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Case Report

Severe disseminated *Mycobacterium avium* complex infection in a pregnant woman with anti-interferon-γ autoantibody

Peng Wen[1*], Min Wei[1*], Yu-Rong Xu[1], Mao-Shui Wang[2]

[1]*Department of Respiratory Medicine, Shandong Chest Hospital, Jinan, China;* [2]*Department of Lab Medicine, Shandong Provincial Chest Hospital, Jinan, China.* [*]*Equal contributors.*

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Abstract: A 33-year-old pregnant woman was admitted to the hospital because of intermittent high fever, pain in multiple bones and muscles, general malaise, cough, expectoration, and body weight loss. Chest computed tomography showed an infiltrate in the right upper and middle lobes of the lung. A systemic bone scan revealed multiple accumulations located in multiple vertebrae, as well as in the skull, mediastinal lymph nodes, sixth and seventh left anterior ribs, right scapula, left distal radius, and the top of the left femur. This case also involved multiple skin soft tissue and muscle abscesses, including the head, chest, back, and paraspinal regions. A biopsy of the right lung upper lobe showed focal granulomatous inflammation. *Mycobacterium intracellulare* was isolated from sputum, chest pus, head pus, and back biopsy tissue, thus she was diagnosed as suffering from disseminated *Mycobacterium avium* complex infection. Flow cytometry of T and B lymphocytes revealed an obvious cellular immunodeficiency. The patient's serum additionally tested positive for autoantibodies against interferon-γ. Her T and B lymphocyte levels gradually returned to near normal after the pregnancy was terminated. Her condition may have been associated with both pregnancy-induced alterations in immunity and autoantibodies against interferon-γ.

Keywords: *Mycobacterium avium* infection, interferon-γ autoantibody, pregnancy

Introduction

Mycobacterium avium complex (MAC) is complex of three species (*M. avium*, *Mycobacterium intracellulare*, and *Mycobacterium chimaera*) of environmental microorganisms that are widely distributed in nature [1]. Immunodeficient hosts with impaired cell-mediated immunity, such as secondary immunodeficiency due to human immunodeficiency virus (HIV) infection, malignancy, or immunosuppressive therapy, are susceptible to and often develop a disseminated form of MAC infection [2, 3]. In the present case, the patient was an otherwise healthy pregnant woman. She tested negative for anti-HIV antibodies, but flow cytometry assays to assess her T and B lymphocyte levels produced abnormal results. Previous studies have shown that alterations to the immune status of the pregnant woman are necessary to allow mothers to tolerate genetically different fetal tissues during pregnancy. These alterations lead to impaired cell-mediated immunity with increased susceptibility to certain infections [4, 5]. Pregnancy may have affected the patient's immune status.

Patients with autoantibodies to interferon-gamma (IFN-γ) were first described by Hoflich et al. in 2004 [6]. Recently, there have been an increasing number of reported cases of disseminated nontuberculous mycobacteria (NTM) infections in immunocompetent patients, especially in Asia. Some of these patients have had detectable levels of neutralizing anti-IFN-γ autoantibodies [6-10]. At present, there are no similar reported cases in mainland China [10-14]. Interestingly, autoantibodies to IFN-γ were detected in the serum of the present patient. The present study reports this unusual case along with a review of related published studies. Written informed consent was obtained from the patient for publication of this case study.

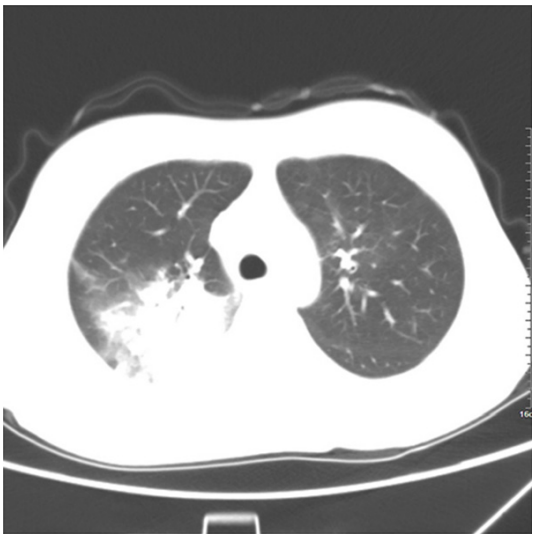

Figure 1. Findings of a chest computed tomography scan. The image reveals an infiltrate in the right upper lobes of the lung.

