CASE REPORT

Thrombotic Microangiopathy Associated with Tuberculous Infection

Shoichi Masumoto, Manami Tada, Ai Katsuma, Eri Minami, Daisuke Katagiri, Maki Shibata and Fumihiko Hinoshita

Abstract

A 32-year-old man was diagnosed as having thrombotic microangiopathy (TMA) and treated by plasma exchange (PE). During the course of admission, he was also newly diagnosed with pulmonary tuberculosis, tuberculous peritonitis and pleuritis, which was thought to be the cause of the TMA. There are only a few previous reports on TMA associated with tuberculous infection. Although its pathogenetic mechanism is not well understood, it would be valuable to recognize that this worldwide infectious disease could cause TMA.

Key words: tuberculous peritonitis, thrombotic microangiopathy (TMA), positron emission tomography (PET)


Introduction

Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) is an acute syndrome presenting with various abnormalities in multiple organ systems. Although TTP and HUS have been clearly distinguished in some studies, the presenting features are essentially the same in most patients, beginning with thrombocytopenia and microangiopathic hemolytic anemia (1-3). It is often regarded as TTP in patients in whom neurologic abnormalities are dominant, and as HUS in patients in whom acute renal failure (ARF) is dominant. If it cannot be precisely classified, it might be reasonable to call it thrombotic microangiopathy (TMA) (4).

TMA sometimes occurs secondary to other conditions, such as autoimmune diseases, Human Immunodeficiency Virus (HIV) infection, Escherichia coli infections, cancer, pregnancy, bone marrow transplantation, and drugs such as ticlopidine and quinidine (1). HUS is typically a juvenile complication of infection with Shiga toxin-producing bacteria, although other infections, such as pneumococcal pneumonia, and inheritable abnormalities in complement regulatory proteins can cause this disorder (5).

Tuberculous peritonitis is a rare disease, which is reported in only 0.1% to 1.5% of all tuberculosis (TB) infection (6, 7). To the best of our knowledge, there has been no report of tuberculous peritonitis associated with TMA. Here, we report a young patient with pulmonary tuberculosis, tuberculous peritonitis and pleuritis, which was diagnosed during admission for treatment of TMA. In this case, positron emission tomography (PET) was useful for the diagnosis combined with ascitic adenosine deaminase (ADA) and serum Cancer Antigen 125 (CA125) levels.

Case Report

A 32-year-old man was referred to our hospital at the end of July 2009, complaining of fever, fatigue, and loss of weight. He had no significant past or family history. On admission, the findings from physical examination showed a blood pressure of 106/58 mmHg, a regular pulse at 88/min, body temperature of 37.7 °C, and SpO₂ 100% (ambient air). He showed a bleeding tendency, and petechiae were found around his mouth. His palpebral conjunctiva was anemic, and the bulbar conjunctiva was icteric. He also had diffuse abdominal pain and tenderness. His mental status was relatively normal.

Laboratory findings revealed ARF, the blood urea nitrogen level was 85.8 mg/dL (30.6 mmol/L), and the creatinine
plasmic antigen (MPO-ANCA), and antinuclear antigen (ANA) were negative. Thus, since he presented with hemolytic anemia, thrombocytopenia, and ARF with fever, he was diagnosed as having TMA. From the day of admission, plasma exchange (PE) was performed for 3 days (fresh frozen plasma 40 units/day) concomitantly with hemodialysis (HD). Consequently, his platelet (Plt) counts increased to 193×10^3/μL, and renal function improved to the normal range on hospital day 4.

Although he recovered from TMA, he complained of intermittent high fever, abdominal bloating, and dull pain. Abdominal CT scan revealed massive ascites (Fig. 1). Then, a paracentesis and peritoneal fluid analysis were performed; white blood cells (WBC) 2,460/μL, protein 5.3 g/dL, and albumin 2.0 g/dL were found. The glucose level was 105 mg/dL, LDH was 452 U/L, and the serum-ascites gradient (SAAG) was 0.3, which suggested exudative ascites. Repeated cultures of the peritoneal fluid for bacteria were sterile, and cytology failed to demonstrate malignant cells. Ascites examination revealed a high ADA level (80.5 U/L), and his serum CA125 level was high (810.5 U/mL). Based on these data, tuberculous peritonitis was suspected. Concurrently, he developed an increasing left-sided pleural effusion, and the chest CT scan showed mediastinal and hilar lymphadenopathy (Fig. 2) and bilateral pleural effusions; thus, thoracentesis and bronchoscopy were performed. The ADA level in the pleural effusion was 58.6 U/L, the cultures of the pleural fluid for bacteria were sterile, and cytology detected no malignant cells. The initial results of Quantiferon-TB-2G (QFT) were: ESAT-6 0.28 IU/mL; CFP-10 0.00 IU/mL; mitogen 0.25 IU/mL; impossible to determine. On the second test, the results were: ESAT-6 0.89 IU/mL; CFP-10 0.01 IU/mL; mitogen 0.03 IU/mL; positive. The tuberculin skin test (TST) was 28 mm (positive), which suggested tuberculous infection. Bone marrow analysis showed a hyponormocellular bone marrow.

In order to rule out malignancy, F-18 FDG positron emission tomography (F-18 FDG-PET) was performed, which showed diffuse and intense FDG-activity on the peritoneum and mesentery, with a maximum standardized uptake value (SUVmax) up to 6.75. This finding also made us suspect carcinomatosis.

