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An insidious presentation of thrombotic thrombocytopenic purpura: A case report and brief literature review

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy with an estimated incidence of 11 cases/million population per year. Early treatment is essential and is curative in this disease where lack of treatment results in 90% mortality. We describe an atypical case of a patient with TTP who presented to the Emergency Department for headache, and was found to have thrombocytopenia but only mild anemia that was explained by another disease process. Case: A 44-year-old female presented to the Emergency Department for worsening headache and weakness over the last week. She had no fever and no focal neurological deficits but was pale and complained of severe headache. A blood test showed her to be anemic and thrombocytopenic. She explained that she had been having prolonged heavy menses over the last year. She was treated with blood and platelet transfusions, and seen by the Gynecology service who treated her for uterine fibroids after which she was discharged. She returned 1 week later with the same complaint, and was found to have a stable hemoglobin level but recurrence of thrombocytopenia. A TTP diagnosis was entertained and the workup confirmed it. The patient was treated with plasmapheresis and discharged home with no sequalae. Conclusion: Emergency physicians should keep TTP in mind when approaching cases of thrombocytopenia with mild anemia, even if an alternative diagnosis exists.

1. Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is a thrombotic microangiopathy, characterized by the formation of microthrombi within vessels of multiple organ systems, leading to microangiopathic hemolytic anemia, thrombocytopenia, and potentially end organ ischemia. TTP was first described by E. Moschowitz in 1925 "as a new disease characterized by unique pathological findings of hyaline thrombi in many organs"[1]. A classic pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, neurological symptoms and renal abnormalities was described by Amorosi and Ultmann in 1966 and was present in 88%-98% of patients at that time[2]. With the advent of plasmapheresis as a first-line treatment modality for TTP, and the lower threshold for initiation of treatment, the number of patients presenting with the classic pentad was down to 40% in a study from 1981[3]. Nowadays however, with the number of patients diagnosed with TTP up 8-fold, and with the increasing use of plasmapheresis early in the course of the disease, the number of patients who presented with the classic pentad is down to 5%[4]. An essential dyad of thrombocytopenia and MAHA in the appropriate clinical setting is now the only requirement for establishing a diagnosis of TTP and initiating treatment[4]. We describe an atypical case of TTP that demonstrates an ambiguous presentation in a patient with clinical manifestations that were explained by other diseases.

2. Casereport

A previously healthy 44-year-old female presented to the

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Emergency Department (ED) with generalized weakness and intermittent diffuse headache, associated with photophobia for the past week.

Three days prior to the ED visit she was seen at an urgent care clinic for the same symptoms and discharged home with a diagnosis of viral syndrome. The following day she returned to the urgent care clinic with worsening of her symptoms and was treated with intravenous fluids and prescribed azithromycin for a presumed infection. Two days later she came to the ED with no improvement in symptoms and a chief complaint of generalized weakness and diffuse headache. During this ED visit, she reported having been diagnosed with uterine fibroids the previous year, and having prolonged and irregular heavy menses since then. The patient's other previous medical history included anemia and autoimmune thyroiditis for which the patient underwent radioiodine ablation. The patient's social history was negative for alcohol or drug use and she was a non-smoker. Her family history was negative for systemic lupus erythematosus (SLE) or rheumatoid arthritis.

On physical examination, the patient had stable vital signs. She had generalized pallor including skin, conjunctiva, palms, and nail beds. The neurological examination showed no focal deficit. A pelvic examination showed no blood in the vaginal vault, with a closed cervix and no adnexal masses or tenderness. Laboratory workup showed a hemoglobin (Hgb) level of 5 g/dL and a platelet count of 24 000/μL, with normal prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and fibrinogen degradation products. The gynecological service was consulted and the patient was admitted to the observation unit with a diagnosis of menorrhagia, and treated with packed red blood cells and a platelet transfusion, with a post transfusion hemoglobin of 10 g/dL and platelet count greater than 50 000/μL. She remained hemodynamically stable throughout her stay, and was discharged home after receiving a progesterone injection.

One week later she presented again to the ED with severe headache, mostly frontal, associated with photophobia and continuous for the past 24 h. On the morning of her presentation, her menses had started and she was passing clots with intermittent heavy bleeding. She denied any prior upper respiratory tract infection, or easy bruising. Vital signs on presentation were: Temperature 36.3 ℃, Blood Pressure 114/61 mmHg, Pulse 86 beats/min, Respiratory Rate 14/min, and O_2 Saturation 100% on Room Air. On pelvic examination, the patient had mild active vaginal bleeding with a closed cervical os and palpable uterine masses consistent with her history of uterine fibroids. The neurological examination was normal with no deficit. Initial laboratory examination showed her hemoglobin was stable at 9.8 g/dL (previous value 10 g/dL) but platelets had decreased to 17 000/μL. Her creatinine level had increased to 1.1 mg/dL (previous creatinine: 0.8 mg/dL) indicating possible early effect on her kidneys.

