high positive titer. Despite aggressive treatment, the patient developed disseminated intravascular coagulation and died. Thus, high-titer nAIGAs may be associated with multiple opportunistic, persistent and disseminated infections.

Keywords: *Burkholderia cepacia*, *Talaromyces marneffei*, adult immunodeficiency, neutralizing anti-interferon-γ autoantibodies

Introduction

An increasing number of cases with *Talaromyces marneffei* (TM) infections had been reported in non-human immunodeficiency virus (HIV)-infected patients who had high-titer neutralizing anti–interferon-γ autoantibodies (nAIGAs) in the peripheral blood. In recent years,[1] *Burkholderia cepacia*, a rare human pathogen, was most likely involved in opportunistic infections in immunocompromised hosts.[2] Cases of osteomyelitis due to *B. cepacia* are rarely described.[3] Herein, we report a rare case of a patient who had osteomyelitis due to disseminated TM and *B. cepacia* infection, and the nAIGAs in the peripheral blood had a high positive titer.

Case Report

A 49-year-old man from Guangxi, China, presented to our hospital with a 7-month history of cough, fever, and emaciation and a 1-month history of a mass on the left side of his neck. He had been treated with ceftazidime at another hospital, and his fever had resolved, but the mass on his neck had grown. He had no history of previous medical illness or medication. Physical examination on admission revealed a body temperature of 38°C and two palpable masses, one on the left side of his neck and the other below the right side of his chin. The larger mass was 8 cm in diameter, and the masses were inflamed and sensitive to touch. He had moist rales in the upper lobe of the left lung. Hematology revealed a white blood

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cell count of 14,200 cells/μL, neutrophil count of 12,200 cells/μL, lymphocyte count of 1.39 cells/μL, platelet count of 167,000/μL, and hemoglobin of 124 g/L. He had a C-reactive protein level of 167.04 mg/L, erythrocyte sedimentation rate of 70 mm/h, and procalcitonin of 0.61 ng/mL. The total CD3+, CD4+, and CD8+ T-lymphocyte counts were 1, 137, 470, and 620 cells/L, respectively. The liver and kidney function test results were normal, and the level of total immunoglobulin was within the normal limit. The galactomannan index was 0.35, and the patient was HIV negative. Computed tomography (CT) of the neck revealed mixed-density lesions on the left side of the neck and in the right submental area (Figure 1A). He was started on ceftazidime and levofloxacin upon admission. Resection of the neck masses revealed that they contained pus and a large amount of hemopurulent necrotic material (Figure 1B and C). A pus sample was sent for culture. *B. cepacia* was cultured from the mass on the neck and submental pus after 1 week. The results of the drug sensitivity test revealed that the patient was sensitive to meropenem, ceftazidime, levofloxacin, cotrimoxazole, and minocycline. Thus, we continued administration of ceftazidime and levofloxacin. The patient's fever resolved, and the masses decreased in size. However, he developed a productive cough after 2 weeks. CT showed that the neck masses shrank, but a large exudative consolidation shadow in the left upper lobe and left hilar lymphadenopathy was also noted (Figure 1D). Bronchofibroscopy revealed bronchial nodules in the left upper and lower lobes, obstructing the lumen, and mucosal hyperplasia and hypertrophy (Figure 1E). The left hilar lymph nodes and tracheal nodules were biopsied, and samples were sent for culture. TM (Figure 2) was cultured from a bronchial nodule, left hilar lymph node, and bronchoalveolar lavage fluid. We also sent the left hilar lymph node for next-generation sequencing (NGS) (The Beijing Genomics Institute, China), and The results of NGS was also TM. Thus, the patient was diagnosed with disseminated TM and *B. cepacia* infection.

