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Case Report

Post-delivery *mycobacterium tuberculosis* infection misdiagnosed as systemic lupus erythematosus

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Abstract

Tuberculosis is a common infectious mycobacterial disease having a wide range of clinical and serological manifestations that are similar to rheumatic disease. Differential diagnosis is a crucial aspect in any rheumatic disease as many other infectious diseases portray clinical similarities and autoantibody positivity. Our case report illustrates of a young woman just after the delivery of a child presented an unusual case of extrapulmonary tuberculosis infection initially misdiagnosed as systemic lupus erythematosus (SLE).

Key words: mycobacterial; misdiagnosis; tuberculous peritonitis.

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Introduction

Tuberculosis may clinically exhibit fever, arthralgia, and leukocytopenia in serology. Extrapulmonary tuberculosis has nonspecific clinical manifestations. A low level of anti-nuclear antibodies (ANA) in some patients with mycobacterial infection can be detected. Therefore, patients infected with mycobacterial infections can manifest similar clinical signs and symptoms that can be easily misdiagnosed as a rheumatic disease and lead to mistreatment. Thus, a physician (rheumatologist) must have a proper knowledge about typical or atypical clinical features of mycobacterial infections. We illustrate here an unusual case of extrapulmonary mycobacterial infections initially misdiagnosed as SLE. After confirmation of mycobacterium tuberculosis and anti-tuberculosis therapy (ATT) () the patient showed a good clinical response.

Case Report

A 32-year-old Chinese woman presented at our center with recurrent fever, abdominal pain and ascites. She had a one-year past history of high grade fever of 38ºC to 39.5ºC, night sweats, sore throat and dry cough that had started just two months after a delivery of her healthy child. She had no other clinical symptoms such as fatigue, loss of appetite, abdominal pain and diarrhea.

Her chest x-ray performed at the previous health center revealed right pleural effusion. Laboratory blood result showed leukocytopenia 3.66×10^9/L (4.0-10.0×10^9/L). Her autoimmune profile revealed seropositive ANA 1:80, positive anti-Sjögren's syndrome related antigen A (anti SSA) () and anti-Sjögren's syndrome related antigen B (anti SSB) (), positive rheumatoid factor (RF) and elevated Immunoglobulin M (IgM) () levels. Her ascitic fluid analysis revealed total nucleated cell number of 3900×10^6/L whereas ascitic fluid culture was negative. She refused to undergo invasive peritoneal biopsy procedure. ATT (isoniazid 0.3gqd, rifampin 0.45gqn, ethambutol 0.75gqd and amino salicylic acid 8g qd) was started as a clinical trial by the physician. Her fever improved after the treatment. However, twenty days later, fever reoccurred, with temperature of 39ºC and she complained of hair loss (alopecia) from the scalp region.

Following the treatment at the other center, her chest and abdominal examinations were normal with no ascitic fluid. Computed tomography (CT) study of her chest revealed calcified nodules sized around one centimeter in diameter within the lung field. Laboratory studies revealed leukocytopenia 1.23×10^9/L (4.0-10.0×10^9/L), autoimmune profile revealed seropositive ANA 1:40, positive anti SSA and anti SSB, positive RF-IgM, negative interferon gamma release assay (T-

SPOT) and negative tubercular skin test. The physician at the center suspected of systemic lupus erythematosus (SLE) with pulmonary tuberculosis (PTB). She was started with ATT (isoniazid 0.3g qd, rifampin 0.45gqd, pyrazinamide 0.5gtid). Three days later, she developed acute papular rash eruption over the trunk region. Thus, as pyrazinamide was considered a probable cause of drug eruption, it was advised to discontinue. The treatment was added with intravenous methyl prednisolone 40mg/day as a medication for SLE. There was improvement in symptoms such as fever and gradually leukocyte count came within normal limits. Then, a week later she discontinued ATT and got discharged from the center with a tapering course of methylprednisolone.