The ED physicians considered the previous anemia, and the persistent thrombocytopenia, and entertained the diagnosis of TTP. Laboratory examination for hemolysis was positive with elevations in lactate dehydrogenase (LDH) and reticulocyte count, up to 643 IU/L (100-220 IU/L) and 4.9% respectively. Unconjugated bilirubin was also elevated with total bilirubin at 1.7 mg/dL and direct bilirubin at 0.3 mg/dL. Haptoglobin levels were low at 16.2 mg/dL (30-200 mg/dL). Coombs test was negative while the peripheral smear was positive for schistocytes.

Autoimmune profile was significant for strongly positive antinuclear antibodies (ANA), normal serum complement levels, positive ribonucleoprotein antibodies, and an ADAMTS-13 level of < 5% (Normal > 67%).

The patient was admitted to the general medical floor and started on daily plasmapheresis. She showed gradual improvement in her platelet counts initially; however, she subsequently became thrombocytopenic again with a nadir of 39 K. Plasmapheresis was continued and the patient was started on prednisone. She improved and was weaned off plasmapheresis gradually and discharged home.

3. Discussion

Thrombotic Thrombocytopenic Purpura is an acute life-threatening syndrome characterized by thrombocytopenia and microangiopathic hemolytic anemia. There is often multi-organ involvement with neurological and renal abnormalities being most common and potentially the most serious[5]. A classic pentad of thrombocytopenia, MAHA, fever, neurological abnormalities and renal dysfunction has been described but is rarely seen in its entirety nowadays[4]. Two major diagnostic criteria, thrombocytopenia and microangiopathic hemolytic anemia without alternate explanation form an essential dyad and are enough to suspect the diagnosis of the TTP and initiate treatment[4,5].

Hemolytic Uremic Syndrome (HUS) shares these essential diagnostic criteria. Although sometimes grouped with TTP in the medical literature, there is debate over whether TTP and HUS are in fact distinct syndromes[6]. For the purposes of this article, they will be treated as such, because each has its own pathophysiology, optimal treatment and prognosis. Initial treatment, however, is the same for both and patients in the Emergency Department should be managed with plasma exchange until a definitive diagnosis can be

established[4].

MAHA is defined as hemolysis with a negative direct antiglobulin (Coombs test), and red cell fragmentation (schistocytes) seen on peripheral smear. A few schistocytes seen on peripheral smear can be normal, especially in patients with renal disease, preeclampsia, or mechanical heart valves but the number is almost always less than 0.5 percent[6]. Patients with TTP are expected to have >1% schistocytes on peripheral smear with one study finding the mean to be 8.4%[7]. Therefore, observation of two or more schistocytes in a microscopic field at 100× magnification suggests the presence of microangiopathic hemolysis[6].

Indirect bilirubin and LDH are typically elevated as would be expected with hemolysis. Thrombocytopenia can be severe but can also be masked by schistocytes being incorrectly interpreted as platelets[6].

About 50% of TTP cases are considered idiopathic[6]. Idiopathic TTP is related to decreased levels of a specific von Willebrand factor (VWF) cleaving protease, called ADAMTS-13 (A Disintegrin and Metalloprotease with a ThromboSpondin type 1 motif, member 13). Deficiency of ADAMTS-13 causes abnormally high platelet consumption and has been linked to patients with TTP and especially those who are at risk for relapse[6,8]. ADAMTS-13 acts to cleave VWF when it is partially unfolded by high levels of shear stress. By cleaving VWF before it is activated fully by shear stress, ADAMTS-13 prevents accumulation of super-active forms of VWF and subsequently prevents VWF-platelet aggregation[8,9]. When ADAMTS-13 is not present, abnormally large von Willebrand factor multimers accumulate in plasma and have a greater ability to react with platelets, causing disseminated platelet thrombi characteristic of thrombotic thrombocytopenic purpura[6]. This explains why a severe deficiency of ADAMTS-13, conventionally considered to be less than 5% activity (Normal is >67%), causes microvascular thrombosis that is characteristic of TTP[7,8].

Researchers looking into causes of severe ADAMTS-13 deficiency have found evidence of both congenital ADAMTS-13 deficiency (called UpshawSchulman syndrome when it causes TTP)[9], and an autoimmune etiology, where autoantibodies to ADAMTS-13 were found in cases of TTP with severe ADAMTS-13 deficiency[4,10]. Furthermore, the association with other autoimmune disorders, namely SLE and certain vasculitides, and the frequent occurrence of a TTPlike picture in patients with autoimmune disorders suggests that idiopathic TTP with severe ADAMTS13 deficiency may represent an autoimmune disorder[9,10].

