Case Report

Thrombotic Thrombocytopenic Purpura Associated with Mixed Connective Tissue Disease: A Case Report

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Thrombotic thrombocytopenic purpura (TTP) is a multisystemic disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia, which may be accompanied by fever, renal, or neurologic abnormalities. Cases are divided into acute idiopathic TTP and secondary TTP. Autoimmune diseases, especially systemic lupus erythematosus, in association with TTP have been described so far in many patients. In contrast, TTP occurring in a patient with mixed connective tissue disease (MCTD) is extremely rare and has only been described in nine patients. We describe the case of a 42-year-old female with MCTD who developed thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurological symptoms. The patient had a good clinical evolution with infusion of high volume of fresh frozen plasma, steroid therapy, and support in an intensive care unit. Although the occurrence of TTP is rare in MCTD patients, it is important to recognize TTP as a cause of thrombocytopenia and hemolytic anemia in any patient with autoimmune diseases. Prompt institution of treatment remains the cornerstone of treatment of TTP even if plasma exchange is not available like what frequently happens in developing countries.

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a multisystemic disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia, which may be accompanied by fever, renal, or neurologic abnormalities [1, 2]. It is almost always acquired, with rare cases of congenital TTP (Upshaw-Schulman syndrome). Acquired cases are divided into acute idiopathic TTP and secondary TTP, which has been seen in association with collagen vascular disease, bone marrow transplantation, malignancy, pregnancy, infections, and drugs such as cyclosporine, tacrolimus, ticlopidine, and antineoplastic agents [1, 3]. Systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, adult onset Still’s disease, systemic sclerosis, polymyositis, dermatomyositis, and rheumatoid arthritis in association with TTP have been described so far in many patients [4–12]. In contrast, mixed connective tissue disease (MCTD) in association with TTP is extremely rare and has only been described in nine patients [13–21]. Here, we describe the 10th case of mixed connective tissue disease (MCTD) complicated by TTP and discuss the complexity of its management in a developing country.

2. Case Report

A 42-year-old Afro-Brazilian woman was admitted to emergency department with gradual neurologic disorientation, accompanied by fever, renal, or neurologic abnormalities [1, 2]. It is almost always acquired, with rare cases of congenital TTP (Upshaw-Schulman syndrome). Acquired cases are divided into acute idiopathic TTP and secondary TTP, which has been seen in association with collagen vascular disease, bone marrow transplantation, malignancy, pregnancy, infections, and drugs such as cyclosporine, tacrolimus, ticlopidine, and antineoplastic agents [1, 3]. Systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, adult onset Still’s disease, systemic sclerosis, polymyositis, dermatomyositis, and rheumatoid arthritis in association with TTP have been described so far in many patients [4–12]. In contrast, mixed connective tissue disease (MCTD) in association with TTP is extremely rare and has only been described in nine patients [13–21]. Here, we describe the 10th case of mixed connective tissue disease (MCTD) complicated by TTP and discuss the complexity of its management in a developing country.
temperature 37.2°C, blood pressure was 180/100 mmHg, pulse 108 per min. and temperature 37.2°C. Clinical examinations of the cardiovascular, respiratory systems, and abdomen were normal. There was edema in the lower limbs (2+/4+). Complete blood cell count showed a normocytic normochromic anemia and thrombocytopenia (Table 1). Peripheral blood smear demonstrated anisocytosis, poikilocytosis with schistocytes, and thrombocytopenia (Figure 1). Biochemical analysis revealed elevated levels of serum LDH (1,830 U/L) and bilirubin (total 4.1 mg/dL, direct 2.1 mg/dL and indirect 2.0 mg/dL). Direct Coombs test was negative, and PT and aPTT were normal. Her urine exam was positive to protein (3+), leukocyte (2+), hemoglobin, (4+), bilirubin (1+), and urobilinogen (2+) with negative nitrite. Other laboratory data are summarized in Table 1.

Clinical identification of nonimmune haemolytic anemia with presence of red cell fragmentation, thrombocytopenia, and altered level of consciousness led to the diagnosis of thrombotic thrombocytopenic purpura secondary to autoimmune disease, since the patient was previously diagnosed as MCTD. Prednisone 1 mg/kg/day (80 mg/day) scheme was initiated after administration of antiparasitic therapy (prophylaxis of strongyloides hyperinfection syndrome [22]), fresh frozen plasma (15 mL/kg/day), and red blood cells transfusion with blood pressure monitoring and use of diuretics to prevent fluid overload.

