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CASE REPORT

Pulmonary Tuberculosis Complicated by Thrombotic Thrombocytopenic Purpura: A Case Report and Literature Review

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Abstract: Thrombotic thrombocytopenic purpura is a rare but life-threatening emergency. Tuberculosis can have hematologic complications. However, concurrent tuberculosis and thrombotic thrombocytopenic purpura are extremely rare. In this study, we report a 53-year-old man who was initially treated for pulmonary tuberculosis but later developed weakness and an altered mental status. Laboratory tests revealed evidence of thrombocytopenia, acute renal insufficiency, and microangiopathic hemolytic anemia. Brain imaging identified intracranial hemorrhage. Further testing revealed low ADAMTS13 activity (1.8%) and positive anti-ADAMTS13 antibody, confirming the diagnosis of thrombotic thrombocytopenic purpura. The patient had a full recovery after anti-tuberculosis treatment, plasma exchange, and supportive care. We present this rare case and review previous relevant studies to remind clinicians about the potential connections between tuberculosis and thrombotic thrombocytopenic purpura. In patients with signs of severe thrombocytopenia and microangiopathic hemolysis, necessary diagnostic tests should be performed to eliminate the possibility of thrombotic thrombocytopenic purpura occurring concurrently with tuberculosis.

Keywords: Thrombotic thrombocytopenic purpura, tuberculosis, case report, literature review

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening emergency. It has an estimated annual incidence of 1.5–6 cases per million adults and a mortality rate of up to 20%.[1] Patients with TTP have a severe deficiency of the plasma metalloprotease ADAMTS13. Primary ADAMTS13 deficiency is caused by inherited recessive genetic mutations. Secondary ADAMTS13 deficiency is attributable to circulating autoantibodies from autoimmune disorders, drugs, malignancy, or infection. These autoantibodies can bind to ADAMTS13 and limit its capacity to cleave von Willebrand factor. The latter can aggregate with platelets to form microthrombi to occlude arterioles, resulting in thrombocytopenia, microangiopathic hemolytic anemia, and multiple-organ failure.

Tuberculosis is a global illness. It has a high prevalence, and it can cause hematologic complications, mainly presenting as anemia and leukocytosis. Tuberculosis accompanied by TTP is extremely rare, and only a few cases have been reported. We present one such case and discuss our experience to improve our understanding and management of patients with similar disorders.

Case Presentation

On April 2, 2023, a 53-year-old man presented to our hospital with weight loss and intermittent cough and fever for 11 months and dizziness and weakness for 3 days. His medical history included gout for 14 years and hypertension for 5 years. Eleven months before presentation, the patient visited a local clinic for weight loss, cough, and fever (Figure 1). Chest computed tomography (CT) revealed pulmonary infiltration. The skin tuberculin purified protein derivative test