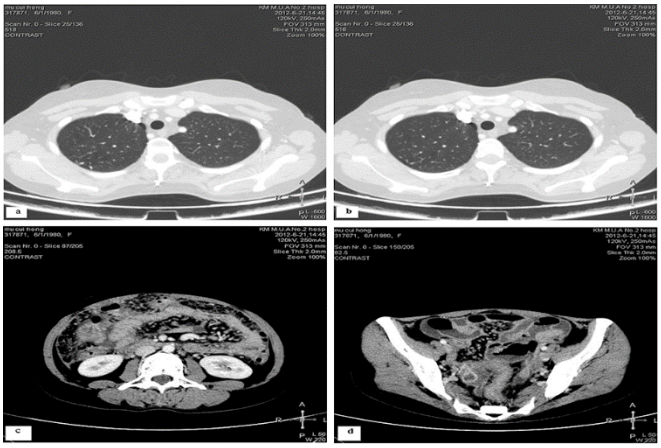
Six months after the first admission she was hospitalized at the other health center for intermittent fever of 39.5ºC, abdominal pain and ascites with passing of watery stools for about two months during the time when she was consuming methyl prednisolone (12mg/day dose). Her autoimmune profile at the time revealed seropositive ANA 1:40 "speckled pattern", positive anti SSA and anti SSB. Laboratory result revealed C-reactive protein(CRP) 3.24mg/dl (<0.8mg/dl), liver function test showed globulin (GLO) 33.2g/L(20-30g/L), alanine aminotransferase (ALT) 95.6IU/L (10-40IU/L) and gamma-glutamyl transferase (γ-GGT) 123.9IU/L (8-30IU/L). A routine urine test showed a positive urinary protein. Similarly, 24-hour urine collection showed 0.24g of protein. Flow cytometry revealed $CD3^+CD8^+$ T cell/$CD45^+$ and $CD3^+$T cell/$CD45^+$T cell ratios were 54% (13-41%) and 88% (59-85%) respectively. The percentage of T helper cell was 16% (31-60%) and the absolute value of T helper cell count was 100 (410-1590). Ultrasonography of abdomen revealed moderate amount of ascitic fluid. CT scan of chest revealed right lung's apical region has old calcifications and left pleural adhesion. In addition, CT scan of abdomen showed linear and nodular thickening of mesentery and omentum associated with numerous lymphadenopathy. Meanwhile, CT scan of pelvis showed enlarged lymph node and small amount of ascites in the peritoneum (Figure 1).

The physician at the center treated her with oral methylprednisolone 20mg in the morning and 12mg in the afternoon along with the diuretics. However, there was no improvement in abdominal pain and ascites, hydroxychloroquine (HCQ) 0.4g/d was started. Intravenous cyclophosphamide (CTX) 0.4g was given one single dose, without a favorable response was changed to mycophenolate mofetil (MMF) 3g/d. The dosage of oral methylprednisolone was increased to 40mg/day at the time when her temperature was fluctuating.

Due to lack of improvement, the patient was admitted to our center for further treatment. Our laboratory findings revealed blood and urine routine were under normal limits. Immunological panel revealed positive ANA 1:320"speckled pattern", positive anti SSA and anti SSB and a positive RO-52. IgG, IgA, IgM and complement fraction 3 and 4 were within normal limit. However, there was an increased erythrocyte sedimentation rate (ESR) 41mm/h(0-20mm/h), CRP (C-reactive protein) 7.8mg/dl (<0.8mg/dl), Cancer antigen 125 (CA125) 662.61u/ml (<35u/ml), RF-IgM 128.45ru/ml (<20ru/ml). Anti cyclic citrullinated peptide (Anti-CCP) and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Hepatitis B virus antibody, anti human immunodeficiency virus (HIV) and tuberculosis antibody and T-SPOT showed negative. There were no dysmorphic cells present in ascetic fluid. The blood, urine and stool cultures were negative. Her ocular surface staining and salivary gland scintigraphy results were negative. We performed a transvaginal ultrasound exam that revealed a bilateral oviduct thickening.

We thought the diagnosis of SLE for the patient was not clear by only on the basis of history and laboratory examinations. We then advised her to discontinue MMF 1.5g/day and the dosage of steroid was tapered. A laparoscopic surgical exploration was performed; diffused miliary nodules were seen on the omentum and

Figure 1. a, b: CT scan of chest showing multiple small nodules are found in posterior segment of right upper lobe with calcification; **c:** CT scan of abdomen showing linear and nodular thickening and omentum associated with numerous lymphadenopathy; **d:** CT scan of pelvis showing diffuse thickening of pelvic peritoneum associated with right pelvic rim-like enhancement of enlarged lymph node and small amount of ascites.



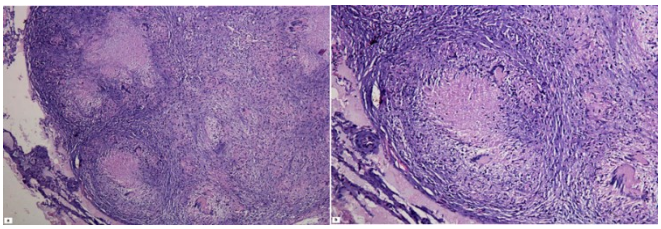
intestinal wall. A total of five nodules were taken for biopsy examination. The histopathology report mentioned of presence of central caseous necrosis, peripheral epithelial cells with fence-like arrangement, multinucleated giant cells and scattered lymphocytes (Figure 2). Various test done at our center made our diagnosis clear. We came to know that this patient suffered from tuberculous peritonitis. She was misdiagnosed as SLE by the physicians at the previous health centers on the basis of various similar clinical and serological manifestations exhibited by mycobacterium tuberculosis.