Amphotericin B (50 mg/d) was added as antifungal therapy. We discontinued ceftazidime and levofloxacin after 4 weeks as his neck mass improved. The patient's cough improved after 1 week. However, he became febrile again, and a new mass appeared on the right side of the neck after 3 weeks. A chest CT scan revealed significant improvement in the pulmonary lesions (Figure 3A). CT of the neck showed an abscess in the posterior pharyngeal wall, a fracture of the 4th cervical vertebra, and a mass on the right side of the neck

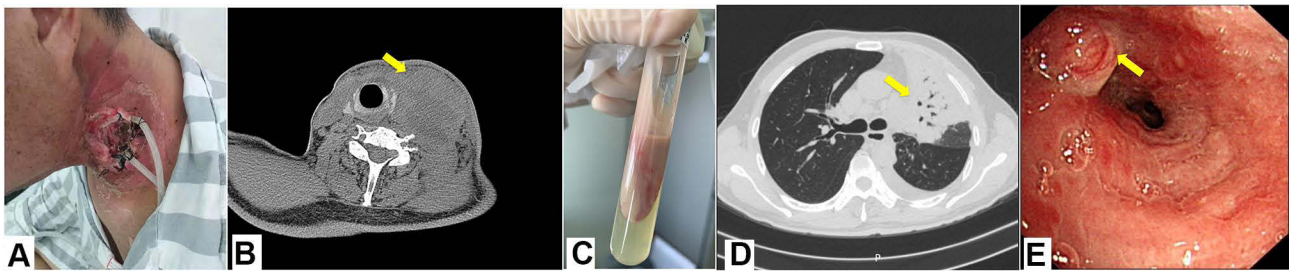

Figure 1 Neck CT findings. Mixed-density lesions on the left side of the neck (**A**). The masses were incised, and a drainage tube was inserted (**B**). Pus and necrotic materials (**C**). A large new exudative consolidation shadow was noted in the left upper lobe after 2 weeks of antibacterial treatment (**D**). Bronchofibroscopy revealed bronchial nodules in the left upper lobes that obstructed the lumen. Mucosal hyperplasia and hypertrophy were also noted (**E**).

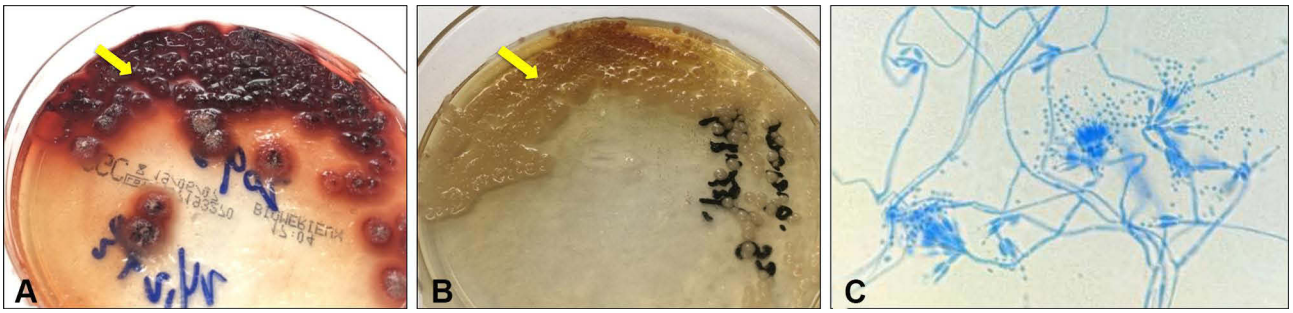

Figure 2 *Talaromyces marneffei* was isolated from the hilar nodes: Yellow colony with distinctive red diffusible pigment on Sabouraud's dextrose slant at 25°C (**A**) and yellow colony on Sabouraud's dextrose slant at 37°C (**B**). Lactophenol blue-stained culture of the ulcerating right supraclavicular subcutaneous mass showing that the conidiophores of this mold were smooth and had a size of 3 um, each of which had several phialides and produced smooth, spherical conidia in chains (**C**).