Overall, the most likely diagnosis was tuberculous peritonitis with associated TMA. Therefore, anti-tuberculosis drugs (rifampicin 450 mg/day, ethambutol 750 mg/day, isoniazid 300 mg/day, pyrazinamide 1400 mg/day) were given empirically from late August. Following this treatment, his general condition recovered gradually, and his fever remitted.

Culture of the ascitic fluid revealed Mycobacterium tuberculosis 2 weeks later (early in September), as did the bronchoalveolar lavage fluid (BALF). He was thus finally diagnosed as having pulmonary tuberculosis, tuberculosis peritonitis and pleuritis. A few weeks after TB treatment was started, his symptoms improved, the ascites and pleural effusion decreased, and his serum CA125 level decreased to 6.75 (Fig. 3). This finding also made us suspect carcinomatosis.

level was 3.76 mg/dL (332.4 μmol/L). The blood cell count indicated a microangiopathic hemolytic anemia (Hb 7.6 g/dL) with schistocytes (10%) and profound thrombocytopenia (39×10^3/μL). Coagulation data were essentially normal. Elevated bilirubin and liver enzymes (T-bil 2.6 mg/dL, AST 78 U/L, ALT 21 U/L, LDH 2841 U/L) and haptoglobin (11.9 mg/dL) indicated intravascular hemolysis. Inflammatory markers were also elevated (ESR 111 mm/h, CRP 5.07 mg/dL). Cytomegalovirus-antigenemia was negative, and βD-glucan was 6.0 pg/mL. Myeloperoxidase antinuclear cytoplasmic antigen (MPO-ANCA), proteinase-3 antinuclear anti-
A case of TMA associated with tuberculous infection was presented. A previous study reported that 37% of TMA was idiopathic (8), but TMA might occur secondary to autoimmune diseases, drug use, pregnancy, infection, and other conditions (1). Infectious agents such as verotoxin-producing \textit{E. coli}, HIV, and shigella have been reported to participate in the pathogenesis of TMA. Although TB has not been considered a TMA-inducing microorganism, there are a few reports regarding the association between TB infection and TTP (9-11). To the best of our knowledge, a case of TMA associated with tuberculous peritonitis or pleuritis has never been reported.

Recent studies have demonstrated that a severe deficiency of the protease that cleaves von Willebrand Factor (ADAMTS13) causes the development of TTP, resulting in release of abnormally large von Willebrand Factor (VWF) multimers (2). Among patients with apparent idiopathic TTP, the fraction with severe ADAMTS13 deficiency (ADAMTS 13 activity <5%) has varied from 33% to 100% across several studies (12).

In the present case, ADAMTS13 activity was 77.1%, its inhibitor was <0.5 BU/mL, and the VWF multimer showed a normal pattern. Because there were no other known causes, such as autoimmune diseases, specific drugs, malignancy, or other types of infection, it would be reasonable to think that the TMA was caused by tuberculous infection.

The mechanism of TMA induced by TB infection is not clearly understood, but direct endothelial injury may be involved. Toscano et al suggested that the pathogenesis of TTP might be increased pro-coagulant activity of interleukin 1 (IL-1) on endothelial cells (9). Lu et al reported that tuberculous pleural and ascitic fluids contain high plasminogen activator inhibitor-1 (PAI-1) levels, which lead to reduced fibrinolytic activity (13). This change in fibrinolytic characteristics might affect the endothelial cell membrane.

The first choice of treatment for TTP is PE. PE or plasma infusion has been reported effective in previous cases, as well as in the present case. PE might eliminate some of the pathogenetic factors in TB. Indeed TMA should be controlled after the treatment of tuberculosis if the pathogenesis of this case is TB infection, but it might be possible to control TMA if the cytokine storm is one of the causes. It seems that the deterioration of disease activity had been stopped by PE treatment.

Tuberculous peritonitis is an uncommon type of extrapulmonary infection caused by \textit{Mycobacterium tuberculosis}. It is difficult to diagnose in most cases because firm evidence of TB can seldom be obtained. The gold-standard for diagnosis is culture growth of mycobacteria from ascitic fluid or peritoneal biopsy (14). In cases with negative culture results, peritoneal biopsy is indicated to make the diagnosis (15). In fact, we were planning to perform peritoneal biopsy to make the diagnosis of tuberculosis and rule out malignancy, but fortunately the ascitic fluid culture was positive for TB.

There are a few reports of intense FDG-activity on PET scanning in peritoneal TB mimicking peritoneal carcinoma (16, 17). However, fluid ADA or serum CA 125 levels may be useful in suspecting tuberculosis peritonitis in such a case. ADA in ascitic fluid has been proposed as a useful non-culture method of detecting tuberculosis peritonitis. ADA levels had high sensitivity (100%) and specificity (97%) using cut-off values from 36 to 40 IU/L (18). Though the usefulness of serum CA 125 alone in the differential diagnosis is limited, a combination with PET and ADA is useful in diagnosis (19), and it can be used as an effective marker for follow-up (20).

In conclusion, the present case shows that TB infection, including extrapulmonary tuberculosis, can induce TMA. In fact, TMA recovered and never relapsed after treatment with anti-tuberculosis drugs. Although tuberculous peritonitis is difficult to diagnose, various methods can be useful as adjuncts to the diagnosis. TB infection remains common in certain regions, even in well-developed countries such as Japan. Therefore, this case indicates that TB infection, including extrapulmonary tuberculosis, should be taken into consideration as a possible cause of TMA, especially in TB-endemic areas.

The authors state that they have no Conflict of Interest (COI).

References


© 2011 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html