A treatment with oral ATT (isoniazid, rifampicin, ethambutol and levofloxacin) was initiated as prescribed earlier. Initially she was afebrile but twenty days later she was febrile, temperature of 39.1ºC and a Jarisch-Herxheimer like reaction was considered. The prednisone 30mg/day was prescribed whereas oral rifampicin and isoniazid were changed to intravenous route. After more than two weeks of treatment, her temperature came within normal limits. A month later on follow up visit she was advised to discontinue levofloxacin and steroidal medication. Similarly, treatment with ethambutol was discontinued after three months. We advised her to continue isoniazid and rifampicin treatment for a year. During a follow up visit at our center's clinic after few months, her laboratory test revealed $CD3^+CD4^+$T lymphocyte and $CD3^+CD8^+$T lymphocyte ratios were 24% (28-58%) and 68% (19-48%), respectively on flow cytometry. The ratio of CD4 to CD8 was 0.45 (0.9-2.0/1). On her last follow up visit, her blood investigation revealed WBC 3.47×10^9/L ($4\text{-}10\times10^9$/L), IgG 17.47g/L (7-16g/L), RF 15.0 IU/ml (<14.0 IU/ml), autoimmune profile revealed positivity of ANA and SSA, whereas Ro-52 and anti SSB were weakly positive. $CD3^+CD4^+$T lymphocyte and $CD3^+CD8^+$T lymphocyte ratios were 31% (28-58%) and 64% (19-48%) respectively, the ratio of CD4 to CD8 was 0.48 (0.9-2.0/1), and $CD3^+CD4^+$T lymphocyte count was 219/ul (410-1590/ul) on flow cytometry.

Discussion

Mycobacterium tuberculosis has been known as the second most common infectious cause of death in adults worldwide after human immunodeficiency virus (HIV). Roughly more than two billion people (accounts about one-third of the world population) are estimated to be infected with Mycobacterium tuberculosis [1,2]. However, the World Health Organization (WHO) reports that intermediate rates of Tuberculosis (TB) (26 to100 cases/100,000) occur in China, Central and South America, Eastern Europe and Northern Africa [3].

Figure 2.a (H&E, ×100 magnification), **b (**H&E, ×200 magnification) histopathological slides showing presence of central caseous necrosis, peripheral epithelial cells with fence like arrangement with multinucleated giant cells, scattered lymphocytes.



Peritoneal tuberculosis is an uncommon site of extrapulmonary infection caused by mycobacterium tuberculosis. Infection occurs most commonly following reactivation of latent tuberculous foci in the peritoneum that were established by hematogenous spread from a primary lung focus [4]. Recent research studies have shown that in tuberculous peritonitis approximately 70% of patients have symptoms for more than four months before the diagnosis is established [5,6]. This is partly due to the insidious onset of the disease and because the diagnosis is frequently unsuspected. It has been estimated that more than 90% of patients with tuberculous peritonitis have ascites at the time of presentation, while the remainder present with a more advanced "dry" phase, representing a fibro adhesive form of the disease [7,8].

TB peritonitis should be added to the differential diagnosis of any patient presenting with several weeks of abdominal pain, fever, and weight loss. The most common features were ascites (93 percent), abdominal pain (73 percent), and fever (58 percent). Abdominal pain and ascites were also the most common presenting features in several other reports [9-11]. Our patient initially presented high grade fever, abdominal pain and ascites from three months after delivery of her child continuously for a year. There were no any such complaints before pregnancy or during the time of pregnancy. Since pregnancy has not been shown to increase the risk of TB, the epidemiology of TB in pregnancy is a reflection of the general incidence of disease [12]. Pregnancy has not been shown to influence the pathogenesis of tuberculosis (TB) or the likelihood of progression from latent to active disease nor has it been shown to affect the response to treatment [13,14]. However, the incidence of TB among women peaks at 25-34 years of age. In this age group, rates among women may be higher than those among men

[15]. Hence, these clinical features and incidence of TB occurring in this particular gender of her age might have brought us more near to suspect for TB peritonitis.