Case report

On November 25, 2016, a 33-year-old woman was admitted to a different hospital with a cough, fever, and back pain. The patient had first developed a cough and low fever two months previously. She had noticed back pain and swelling after one month. The patient was in the sixth month of her second pregnancy. She was an otherwise healthy pregnant woman. Chest computed tomography (CT) showed an infiltrate in the right upper and middle lobes of the lung (**Figure 1**). Magnetic resolution imaging (MRI) revealed a massive infiltration shadow in the vertebrae and in the muscles around the vertebrae. She was suspected of lung cancer with multiple bone metastases. During her initial hospital stay, the pregnancy was terminated due to oligohydramnios. To investigate the cause of her symptoms, a lung biopsy was performed. The biopsy of her right lung upper lobe showed focal granulomatous inflammation. Her condition gradually became worse, with a high fever of >39.5°C and onset of persistent bone pain.

On December 26, 2016, the patient was transferred to the hospital for definitive diagnosis and treatment. She suffered from intermittent high fever, pain in multiple bones and muscles, general malaise, cough, expectoration, and body weight loss. On admission, her vital signs were: body temperature, 39.1°C; blood pressure, 123/64 mmHg; and pulse rate, 106 beats/minute. Multiple parts of her body had skin swelling. An ulcer containing yellow pus was present on her anterior chest and multiple soft masses were present on her head, chest, and back (**Figure 2**). Breath sound over the right lung was diminished. Flow cytometry of T and B lymphocytes revealed an obvious cellular immunodeficiency (**Table 1**). As shown in **Table 2**, laboratory data revealed elevations in both her CRP levels and erythrocyte sedimentation rate (ESR). She was found to have a leukocytosis, with a white blood count of 15.53×10^9 cells/L. Normocytic anemia and decreased albumin levels were also noted. Anti-HIV antibody was not detected. Multiple testing procedures were performed to assess potential multifocal bone or visceral involvement, including chest CT, Emission Computed Tomography (ECT), and ultrasound. Resulting CT images showed an infiltrate in the right upper and middle lobes of the lung. Resulting ECT images revealed multiple accumulations in multiple vertebrae, as well as in the skull, mediastinal lymph nodes, sixth and seventh left anterior ribs, right scapula, left distal radius, and on the top of the left femur. This case also had multiple skin soft tissue and muscle abscesses, including the head, chest, back, and in the paraspinal region. Ultrasound analysis indicated that those masses were all subcutaneous abscesses. An open biopsy of the back mass was performed, revealing focal granulomatous inflammation (**Figure 3**).

M. intracellulare was isolated from multiple samples, including sputum, chest pus, and head pus, as well as back biopsy tissue. All bacterial strains were confirmed to be *M. intracellulare* using a Mycobacteria Identification Array Kit (CapitalBio, Beijing, China). Based on results of these bacteriological tests, the patient was diagnosed as having disseminated MAC infection. The vertebral lesion was suspected to be an abscess with osteomyelitis caused by MAC. Multidrug therapy was started. Daily administration of 1000 mg of clarithromycin (CAM), 450 mg of rifampicin (RFP), 750 mg of hydrochloride (EB), and 400 mg of amikacin sulfate (AMK) was initiated, but there was no improvement in the patient's condition. Despite adding moxifloxacin hydrochloride (MFLX, 400 mg/day) to the abovementioned treatment foundation and removing the pus from the masses of the head, chest, back, and paraspinal region, the patient still had a recurrent high fever and

