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Blood film says it all! Rare case of congenital TTP misdiagnosed as ITP

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ABSTRACT

We report a case of a 16-year-old female who presented with bleeding diathesis. Peripheral blood film examination was consistent with microangiopathic hemolytic anemia with 7% fragmented red blood cells. The ADAMTS13 level was 40 ng/ml (reference range: 630–850 ng/ml). She responded to plasma exchange therapy and methylprednisolone and was discharged in a stable condition.

1. Introduction

Congenital thrombotic thrombocytopenic purpura (TTP), which is also called as Upshaw-Schulman Syndrome, is a rare syndrome caused by inherited deficiency of the metalloprotease ADAMTS13 (A Disintegrin and Metalloprotease with Thrombospondin-1–like domains) [1]. Unlike the more common acquired form of TTP, which is characterized by an acquired inhibitor of ADAMTS13, congenital TTP shows deficiency of ADAMTS13,[2] without an inhibitor [3]. It is an autosomal recessive condition caused by several genetic mutations on chromosome 9q34. The function of ADAMTS13 is that it cleaves a specific peptide bond in the von Willebrand factor (VWF) subunit [2,3].

As ADAMTS 13 cleaves large multimers of von Willebrand factor, its absence causes persistence of large multimers that are uncleaved, thereby causing “spontaneous” platelet adhesion and aggregation leading to thrombocytopenia [4,5].

Clinically, patients complain of fever, nausea, and vomiting while the disease progresses; it may involve vital organs like the brain and kidney and cause neurological deficits and renal failure [6].

Hematological examination reveals signs of hemolysis, which include pallor, purpura, and jaundice, while laboratory findings show thrombocytopenia, unconjugated hyperbilirubinemia, increased LDH levels, and low haptoglobulin levels [7].

Peripheral blood smears are usually diagnostic, showing signs of intravascular hemolysis like fragmented erythrocytes (schistocytes), nucleated red blood cells, and polychromatic red cells [4].

Here, we present a case of a 16-year-old girl with congenital TTP who initially presented with a misdiagnosis of ITP. The purpose of this case report is to spread awareness among clinicians regarding this rare subtype of TTP, which can be treated promptly and effectively and can also be fatal if left untreated. The case report also emphasizes on the importance of peripheral blood film, as fragmented red blood cells are pathognomonic for this condition.

2. Case report

A-16-year-old girl presented in the emergency department of Aga Khan University, Karachi, with complaints of epistaxis, menorrhagia, fever, and vomiting for one month. General physical examination revealed pallor and jaundice with no visceromegaly. The patient had history of repeated hospital admissions with low platelet counts along with a low hemoglobin level, for which she received multiple red cell units and platelet concentrates. Her bone marrow examination was performed three years ago, which was reported as peripheral destruction, and she was diagnosed as a case of immune-mediated thrombocytopenic purpura (ITP). Her parents had a consanguineous marriage, and she had five siblings who were

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healthy. Two months ago, she had undergone splenectomy at her hometown for ITP.

At the time of admission in our hospital, the hemoglobin (Hb) level was 6.2 g/dL, white blood cell (WBC) count was 5.6×10^9/L, and platelet count was 9×10^9/L. Coagulation profile showed prothrombin time of 10.9 seconds and activated partial thromboplastin time of 22.2 seconds. Peripheral smear revealed 7% fragmented red blood cells (FRBC) and nucleated red cells along with polychromatic red cells (Figs. 1 and 2). Other investigations included a bilirubin level of 4.5 mg/dl with indirect component of 2.9 mg/dL, serum creatinine of 0.7 mg/dl, and LDH of 1401 I.U./L (normal = 208–378 I.U./L). Direct Coomb's test result was negative.

Because of a history of fever, samples were sent for blood culture, which revealed no growth. Chest X-ray along with ultrasound of the abdomen and pelvis was performed, which were unremarkable. She was diagnosed as a suspected case of microangiopathic hemolytic anemia (MAHA) on the basis of history, physical examination findings, and peripheral smear examination. Subsequently, serum ADAMTS 13 levels were extremely low, i.e., 40 ng/ml (reference 630–850 ng/ml). Depending on the ADAMTS13 levels, she was diagnosed with Upshaw Schulman syndrome (congenital thrombotic thrombocytopenic purpura).

She underwent treatment with plasma exchange (a total of five sessions) and immunosuppression in the form of methyl prednisolone (1G x once daily for three days followed by prednisolone 1 mg/kg twice daily). Menorrhagia was treated with oral norethisterone 5 mg thrice a day.

She responded to the above-mentioned treatment, and after five sessions of plasma exchange, her Hb improved to 10.6 g/dL, with the absence of FRBCs on peripheral blood film. Her platelet count increased to 221×10^9 cells/L. All other symptoms of bleeding diathesis resolved, and LDH reduced to 683 I.U./L.

She was discharged in a stable condition and was referred to a hematologist in her hometown, as it was not easy for the patient to visit hematology clinics in Karachi.