The gold-standard for diagnosis of peritoneal TB has been culture growth of mycobacterium on ascitic fluid or a peritoneal biopsy [16]. T-SPOT (interferon gamma release assay) is considered to be the index of laboratory diagnosis of tuberculosis. The aim of examining for T-SPOT is to identify individuals who are at increased risk for the development of tuberculosis and therefore who would benefit from treatment of latent TB infection [17] and the active tuberculosis T-SPOT is negative [18]. This patient's T-SPOT was negative on two occasions; the results may be due to condition related to active tuberculosis or may be because of the use of corticosteroids. Hence, the diagnosis for this type of special case required a peritoneal biopsy performed under direct visualization [7,19-22]. The patient had refused to undergo invasive peritoneal biopsy procedure at the previous health center. However, at our center after proper assurance she agreed to undergo for peritoneal biopsy via laparoscopy. Hence, we could confirm the diagnosis of peritoneal TB. The patient had fever at two occasions in the interval of three weeks after initial intake of ATT. We considered that she had fever due to reaction to endotoxin released by the bacteria during antibiotic treatment also known as Jarisch–Herxheimer reaction.

According to the American College of Rheumatology (ACR) criteria for the classification of SLE, a patient is defined as having SLE if he or she fulfills with four or more of the eleven criteria having a sensitivity of 71%–96% and a specificity of 90%–100% [23]. Our patient met the criterion of: i) Serositis: pleuritic; ii) Hematologic disorder: leukocytopenia 1.23 $\times 10^9$/L (4.0-10.0$\times 10^9$/L) iii) ANA 1:40 "positive". Thus, SLE was highly suspected at the beginning by the physicians. However, as the patient's pleural effusion was unilateral, firstly we had to exclude the possibility of mycobacterium tuberculosis infection. In this particular case tuberculosis infection was confirmed by the peritoneal biopsy in the end, hence pleural effusion couldn't be used as the diagnostic criteria for SLE. Leukocytopenia could be caused by mycobacterium tuberculosis infection or ATT drug such as isoniazid, so when leukocytopenia of the case is regarded as a hematology index of SLE we must rule out the factors related to infection and medicine. She was suffering from alopecia but during our inspection there was absence of well-demarcated inflammatory plaques that develop into atrophic scars or follicular hyperkeratosis (follicular plugging), telangiectasias, hypopigmentation, and hyperpigmentation over the scalp which are typical common clinical features of discoid lupus erythematosus. In addition, our patient also didn't had features of "lupus hair" as in SLE, which is described by dry, coarse hair along the frontal hair line that usually occurs in association with disease flares [24].

It is possible that mycobacterium tuberculosis infection can induce SLE in an individual with genetically predisposed SLE [25]. Some studies show that monoclonal antibodies raised against mycobacterium tuberculosis can cross react with DNA. It is possible in individuals with appropriate genetic background, and mycobacterial infection could induce to generate anti-DNA antibodies without clinical manifestations of SLE. Besides, 3% of healthy people may have low titer of ANA positive. We cannot reluctantly determine connective tissue diseases for patients only on the basis of positive ANA, although some patients with positive auto-antibodies may develop connective tissue diseases after years. In our case report, the patient had a low titer positive ANA. We couldn't identify whether the patient with positive ANA had been caused by mycobacterium tuberculosis infection or not. During follow up visits for two years after ATT treatment, we observed that her clinical symptoms disappeared and didn't have any symptoms related to SLE after discontinuation of glucocoticosteroid and immunosuppressant. Hence, the diagnosis of SLE for the patient was not sufficient. Though she had positive anti-Ro/SSA and anti-La/SSB antibodies which are present in approximately thirty and twenty percent of patients with SLE, respectively; however, both antibodies are more commonly associated with Sjögren's syndrome [26]. The salivary gland scintigraphy and ocular surface staining findings was negative, without any clinical features for Sjögren's syndrome. Therefore, the patient did not fit the diagnosis of Sjögren's syndrome either.

TB infection and rheumatic diseases have different principles of treatment. When she was misdiagnosed as SLE, the glucocorticosteroid and immunosuppressant was given. During the course of treatment, the dosage of glucocorticosteroid was increased due to fever, abdominal pain and ascites that resulted in extensive tubercular peritonitis.

Infection has always been a serious complication in SLE due to the prolonged use of glucocorticosteroids and immunosuppressants. Approximately 80% of infections are caused by pathogenic bacteria [27]. However, the presence of clinical symptoms and serological manifestations can mimic SLE. In our case

report, due to the lack of clinical suspicion and knowledge of mycobacterium tuberculosis led to misdiagnosis and inappropriate treatment for our patient. It is very important to recognize rheumatic manifestations in TB as they may be confused with SLE. Hence, it is necessary to increase medical practitioner awareness about TB and rheumatologic disease in order to prescribe a proper treatment.

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