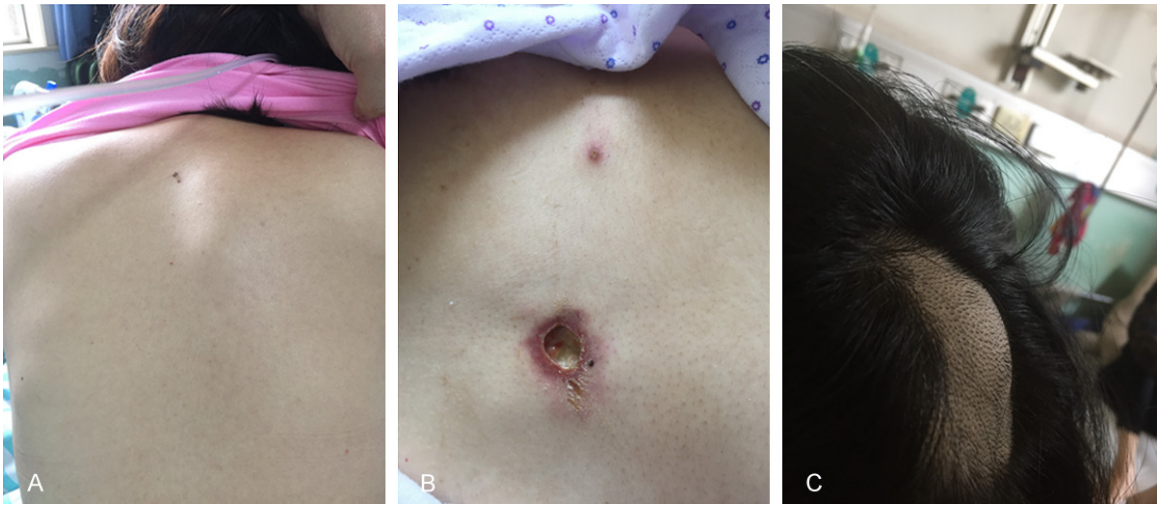

Figure 2. The patient's dermal manifestations. A. A soft mass on the back. B. An anterior chest ulcer. C. A soft mass on the head.

Table 1. Flow cytometry of T and B lymphocytes

	TCD3 cells (%)	CD4 cells (%)	CD8 cells (%)	CD19 cells (%)	CD4/CD8 ratio
2016/12/31	83.2	19.9	61.9	1.2	0.32
2017/1/30	90.4	32.1	57.2	1.5	0.56
2017/5/20	79.0	28.5	49.4	1.5	0.58
2017/8/19	83.9	35.8	46.2	4.8	0.77
2017/9/18	82.0	35.0	45.0	5.3	0.78
2017/10/19	79.4	35.7	41.3	9.0	0.86

Table 2. The patient's laboratory data on admission

WBC (/L)	15.53×10^9	IgG (mg/dl)	33.06	Acid-fast test
Neu (%)	71.7	IgM (mg/dl)	2.51	Sputum
Mon (%)	6.8	IgE (IU/ml)	2.54	Smear (2+)
Lym (%)	17.7	CRP (mg/L)	97.2	Culture (+)
Eos (%)	1.4	HBs-Ag	(-)	pus
Hb (g/dl)	93	HCV-Ab	(-)	Smear (1+)
Plt (/L)	391×10^9	HIV-Ab	(-)	Culture (+)
ESR (mm/h)	74	CEA (ng/ml)	0.34	Blood
		CA125 (U/ml)	108	Smear (-)
TP (g/L)	77.4	CA153 (U/ml)	19.3	Culture (-)
Alb (g/L)	34.8	CA199 (U/ml)	4.2	
AST (U/L)	21	AFP (ng/ml)	3.37	
ALT (U/L)	25	RF (IU/ml)	<10.6	
LDH (U/L)	183	T-SPOT TB	(-)	
ALP (U/L)	282			
T-Bil (μmol/L)	17.85			
Cre (μmol/L)	68			
Na (mEq/l)	143			
K (mEq/l)	4.5			
BUN (mmol/L)	3.02			

bone pain. The disease was steadily getting worse and becoming more difficult to control. Immunoglobulin was then administered and titrated to 10 g/day. However, her condition continued to worsen, thus immunoglobulin treatment was discontinued after 5 days.