Not all patients with idiopathic TTP have severe deficiency of ADAMTS-13. In a study by Hovinga et al. from 2010 that analyzed 107 patients with idiopathic TTP, only 51 patients had severe ADAMTS-13 deficiency[11]. Those patients with ADAMTS-13 deficiency did however have some distinctions. They were younger, had more severe anemia and thrombocytopenia, and less severe renal failure. Mortality was the same in both groups of patients but the risk of relapse was much higher (40%) among patients with severe ADAMTS-13 deficiency[11]. Therefore ADAMTS-13 activity level should not be used for diagnosis, and treatment should never be delayed waiting for results of this test.

Although many cases of TTP are considered idiopathic, a number of underlying causes have been discovered. Hemolytic uremic syndrome consists of hemolytic anemia, thrombocytopenia, and renal impairment. HUS most often results from exposure to Shiga toxin produced by *Escherichia coli* or *Shigella* species resulting in a prodrome of bloody diarrhea. Essential diagnostic criteria for HUS, MAHA and thrombocytopenia, matches those of TTP and it is often treated as such, although in children, HUS is managed with only supportive care. Autoimmune TTP is a category of TTP associated with diseases such as systemic lupus erythematosus, antiphospholipid syndrome and collagen vascular diseases. People with these diseases have a higher incidence of TTP, and antibodies against ADAMTS-13 have been discovered in some[4-6]. Drug induced TTP is mostly commonly attributed to quinine, an over-the-counter medication used for leg cramps[4], but also found in tonic water. Other drugs that may induce TTP include the antiplatelet agents Ticlopidine and Clopidogrel, and immunosuppressants like Cyclosporine[5]. Certain chemotherapies may also cause TTP but the onset is usually insidious and is believed to be dose-dependent. The mechanism is also different and is most likely related to direct endothelial injury inciting the event[6]. It should also be noted that pregnancy may be a trigger of TTP in patients with congenital or acquired severe ADAMTS-13 deficiency as it is associated with a decrease of ADAMTS-13 by as much as 30%[5].

First-line therapy for TTP is plasma exchange, which has an 80% success rate and is often curative[6], although relapses are common. Plasma exchange reverses the platelet consumption responsible for the thrombus formation and symptoms that are characteristic of this disorder[4]. It is believed that clinical improvement results from depletion of circulating levels of autoantibody to ADAMTS-13 if present, and likely also depletes the circulating very high molecular weight von Willebrand factor multimers[6]. If some improvement occurs after plasma infusion alone, it is likely as a result of replacement of the missing protease ADAMTS-13[6].

Those patients diagnosed with TTP with severe ADAMTS-13 deficiency may benefit from the addition of glucocorticoids or rituximab[4,5]. Plasma transfusion is a second-line treatment modality and used mostly as a temporizing measure while preparing for plasma exchange. Without rapid intervention, TTP has a reported mortality rate as high as 90%, which drops to around 10-20% with plasma exchange[5,6].

Acute morbidities include stroke/transient ischemic attacks, myocardial infarction, arrhythmias, bleeding, and renal failure. Survivors generally have no long-term sequalae, with the exception of residual neurologic deficits in a minority of patients. Relapses occur in around 13%-36% of patients with the likelihood of recurrence dependent on a number of recognized risk factors, which include ADAMTS-13 deficiency and pregnancy after a previous episode of TTP[8]. A randomized trial of 102 patients by Rock, Shumak, Buskard et al. found the relapse rate to be 50% in patients with severe ADAMTS-13 deficiency[12].

There is limited data available on patients with TTP who are not treated. The data available shows that without treatment, the disease is often rapidly progressive and fatal, with death most often occurring within 1-2 weeks from the onset of symptoms[2,8]. Our case demonstrates an insidious case of TTP. The patient's only symptoms were weakness and headache, and during the 2 weeks before she received plasma exchange, she had almost no progression in her symptoms other than a worsening of her headache. The patient's history of uterine fibroids and menorrhagia, with subsequent anemia was distracting and offered an alternative diagnosis that negated a laboratory examination for hemolysis during her first ED visit. To further distract physicians away from a diagnosis of TTP during her second ED visit, her hemoglobin was relatively stable after receiving the blood and platelet transfusion one week earlier (during her first ED visit.) In Ridolfi and Bell's 1981 review of 237 cases of TTP, only 3% of cases (6 of 237) had normal hematocrit values[3]. O'Brien and Crum hypothesized that: "Even the rare patient without anemia presumably exhibits fragmented red cells on a peripheral smear with a compensatory reticulocytosis"[13]. Our patient matches O'Brien and Crum's prediction with only borderline anemia but with schistocytes on a peripheral smear and compensatory reticulocytosis.

Emergency physicians in particular should keep TTP in mind when evaluating cases of combined anemia and thrombocytopenia, even when the anemia is mild or when an alternative diagnosis exists. A peripheral smear can help identify TTP or other thrombotic microangiopathies if there is hesitation to order a full laboratory examination for hemolysis. Physicians should also remember that the absence of fever, neurological deficits, renal abnormalities, or skin findings should not be used to rule out TTP.

Conflict of interest statement

We declare that we have no conflict of interest.

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