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CASE REPORT

Acquired thrombotic thrombocytopaenic purpura of an atypical, oligosymptomatic course in an adolescent girl

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ABSTRACT

Acquired thrombotic thrombocytopaenic purpura (TTP) in children is a rare immune-mediated haematological disease (iTTP) in which active thrombus formation and multiorgan symptoms resulting from ischaemia of specific organs occurs. A 16-year-old girl was admitted to the hospital with symptoms of haemorrhagic diathesis. Physical examination showed numerous small petechiae all over her body. Laboratory tests revealed thrombocytopaenia, increased parameters of inflammation, lactate dehydrogenase activity, and total bilirubin. Decreased a disintegrin and metalloproteinase with thrombospondin motifs, member 13 (ADAMTS-13) activity, and the ADAMTS-13 inhibitor were detected. At first, the symptoms were not specific enough, therefore initially some difficulties establishing a proper diagnosis occurred. Finally, the patient was diagnosed with primary autoimmune thrombocytopaenia and then underwent an adequate therapy with fresh frozen plasma (plasmapheresis and multiple infusions) combined with corticosteroids, which induced a sustained remission of the disease. The authors aimed to raise the awareness of the iTTP, especially with limited characteristic features, as presented, and highlight the significance of differential diagnosis.

KEY WORDS:

children, ADAMTS-13, acquired thrombotic thrombocytopaenic purpura, oligosymptomatic.

INTRODUCTION

Thrombotic thrombocytopaenic purpura (TTP) belongs to the thrombotic microangiopathies (TMA) and is characterized by thrombocytopaenia and microangiopathic haemolytic anaemia (MAHA) [1, 2]. There are 2 main forms of TTP: hereditary (Upshaw-Schulman syndrome, congenital TTP) and acquired (immune-mediated TTP – iTTP) [1]. Immune-mediated thrombotic thrombocytopaenic purpura can be further described as primary or secondary. Primary iTTP is associated with the acquired deficiency of disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) – a member of the family of disintegrin and metalloproteinases, necessary for the breakdown of ultra-large von Willebrand factor (ULvWF) multimers [1, 3]. The secondary form, on the other hand, is triggered by a co-morbid condition, namely connective tissue disease or infection, as well as drug-induced cause or other clinical conditions, such as pregnancy [4]. There are sev-

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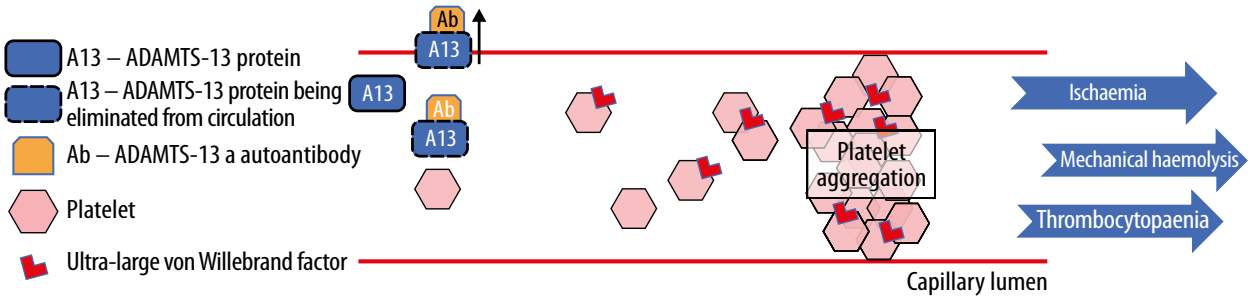

FIGURE 1. Mechanism of platelet aggregation involving ADAMTS-13 autoantibodies in circulation [1, 3, 6, 8, 9]

eral reports on the development of iTTP in response to vaccinations, especially antiviral. Moreover, COVID-19 virus vaccine from Pfizer-BioNTech was recently described as a possible trigger of iTTP [5].

Acquired TTP is often referred to as an autoimmune form due to the involvement of anti-ADAMTS-13 antibodies in the pathogenesis. Those autoantibodies increase the clearance of ADAMTS-13 from the bloodstream or inhibit the activity of this enzyme, consequently leading to accumulation of ULvWF multimers released by the endothelium in the circulatory system [3, 6, 7]. Ultra-large von Willebrand factor multimers then bind to thrombocytes and, owing to a high shear force in microcirculation, they cause formation of platelet aggregates capable of clogging the lumen of arterioles [1, 3]. Microvascular thrombosis results in ischaemia and multi-organ failure, when mechanical haemolysis and lack of thrombocytes due to clotting induce thrombocytopaenia and bleeding [1, 3, 6, 8] (Figure 1). Micro-clots most frequently occur in the heart, pancreas, kidneys, and brain, and less often in the lungs and liver [1, 9].

The incidence of TTP varies between 1 and 13 cases per million people, depending on geographic location, and is twice as high in women as in men. Most often, first symptoms appear in the fifth decade, although in the case of hereditary TTP the symptoms may appear in childhood. Among all thrombotic microangiopathies, iTTP accounts for 1% only, and this form is extremely rare in children [10].

Up to this point, proper treatment reduced mortality among patients from 90 to 10–20%; however, the recurrence rate is still high, reaching 36% of cases [3, 8].

The aim of the study was to present a rare, atypical, oligosymptomatic course of iTTP in an adolescent girl to raise awareness of the disease's characteristics among clinical practitioners and highlight the significance of differential diagnosis.