On May 1, 2017, a CT scan revealed an aggravation of her lung lesions along with multiple musculoskeletal abscesses. There was serious damage in several locations, including the vertebrae, ilium, acetabulum, and femoral head (**Figure 4**). Based on results of an *in vitro* drug susceptibility test, linezolid (LZD) was added to the treatment regimen. Reinforcement of therapy with LZD (1200 mg/d) was begun on May 5, 2017. However, the patient still did not improve. The patient's platelets decreased gradually, so LZD was discontinued after 2 weeks. On June 6, 2017, when her platelet levels were restored, a lower dose of LZD (600 mg/d) was added to therapy. There were no obvious adverse reactions over the next two months.

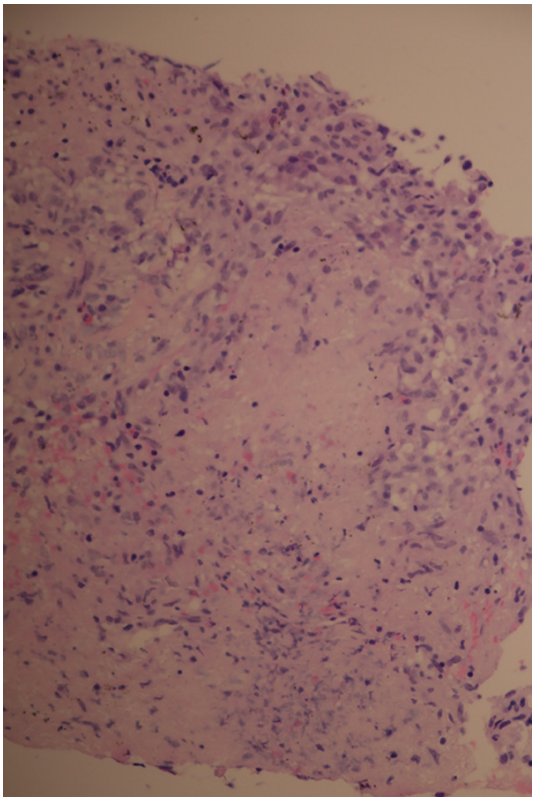

Figure 3. Pathological findings of biopsy specimens from the patient's back mass. Granulomatous change, multinuclear giant cells, and epithelioid cells (H-E staining, ×400).

The disease condition was reversed following the continuation of chemotherapy with RFP, EB, CAM, AMK, MFLX, and LZD. The patient's fever was alleviated without non-steroidal anti-inflammatory drugs (NSAIDs) and her sputum cultures for MAC switched to producing negative results. She also had an improved inflammatory response based on blood examinations, including normal ESR and CRP values. Chest CT scans revealed an improvement of pulmonary lesions. At 2 months after the start of LZD (600 mg/d) therapy, due to economic reasons, the patient stopped applying LZD but continued to receive RFP, EB, CAM, AMK, and MFLX. She was finally discharged on September 25, 2017. Throughout the treatment process, flow cytometry assays of the patient's T and B lymphocytes were repeatedly performed, with results gradually approaching normal (**Table 1**). The patient's improvement occurred nearly concurrently with improvements in her cellular immunity (**Figure 5**).