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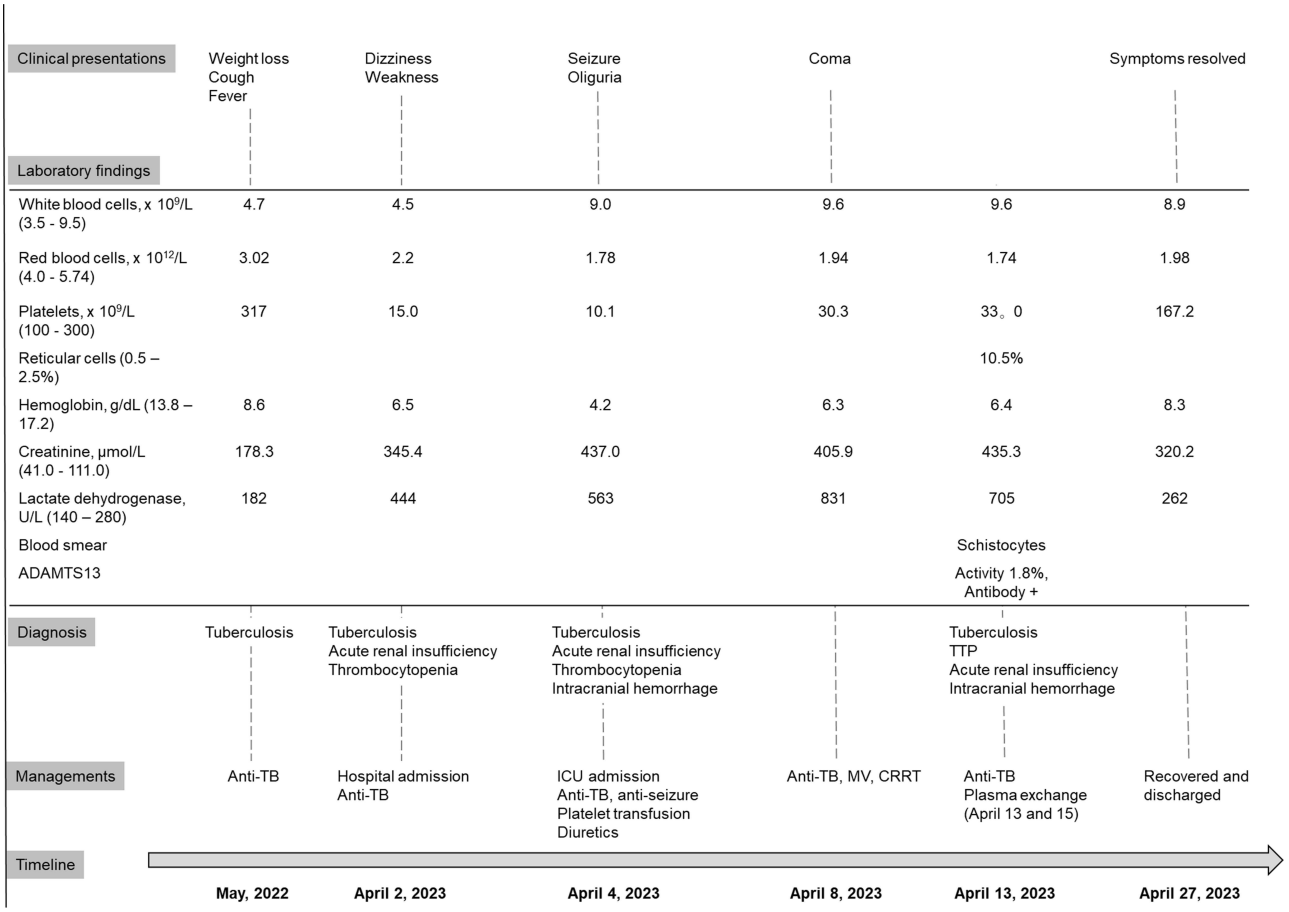

Figure 1 Timeline of the disease course.
Abbreviations: CRRT, continuous renal replacement therapy; ICU, intensive care unit; MV, mechanical ventilation; TB, tuberculosis; TTP, thrombotic thrombocytopenic purpura.

was positive. He was diagnosed with pulmonary tuberculosis. Anti-tuberculosis treatment was started with isoniazid, rifampicin, and moxifloxacin. Three days before admission to our hospital, the patient reported dizziness and weakness, and he was transferred to our hospital.

Upon admission to our hospital, the patient was awake but slightly lethargic. His vital signs were as follows: temperature, 37.4°C; pulse, 91 beats/min; respiration, 20 breaths/min; blood pressure, 143/94 mmHg; and oxygen saturation, 93% on room air. The results of the physical examination were unremarkable, excluding lip cyanosis, decreased breath sounds in the right lower chest, and several tophi in the feet and hands. There was no skin rash. Electrocardiography revealed sinus rhythm with biphasic T waves in the lateral leads. Chest X-ray revealed multiple bilateral patchy infiltration with increased interstitial markings (Figure 2). The laboratory tests included a white blood cell count of 4.5×10^9/L, neutrophil percentage of 64.8%, lymphocyte percentage of 13.0%, red blood cell count of 2.2×10^{12}/L, hemoglobin level of 65 g/L, platelet count of 15.0×10^9/L, creatinine level of 345.4 μmol/L (normal range, 60.0–120.0 μmol/L), and troponin I level of 2.3 μg/L (normal, <0.1 μg/L). We made a diagnosis of secondary tuberculosis, acute renal insufficiency, and thrombocytopenia.