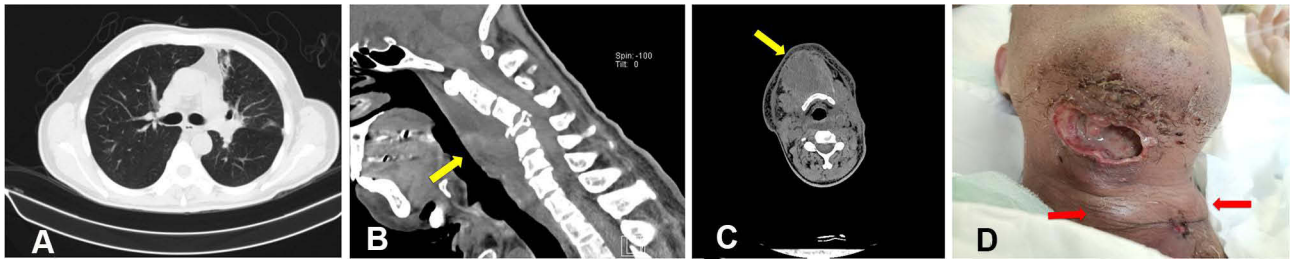

Figure 3 Computed tomography findings. Chest: The pulmonary lesions were markedly improved after 3 weeks of antifungal therapy (**A**). Neck: An abscess in the posterior pharyngeal wall, a fracture of the 4th cervical vertebra (**B**), and new mass on the right side of the neck (**C**) were found. The abscess disseminated to the lower right neck and sternum (**D**).

(Figure 3B and C). Ceftazidime and levofloxacin were added as antibacterial treatment, but there was no obvious treatment effect. The antibiotics were switched to meropenem and cotrimoxazole according to the drug sensitivity results, but the *B. cepacia* infection remained uncontrolled. He developed acute-onset quadriplegia and underwent an emergency subtotal resection of the 4th cervical vertebra and widening and decompression of the spinal canal. He was transferred to the intensive care unit and treated with meropenem and tigecycline as antibiotics and voriconazole as an antifungal agent. *B. cepacia* was cultured repeatedly from the blood and pus. The pulmonary lesions were improved, but the neck abscess could not be contained and disseminated widely to multiple body parts (Figure 3D). After 1 week, he developed hepatorenal dysfunction, cardiac insufficiency, and hypotension and became hypoxic. Repeated immune function test revealed CD3+, CD4+, and CD8+ T-lymphocyte counts of 158, 48, and 99 cells/L, respectively. After 2 weeks, he developed disseminated intravascular coagulation and died of *B. cepacia* sepsis. We considered that the patient might be infected with a special pathogen. According to our experience, we measured the nAIGAs in the peripheral blood at 1 week after admission. Serum AIGA was determined by an enzyme-linked immunosorbent assay kit (USCN Life Science Inc., Wuhan, China) according to the manufacturer's protocols. We found that he had a persistently high positive titer (11,025 ng/mL), and the antibody titer increased gradually to 50,566 ng/mL at 8 weeks after admission (Figure 4). The positive titer value was based on our previous study.[1]

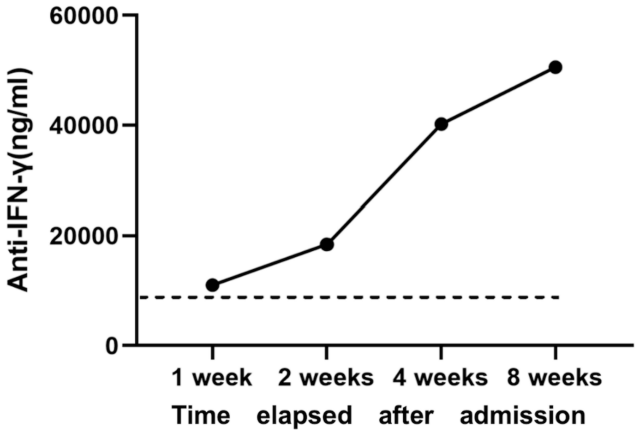

Figure 4 Neutralizing anti–interferon-γ autoantibody titers of the patient after admission. The dotted line indicates the level of the positive titer at each certain time point, peaking at 50,566 ng/mL at 8 weeks after admission.