She evolved in 24 hours with high fever (39.2°C); blood pressure was 160/80 mmHg, and subsequently, with decreased level of consciousness, she underwent endotracheal intubation and was transferred to the Intensive care unit (ICU). The infusion of fresh frozen plasma was progressively increased to 25–30 mL/kg/day. During hospitalization, she presented with pneumonia and received ceftriaxone and clindamycin. Abdominal ultrasonography, computed tomography, and magnetic resonance imaging of the brain showed no specific abnormalities.

After 5 days in the ICU, she showed good clinical outcome, with improvement of neurologic and respiratory parameters, allowing weaning and withdraw of mechanical ventilation. Throughout the period her blood pressure was kept under strict control with captopril, amlopidine, atenolol, methyldopa, and losartan, as well as periods of sodium nitroprusside.

After 20 days of hospitalization, the patient presented progressive improvement in microangiopathic anemia, increased hemoglobin, and platelets, and a progressive decrease of LDH and reticulocytes (Table 1). She was not submitted to plasmapheresis. There was normalization of blood pressure with concomitant gradual reduction in the volume of fresh frozen plasma infused and reduction of prednisone. She was discharged from the hospital with antihypertensive drugs (clonidine and amlopidine) and prednisone (20 mg/day). After 40 days of symptom onset and 20 days after discharge the patient was asymptomatic and laboratory tests improved (Table 1).

### 3. Discussion

Following the discovery that TTP is associated with a severe deficiency of ADAMTS13 activity [23, 24], it was suggested that ADAMTS13 deficiency may become the definition and diagnostic criterion for TTP. But many patients who fulfill the clinical diagnostic criteria for TTP do not have ADAMTS13 deficiency [10, 25]. For some authors, measurements of ADAMTS13 activity are not required and do not conclusively confirm the diagnosis of TTP [26]. In this way, the diagnosis of TTP is based on the presenting clinical features [1]. Prompt diagnosis of TTP is critical to begin treatment and reduce patient’s mortality.

Patients diagnosed with TTP may have additional disorders including autoimmune diseases. In this group systemic lupus erythematosus (SLE) is the most common, followed by antiphospholipid antibody syndrome, adult onset Still’s disease, rheumatoid arthritis, systemic sclerosis, polymyositis and dermatomyositis [4–12].

TTP associated with mixed connected tissue disease is rare and has only been described in nine patients (Table 2) [13–21]. Most of these cases were women (8:1) with the median age of 40 years. The mortality was high (45%), early, (within 2–45 days) and associated with serious neurological impairment (seizure and coma). Our case presented a good clinical evolution in spite of serious neurological manifestations which points to a worse prognosis [17, 19].

The pathogenic processes of thrombotic microangiopathy in patients with connective tissue diseases are heterogeneous. ADAMTS13 activity is significantly decreased in this group of patients. However, only a minor population presents neutralising autoantibodies against ADAMTS13, which was associated with severe ADAMTS13 deficiency, lower
| Table 1: Laboratory data. |
|---------------------------|
| On admission | After 20 days | After 40 days |
| Complete blood count | | | |
| RBC ($\times 10^{12}/L$) | 2.88 | 3.97 | 4.55 |
| Hemoglobin (g/dL) | 7.8 | 11.5 | 12.4 |
| Hematocrit (%) | 23.8 | 35 | 39.6 |
| MCV (fl) | 82.6 | 88 | 87 |
| MCH (pg) | 27 | 29 | 27 |
| MCHC (g/dL) | 32.7 | 33 | 31 |
| RDW (%) | 21.2 | 17.6 | 13.2 |
| WBC ($\times 10^9/L$) | 9.8 | 5.72 | 7.23 |
| Platelet ($\times 10^9/L$) | 5.1 | 243 | 312 |
| Reticulocytes (%) | 8.4 | 1.1 | 0.8 |
| Blood chemistry | | | |
| AST (IU/L) | 46 | 22 | 21 |
| ALT (IU/L) | 43 | 29.2 | 31 |
| GGT (IU/L) | 98 | 230 | 80 |
| ALP (IU/L) | 98 | 130 | 72 |
| LDH (IU/L) | 1830 | 365 | 176 |
| Total bilirubin (mg/dL) | 4.1 | 0.5 | 0.6 |
| Direct bilirubin (mg/dL) | 2.1 | 0.23 | 0.28 |
| Indirect bilirubin (mg/dL) | 2 | 0.27 | 0.32 |
| Glucose (mg/dL) | 128 | 98 | 89 |
| Urea (mg/dL) | 19 | | |
| Creatinine (mg/dL) | 0.6 | | |
| Uric acid (mg/dL) | 3.0 | | |
| Sodium (mEq/L) | 139 | | |
| Potassium (mEq/L) | 2.9 | | |
| Hormones | | | |
| TSH ($\mu$U/mL) | 2.72 | | |
| Free T4 (pg/dL) | 1.08 | | |
| Serology | | | |
| HBsAg | Negative | | |
| Anti-HBs | Negative | | |
| Anti-HBc | Negative | | |
| Anti-HCV | Negative | | |
| Anti-HIV | Negative | | |
| Blood culture | Negative | | |
| Other blood tests | | | |
| ESR (mm/hr) | 78 | | |
| PT (s) | 10.2 | | |
| aPTT (s) | 21.3 | | |
| Direct Coobs test | Negative | | |
| Urinalysis | | | |
| Protein | (3+) | | |
| Leukocyte | (2+) | | |
| Hemoglobin | (4+) | | |
| Bilirubin | (1+) | | |
| Urobilinogen | (2+) | | |
| Nitrite | (—) | | |
| Urine culture | negative | | |

RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red blood cell distribution width, WBC: white blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, PT: prothrombin time, aPTT: activated partial thromboplastin time, TSH: Thyroid-stimulating hormone.
Table 2: Characteristics of TTP in patients with MCTD.

| Age | Sex | Duration of MCTD (years) | Prodrome | Treatment | Prognosis | Reference |
|-----|-----|--------------------------|----------|-----------|-----------|-----------|
| 29 F | 5  | Chest pain, fever, loin pain, confusion | PDN | Died (2 days) | [13] |
| 33 F | 2  | Flu-like syndrome | PDN, FFP, vincristin, prostacyclin | Alive | [14] |
| 40 F | 2  | Headache, confusion, seizure | PE, PDN, vincristin, aspirin | Died (12 days) | [15] |
| 55 F | ? | Fever, confusion, seizure, coma, myocardial infarction | PE, PDN | Alive | [16] |
| 64 F | 8  | Headache, confusion seizure, coma | PE, PDN | Died (45 days) | [17] |
| 15 M | ? | Headache, visual blurring, vomiting, Paresthesia | PE, PDN, vincristin, cyclosporine | Alive | [18] |
| 73 F | 10 | Confusion, coma | PE, PDN | Died (34 days) | [19] |
| 46 F | 2  | Fever, headache | PE, PDN, aspirin, Cyclophosphamide, rituximab | Alive | [20] |
| 24 F | <1 | Laboratory detection | PE | Alive | [21] |
| 42 F | 4  | Headache, confusion seizure, coma, Fever, vomiting, hematuria | FFP, PDN | Alive | This case |

F: female, M: male, PDN: prednisone or prednisolone, FFP: fresh frozen plasma, PE: plasma exchange.

platelet counts, and better therapeutic outcomes. A major population has normal or moderately reduced ADAMTS13 activity [4]. In this group, the mechanisms of development of TTP remain unclear. There is a higher prevalence of anti-endothelial cell antibodies in the sera of MCTD patients [27] and depressed plasma fibrinolytic activity [28], suggesting that a MCTD related vasculitis and thrombotic microangiopathy may have been involved in the pathogenesis of TTP [15, 17]. In patients with systemic sclerosis, renal crisis remains one of the potential processes related to microangiopathic hemolytic anemia, thrombocytopenia, accelerated hypertension and acute renal failure [29, 30].

Previous reported cases were treated with various therapies including steroids, fresh frozen plasma (FFP), plasma exchange (PE), prostacyclin, vincristine, cyclosporine, cyclophosphamide, rituximab and aspirin [13–21]. Today, the mainstay of treatment of acute TTP is plasma exchange [1]. Before the plasma treatment era, survival of patients with TTP was only 10%. Then, almost 20 years ago, plasma exchange was reported to increase survival to 78%, compared to 51% survival for patients treated with plasma infusion [31]. Nowadays, however, there are some places that plasma exchange still unavailable. In these cases, high volume of fresh frozen plasma could only be provided because of patient’s good cardiac and renal function associated with a strict blood pressure control.

4. Conclusion

Although the occurrence of TTP is rare in MCTD patients, it is important to recognize TTP as a cause of thrombocytopenia and hemolytic anemia in any patient with autoimmune diseases. Prompt institution of treatment remains the cornerstone of treatment of TTP even if plasma exchange is not available like what frequently happens in developing countries.

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