After hospital admission, anti-tuberculosis treatment with isoniazid, rifampicin, and moxifloxacin was continued. Amlodipine was given for hypertension, atorvastatin was given for acute coronary syndrome, and dexamethasone (10 mg, intravenous) was given because of thrombocytopenia (PLASMIC score = 5). One day after hospital admission, the patient developed fever with a temperature of 37.8°C. The laboratory tests revealed a procalcitonin level of 0.5 ng/mL. Anti-bacterial treatment with piperacillin-tazobactam was initiated. On April 4, 2023, the patient had a generalized seizure lasting for 3 min. Head CT revealed a small intracranial hemorrhage in the right occipital

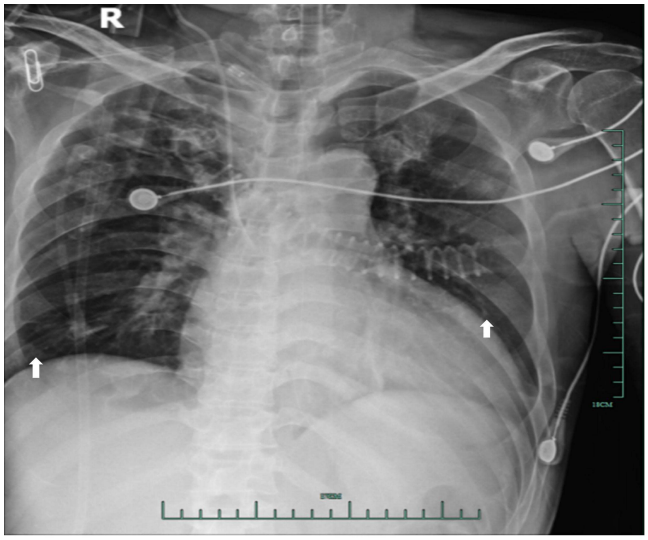

Figure 2 Chest X-ray image during hospital admission revealed multiple bilateral patchy infiltration with increased interstitial markings (arrows).
Abbreviation: R, right side.

lobe. Valproate, levetiracetam, and midazolam were given. Blood tests revealed that the creatinine level had increased to 437.0 μmol/L and the platelet count had decreased to 10.1 × 10^9/L. His daily urine output was also reduced to 300 mL. Furosemide was given for diuresis. Recombinant thrombopoietin and platelet transfusion were given to correct thrombocytopenia. The patient was transferred into the intensive care unit (ICU) for close monitoring.

Four days after transfer to the ICU (April 8, 2023), the patient gradually became comatose. The repeated laboratory tests revealed metabolic acidosis, a platelet count of 30.3 × 10^9/L, and a creatinine level of 405.9 μmol/L. He received endotracheal intubation, and he was maintained on mechanical ventilation. Continuous renal replacement therapy was also initiated. One week after ICU admission, bone marrow biopsy was performed, which revealed active myeloproliferation with 65% nucleated myeloid cells, active granulopoiesis with predominantly neutrophil granulocytes and metamyelocytes, active erythropoiesis with polychromatic and orthochromatic normoblasts, and a normal karyotype. The blood smear revealed schistocyte and reticulocyte percentages of <1% and 10.5%, respectively. In addition, blood ADAMTS13 activity was 1.8% (normal range, 42.1%–126.3%), and the anti-ADAMTS13 antibody test was positive. Considering the patient's medical history and laboratory test results, we made a diagnosis of TTP. After two sessions of plasma exchange treatment (2000 mL each time, April 13 and 15), the patient's mental status returned to normal. He was extubated on April 16, 2023 and transferred to the medical floor on April 21, 2023. Brain magnetic resonance imaging revealed small infarcts in the bilateral parietotemporal lobes. A repeated examination revealed a gradually increased platelet count of 167.2 × 10^9/L and a decreased creatinine level of 320.2 μmol/L. Chest X-ray revealed no pulmonary infiltration. The patient was discharged from the hospital on April 27, 2023. During the clinic visit 1 month later, the patient reported no clinical symptoms, and his platelet count and creatinine level were 140.4 × 10^9/L and 315.3 μmol/L, respectively. His anti-tuberculosis treatment lasted for 10 months, and sputum acid-fast bacillus staining was negative.