3. Discussion

The purpose of this case report is to increase knowledge and awareness among clinicians regarding this rare syndrome, which can easily be treated if properly diagnosed, while its misdiagnosis may lead to fatal consequence. In neonates and children, clinicians can suspect congenital TTP with jaundice, hemolytic anemia, and thrombocytopenia.

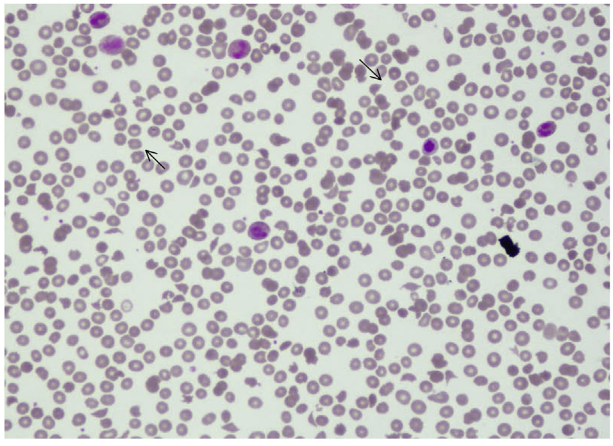

Fig. 1. Peripheral blood film showing microangiopathic hemolytic anemia (40X).

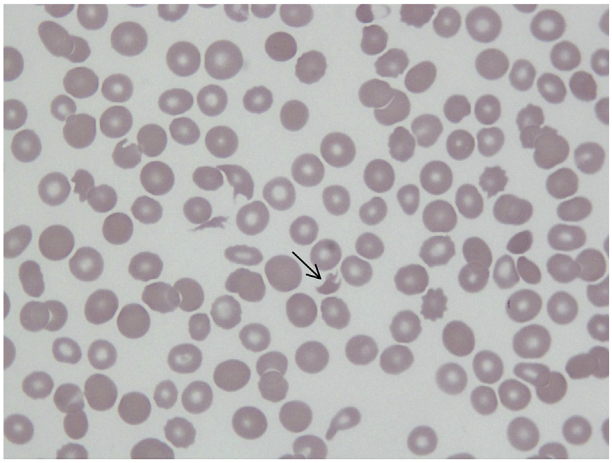

Fig. 2. Peripheral blood film showing microangiopathic hemolytic anemia (40X).

This rare syndrome was first diagnosed in 1960 by Schulman, in an eight-year-old girl who experienced repeated episodes of thrombocytopenia, which improved with plasma infusions [8]. In 1978, Upshaw described a similar case of a 29-year old with recurrent episodes of thrombocytopenia associated with microangiopathic hemolytic anemia (MAHA), which also responded to plasma infusions. He documented numerous episodes of MAHA in his patient, and majority of these symptoms were precipitated by acute infections or factors that culminated in stress, e.g., pregnancy or surgery [9].

TTP classically consists of pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, and variable renal and neurologic dysfunction present on 20–30% of patients, while the majority lack this classical presentation [6,7].

TTP is less commonly seen in children while usually seen in women in their third or fourth decades of life [10]. There are two forms of TTP: acquired and congenital.

It is essential to distinguish between congenital and acquired forms of TTP. In female patients, it is important to discuss the implications of pregnancy, which can precipitate an episode of microangiopathic hemolytic anemia (MAHA) [10,11]. For congenital TTP, it is important to screen asymptomatic family members, as the disease may precipitate in those individuals during times of stress [11,12].

The treatment depends on restoring the ADAMST13 function and removing/restoring the highly active von Willebrand proteins by plasma exchange or fresh frozen plasma infusions [13]. Once these patients achieve remission, the treatment is then subject to the phenotype of individual patient. In few patients, the practice is to transfuse plasma every 3–4 weeks to replace the deficient ADAMTS13 protein, while others will require plasma infusions if there are any stimulating factors of TTP present, e.g., sepsis, pregnancy, etc. [14].

Scully et al. [15] recently reported a phase 1 study on human subjects with congenital TTP who were treated with recombinant ADAMTS 13. The study showed safe tolerability and no immunological reactions. This product is a potential treatment option in patients with congenital TTP, which decreases the risk of transfusion-transmitted infections associated with plasma infusion.

Our patient was misdiagnosed as ITP previously and underwent unnecessary splenectomy. The surgery could have been avoided if peripheral blood film examination was performed for FRBCs. At our center, she responded well to the above-mentioned treatment. To

prevent further episodes, she was started on prophylactic plasma infusions (10–15 ml/kg) at four-weekly intervals for six months, which was then tapered off.

To date, she has had no further episodes of microangiopathy and remains healthy.

4. Conclusion

Congenital TTP is uncommon condition which presents with MAHA, thrombocytopenia and severely low levels of ADAMTS13. Plasma exchange and high dose corticosteroids are the recommended treatment options. Peripheral blood film examination is mandatory for FRBCs.

Ethics statement

1.Ayesha Majeed Memon, drafted manuscript and took pictures.

2.Natasha Ali, drafted manuscript, critical review.

Conflict of interest

The authors declare no conflict of interest.

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