According to previous reports [6-15], autoantibodies against IFN-γ are associated with severe

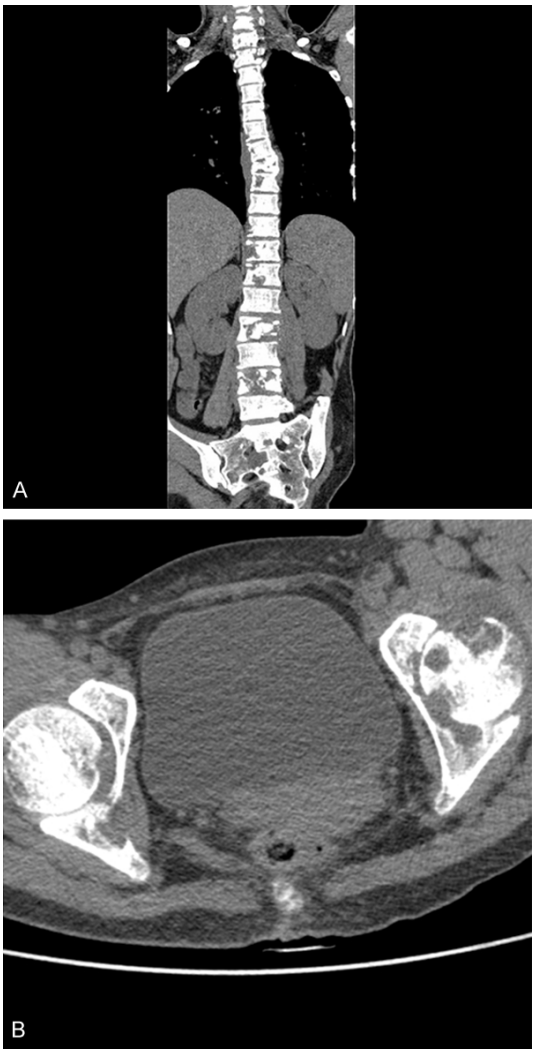

Figure 4. Findings of bone computed tomography scans. A. Serious damage is visible in multiple vertebrae. B. Bilateral acetabulum and the femoral head were seriously damaged.

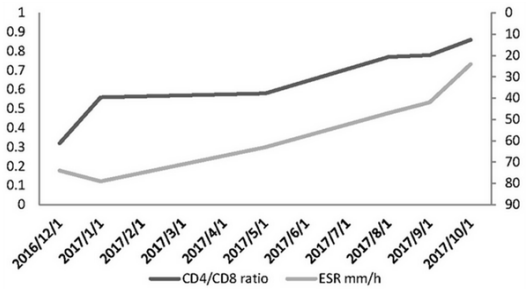

Figure 5. Changes in the CD4/CD8 ratio and erythrocyte sedimentation rate (ESR) over time.

disseminated opportunistic infections, especially disseminated MAC infections. To determine whether the patient's plasma contained

autoantibodies against IFN-γ, a sample of the patient's serum was sent to Cusabio, a company in Wuhan, China. Levels of anti-IFN-γ antibody were measured by enzyme-linked immunosorbent assay (ELISA). In this assay system, the cutoff was 0.4095 and the optical density (450 nm) value of the patient's serum was 0.4663, which were considered positive for the presence of an autoantibody against IFN-γ.

Discussion

The present study reports an HIV-negative pregnant woman with disseminated NTM infection with an autoantibody against IFN-γ. In this case, the patient had no relevant medical history and underlying diseases were not found. However, the patient's T and B lymphocytes revealed an obvious abnormality in these cell populations.

The maternal immune response changes during pregnancy. For example, Tallon et al. [16] found that $CD4^+$ T-cell levels decreased in the second trimester and both $CD4^+$ and $CD8^+$ T-cell levels decreased during the third trimester. Alterations to the immune status in pregnant women are necessary to allow mothers to tolerate genetically different fetal tissues during pregnancy. However, these alterations also lead to impaired cell-mediated immunity with increased susceptibility to certain infections, such as tuberculosis [4, 5, 17]. Furthermore, pregnant women are more severely affected by infections with certain viruses, including influenza A virus, hepatitis E virus (HEV), and herpes simplex virus (HSV), compared with nonpregnant counterparts [18]. Raj et al. [19] reported that pregnancy-induced alterations in immunity may contribute to increased morbidity associated with influenza A virus infections during pregnancy. Pregnant women are at a high risk of developing severe and even fatal influenza. The high vulnerability of women to influenza A virus infections during pregnancy has been repeatedly highlighted during influenza pandemics, including the most recent influenza pandemic. However, current understanding of the molecular mechanisms involved in severe disease development during pregnancy is still very limited [20]. However, cases of disseminated Mycobacterium avium complex infections caused by immunodeficiency in pregnant women are rarely reported, Song JY et al. previously reported a case of a disseminated Mycobacterium avium complex infection in pregnant women, but cellular immunity was not tested [21]. In the present case, flow cytometry of T and B lymphocytes revealed an obvious cellular immunodeficiency. It was speculated that pregnancy termination was the primary cause of the patient's T and B lymphocyte populations recovering from severe abnormality back to near-normal levels. It is possible that maternal immune response changes played a crucial role in her disease course.