Discussion

Patients with tuberculosis can frequently have anemia and leukocytosis. Platelets are occasionally affected, which often presents as thrombocytosis. In this study, we report an extremely rare case of TTP developing during the treatment of pulmonary tuberculosis. TTP is a medical emergency that carries a high mortality rate. Prompt diagnosis and treatment are essential to save lives.

The most common organ involvement in tuberculosis is respiratory symptoms. TTP is characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurological disorders, and renal failure. Both tuberculosis and TTP can induce multiple-organ system failure. Tuberculosis causes tissue damage via direct bacterial infection and dysregulated immune responses. Most cases of TTP were also considered to be attributable to the autoimmune antibody against ADAMTS13. Whether there is a potential innate connection between tuberculosis and TTP is unknown. We reviewed the previous case reports on concurrent tuberculosis and TTP (Table 1). Most cases involved adults rather than young children, making the possibility of an inherited mutation in the *ADAMTS13* gene (a main cause of primary TTP) a less likely etiology for their TTP because the primary TTP is more rare in adulthood than secondary TTP. Two previous studies considered that TTP was caused by anti-tuberculosis treatment with rifampin because both patients first had tuberculosis and TTP developed after the initiation of rifampin treatment.[2,3] Rifampin can induce the production of an anti-rifampin antibody that might destroy platelets. However, in most other case reports on tuberculosis and TTP, TTP was identified before rifampin treatment for tuberculosis. TTP was resolved without recurrence after treatment with plasma exchange, fresh frozen plasma infusion, or steroids despite continued rifampin treatment for tuberculosis. Therefore, rifampin treatment cannot explain all cases of concurrent tuberculosis and TTP. Some other studies suggested that interleukin-1 could play a role in the pathogenesis of TTP during tuberculosis.[4,5] Patients with tuberculosis could have dysregulated levels of interleukin-1. Interleukin-1 has procoagulant activity, and it can damage endothelial cells with subsequent microthrombosis and TTP development. Other authors suggested that molecular mimicry between antibodies against microbes and ADAMTS13 could cause cross-reactions to induce TTP in patients with tuberculosis.[6] The exact pathogenic mechanism of TTP during tuberculosis requires more studies with the accumulation of additional similar cases.

The management of tuberculosis and TTP follows the general treatment guidelines recommended for each illness. The treatment of tuberculosis should include triple or quadruple regimens for dedicated periods. TTP should be treated with plasma exchange, fresh frozen plasma infusion, and steroid treatment, as well as platelet or red blood cell transfusion when necessary. All previously reported cases of tuberculosis with TPP had successful recoveries (Table 1). From these reported cases, TTP could arise in all age groups and in both men and women. Considering that tuberculosis has a high global prevalence and a high mortality rate and that approximately 5% of patients with pulmonary tuberculosis could have thrombocytopenia, we suspected that some patients with tuberculosis and thrombocytopenia might have TTP, which was not promptly recognized and diagnosed. The consequence of a missed TTP diagnosis is lethal. Untreated TTP has a mortality rate of up to 90%, which can be decreased to 10% by prompt treatment.[1] In our case, we diagnosed TTP 11 days after the patient was admitted to our hospital. Fortunately, the patient had a full recovery, probably because of the platelet transfusion given before the final diagnosis of TTP was made. Therefore, clinicians should be reminded about concurrent TTP in patients with tuberculosis. Patients with tuberculosis and severe thrombocytopenia and evidence of microangiopathic hemolysis should undergo necessary tests to eliminate the possibility of TTP. Several recent case reports conducted ADAMS13 activity and antibody tests to confirm the diagnosis of TTP (Table 1). However, the ADAMTS13 test might not be widely available, but this should not delay the management of suspected TTP. The presence of thrombocytopenia, acute renal failure, and altered mental status should prompt a blood smear test to detect schistocytes, a characteristic of microangiopathic hemolytic anemia. In addition, the PLASMIC score should be calculated to estimate the possibility of TTP. The PLASMIC score has high sensitivity, but low specificity, for TTP screening.[10] Appropriate treatments, such as plasma exchange and fresh frozen plasma infusion, should be considered.