Discussion

The high titer of serum nAIGA can cause immunodeficiency associated with severe or disseminated infections caused by nontuberculous mycobacteria, nontyphoidal *Salmonella, Burkholderia* spp., TM, *Cryptococcus neoformans, Histoplasma capsulatum*, and the *Varicella zoster* virus. It is an emerging adult-onset immunodeficiency syndrome in non-HIV-infected patients.[4,5] We previously found that up to 60% of HIV-negative patients with TM infection were nAIGA positive.[1,6] The positive nAIGA is also the most common immunodeficiency condition in patients with TM infection and is a risk factor for polymicrobial opportunistic infections.[5] *B. cepacia* and *TM* are rare pathogens that are always involved in opportunistic infections in immunocompromised hosts. Our patient had no previous medical illness, and he was infected by *B. cepacia* and TM as a result of positive nAIGA. It is extremely rare for a patient to be co-infected with these two rare opportunistic pathogens. Specific human leukocyte antigen class II haplotypes (eg, HLA-DRB1*16:02 and HLA-DQB1*05:02) have been reported to be associated explicitly with AIGAs, especially in Southeast Asia. Further, production of this antibody might be related to the stimulation of pathogen infection.[7,8] However, the relationship among the expressions of HLA-DRB1*16:02 and HLA-DQB1*05:02, type of pathogen infection, and AIGA titers remains unclear. Among patients with TM, those with positive nAIGAs relapse more frequently, have more severe infections,

and are harder to treat.[1,6] Therefore, when HIV-negative hosts, especially those infected by TM with or without other opportunistic infections, develop intracellular opportunistic infections, caution should be taken to rule out whether the immunodeficiency is caused by AIGAs.

TM was cultured from the patient's hilar lymph node, bronchial nodules, and bronchoalveolar lavage fluid, and antifungal therapy was effective. Therefore, we think that the TM infection involved the lungs, lymph nodes, and bronchi. Although TM can also cause neck abscesses or osteomyelitis, repeated cultures only found *B. cepacia*. Further, as the initial antibacterial treatment was effective, it is likely that the neck abscesses and osteomyelitis were caused only by the bacterium. *B. cepacia* can cause disseminated soft tissue infection of the neck, followed by severe sepsis, but it rarely causes suppurative spinal infection or osteomyelitis.[2,9]

The progressive increase in the patient's serum nAIGA titer may explain the difficulty in controlling the infection. Although the *B. cepacia* isolate was a sensitive strain, the patient was treated with systemic antibiotics according to the drug sensitivity test and underwent multiple local surgeries. However, the infection persisted and progressed to sepsis, eventually leading to secondary cellular immune failure and death. Lowering the nAIGA titer may be beneficial for infection control, and a high nAIGA titer may lead to difficult control of the infection.[1,6] We suggest that patients with positive nAIGA titers should have an extended course of antibiotics to reduce recurrence. In previous studies, patients showing progressive or relapsed infections despite at least a 3-month or over 1-year course of intensive antimicrobial therapy were treated with rituximab, and favorable clinical outcomes were achieved.[10,11] Our patient had a severe infection and had no significant benefit from antibiotic treatment. We are unsure whether this immunosuppressive drug benefitted the patient or exacerbated the infection.

Conclusion

We herein report concurrent TM and *B. cepacia* infections in a patient with nAIGA-associated adult-onset immunodeficiency. It is unclear how nAIGAs are produced, regulated, or cleared from the peripheral blood. nAIGAs are also strongly associated with disseminated intracellular opportunistic pathogens. Thus, high-titer nAIGAs may be associated with multiple opportunistic infections, persistent infections, and disseminated infections.

Abbreviations

CT, computed tomography; HIV, human immunodeficiency virus; nAIGAs, neutralizing anti–interferon-γ autoantibodies; NGS, next-generation sequencing; TM, *Talaromyces marneffei*.

Ethics Approval and Informed Consent

Signed consent was obtained for the publication of the case details from the participant. This study was approved by the First Affiliated Hospital of Guangxi Medical University's Ethical Review Committee (2020.KY-E-139)

Consent for Publication

Signed consent was obtained for the publication of the case details from the participant.

Author Contributions

All authors contributed to study conception, study desing, data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This study was approved by the Ethical Review Committee of the First Affiliated Hospital of Guangxi Medical University (2018.KY-E-094). The clinical trial was registered on www.clinicaltrials.gov (NCT03819348). Written informed consent was provided by all participants in the prospective cohort study.

Disclosure

The authors report no conflicts of interest in this work.

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