Previous studies have shown that autoantibodies against IFN-γ are associated with severe disseminated opportunistic infections. Autoantibodies against IFN-γ were detected in 88% of Asian adults with multiple opportunistic infections. Notably, these patients had no cellular immune deficiency and had normal numbers of $CD4^+$ T-cells and other lymphocytes [8]. It is remarkable that autoantibodies against IFN-γ and defective cellular immunity occurred concurrently. Moreover, this patient had a more severe case than most previously reported cases. Although the patient's condition eventually improved, it required more than five months of continuous treatment. Cellular immune deficiency and autoantibodies against IFN-γ are both strongly associated with disseminated MAC infection. It is unlikely that autoantibodies against IFN-γ, alone, could explain the severe multifocal nature of the patient's disseminated MAC infection, suggesting that her disease may be associated with both pregnancy-induced alterations in immunity and autoantibodies against IFN-γ.

Disseminated MAC infections are the most difficult of the NTM infections to treat. The 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) statement does not include an established treatment regimen [22]. Multidrug combination therapy is expected to suppress the progression of symptoms. In the present case, after diagnosis of disseminated MAC was made, the patient began receiving multiple drugs to treat the MAC infection, including RFP, AMK, EB, CAM, and MFLX. However, her disease continued to worsen and became difficult to control. Prior reports have revealed that some isolates of *M. intracellulare* showed sensitivity to LZD during *in vitro* sensitivity tests. LZD has been described as a potentially effective drug against bacterial infections [23]. Additionally, other studies have found that the use of LZD had promising results for bone and joint infections [24]. Due to the severity of

its potential side effects, such as peripheral neuropathy, anemia, gastrointestinal symptoms, and thrombocytopenia, LZD is usually considered to be a second-line agent for mycobacterial infections [25]. In the present case, the patient's condition did not improve immediately after LZD was added. Although the patient's condition was significantly improved after two weeks of administered LZD (600 mg/d), it is very difficult to determine whether LZD played a critical role in this change because the patient's improvement occurred nearly concurrently with improvements in her cellular immunity. It appears that improvement in cellular immunity is a critical factor in the control of MAC disease, at least in the case of the present patient.

Although previous reports have indicated that most patients with NTM disease associated with anti-IFN-γ autoantibody present with disseminated NTM disease with generalized lymphadenitis, often with reactive skin lesions, this feature was not found in the present patient [26]. There were several limitations associated with this report, however. The number of CD4-positive T lymphocytes was not detected and the autoantibody to IFN-γ was detected only once.

Conclusion

To the best of our knowledge, this is the first report to describe a disseminated NTM infection occurring in a patient from mainland China with autoantibody to IFN-γ. This is only the second report of disseminated MAC infections associated with pregnancy. This retrospective evaluation of the patient's clinical course demonstrates that persistent treatment is critical to clinical outcomes for patients with disseminated MAC infections.

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Disclosure of conflict of interest

None.

Address correspondence to: Peng Wen and Yu-Rong Xu, Department of Respiratory Medicine, Shandong Chest Hospital, 46# Lishan Road, Jinan 250013, China. Tel: +86 531-86568041; Fax: +86 531-86956760; E-mail: wp1980jn@163.com (PW); xyr640322@163.com (YRX)

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