In conclusion, we report an extremely rare case of pulmonary tuberculosis complicated by TTP. Clinicians should be reminded to eliminate the possible concurrence of these two illnesses. Necessary diagnostic tests should be performed in patients with evidence of severe thrombocytopenia and microangiopathic hemolysis to eliminate the possibility of TTP. Appropriate management should be applied because a delayed or missed diagnosis can lead to death in these patients.

Table 1 Clinic Characteristics, Hematologic Tests, and Treatments in Patients with Tuberculosis and TTP.*

Author, year	Country	Age, years	Sex	Duration from presentation to TTP diagnosis	Tuberculosis		TTP		
					Location	Treatments	Hematologic tests	ADAMTS13	Treatments
Fahal et al 1992[2]	United Kingdom	57	Male	N/A	Renal	Isoniazid, ethambutol rifampin (*stopped after the TTP diagnosis*)	Thrombocytopenia, schistocytes, spherocytes, polychromasia		Platelet transfusion, FFP
Toscano et al 1994[4]	Italy	24	Male	4 days	Pulmonary	Isoniazid, rifampin, ethambutol, streptomycin	Anemia, thrombocytopenia, schistocytes, poikilocytes, helmet cells		Plasma exchange, FFP, transfusion
Iwamatsu et al 1998[7]	Japan	65	Female	8 days	Military	Isoniazid, rifampicin, streptomycin	Anemia, thrombocytopenia		FFP, platelet transfusion
Askari et al 2014[5]	United States	25	Female	N/A	Cardiac tuberculoma	Isoniazid, rifampin, pyrazinamide, ethambutol	Anemia, thrombocytopenia, schistocytes		Plasma exchange
Rodrigo et al 2015[8]	Argentina	60	Male	N/A	Pulmonary, intestine	Isoniazid, rifampin, pyrazinamide, ethambutol	Anemia, thrombocytopenia, anisocytosis, poikilocytosis, polychromasia		FFP, steroids
Hamad et al 2020[3]	United States	55	Female	Day of admission	Latent tuberculosis	Isoniazid, rifampin (*stopped after the TTP diagnosis*)	Anemia, thrombocytopenia, schistocytes, polychromasia	Activity 4.6%, antibody +	Plasma exchange, steroids
Maheshwari et al 2021[6]	India	5	Male	5 days	Disseminated tuberculosis	Anti-tuberculosis	Anemia, leukocytosis, thrombocytopenia, schistocytes, spherocytes, teardrop cells	Activity 20%	FFP, steroids
Contreras et al 2023[9]	Colombia	49	Female	Day of admission	Pulmonary	Isoniazid, rifampin, pyrazinamide, ethambutol	Anemia, thrombocytopenia, schistocytes	Activity 1.4%	Plasma exchange, steroids
Current case	China	53	Male	11 days	Pulmonary	Isoniazid, rifampicin, moxifloxacin	Anemia, thrombocytopenia, schistocytes	Activity 1.8%, antibody +	Plasma exchange

Notes: *all cases had successful recoveries after treatment. †case was reported as thrombotic microangiopathy because the authors considered it difficult to differentiate between TTP and hemolytic uremic syndrome.
Abbreviations: FFP, fresh frozen plasma; N/A, not available, TTP, thrombotic thrombocytopenic purpura.

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Abbreviations

CT, computed tomography, TTP, Thrombotic thrombocytopenic purpura, ICU, intensive care unit.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Written informed consent was obtained from participant. This case report was also approved by the hospital ethics committee.

Consent for Publication

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

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Disclosure

We declare that we have no conflict of interest.

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