CASE REPORT

A 16-year-old girl was admitted to the paediatric ward with symptoms of haemorrhagic diathesis. Three days before admission, the patient was febrile (up to 38.5°C) and suffered from headaches, muscle aches, and general weakness. The medical history did not reveal any previous hospitalizations nor any medications administered on a regular basis. The patient denied having used psychoactive substances. On the day of the admission, numerous small petechiae appeared all over her body, most severely in the area of the right elbow flexion. The girl was obese (158 cm in height [25%], 76 kg of body weight [94%], with body mass index 30.4 kg/m^2 [99%]). Physical examination showed a bruise on the chest near the left breast and on the left elbow. The day of admission to the hospital was day 4 of the patient's menstrual cycle. Initial laboratory tests showed thrombocytopaenia (PLT 7 G/l, N: 150–450 G/l), with normal coagulation parameters, increased parameters of inflammation (C-reactive protein – CRP: 45.28 mg/l, N: 0–5 mg/l), normal leukocytosis, increased lactate dehydrogenase (LDH) activity (744 IU/l, N: 120–300), increased total bilirubin (40.6 µmol/l, N: 3.4–22): direct (8.8 µmol/l, N: 0–3.4 µmol/l) and indirect (17.5 µmol/l), with negative parameters of cholestasis. The IgM concentration remained slightly below the lower limit (0.33 g/l, N: 0.35–2.39 g/l), and a low concentration of vitamin D (8.53 ng/ml, N: 30–80 ng/ml) was noted. The initial diagnosis of haemorrhagic diathesis in the course of immune thrombocytopaenia was established; thus, the treatment included parenteral antibiotic therapy (ceftriaxone), antihistamines (clemastinum), angioprotective (etamsylate) and antipyretic (paracetamol) drugs, as well as human immunoglobulin in a total dose of 2 g/kg b.w. (for 3 consecutive days). An anti-haemorrhagic therapy with tranexamic acid was also initiated; however, undesirable gastrointestinal symptoms resulted in treatment discontinuance within 2 days.

It was decided to perform a bone marrow biopsy, which revealed medium-rich marrow, the erythroblast system reaching 23.2% and a normoblastic erythropoiesis, quantitatively normal granulocyte system at 55.2%, with a predominance of mature forms, lymphatic system at the level of 14.8%, and the reticular system at 6.8%. No megakaryocytes were found, but numerous clusters of platelets were visible. Bone marrow investigation did not provide any evidence of the proliferative disease in the haematopoietic system. An abdominal ultrasound, performed on the 10th day of treatment, revealed gallbladder deposits, while a chest X-ray showed a thoracic scoliosis. Trace proteinuria persisted during the hospital-

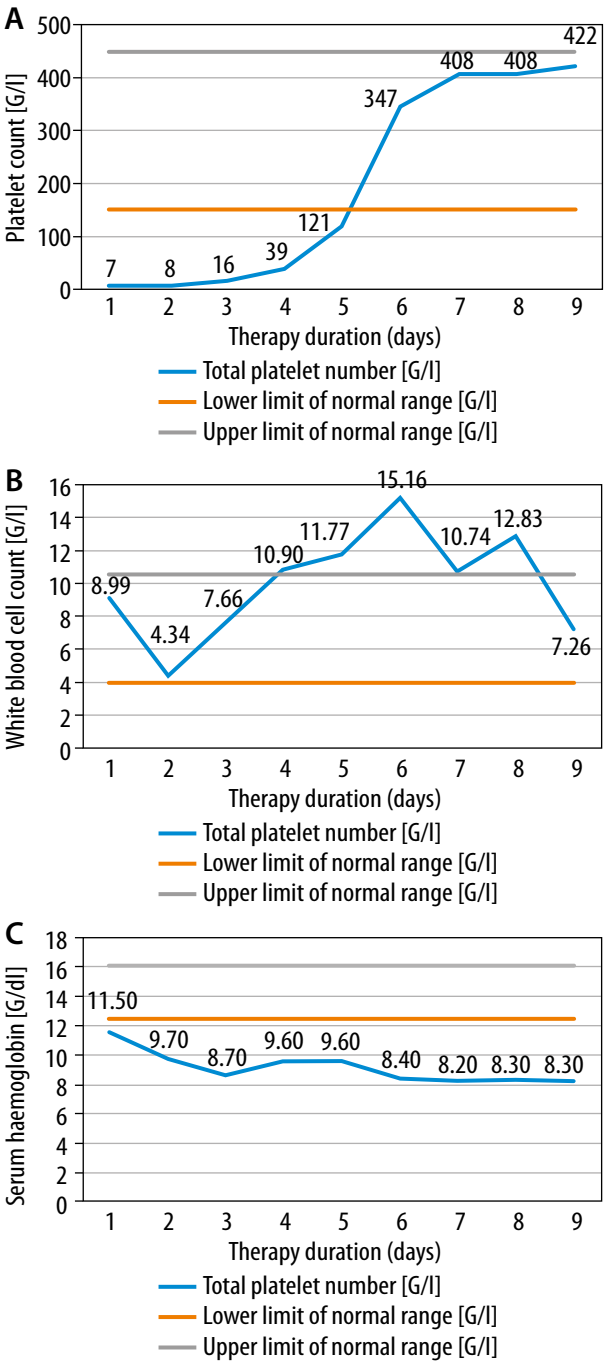

FIGURE 2. Fluctuation of selected laboratory parameters throughout the first hospitalization. A) Platelet count. B) White blood cell count. C) Serum haemoglobin

ization. During the 10-day hospitalization, no new petechiae appeared, and the skin rash described on admission gradually disappeared with treatment progression. There was an increase in the number of platelets and leukocytes alongside a worsening of red cell parameters (features of normocytic anaemia and an elevation of the reticulocytes percentage) (Figure 2A–C, Table 1).

Additional laboratory tests revealed IgG antibodies against cytomegalovirus and both EBNA antigen and EBV-CA IgG antibodies against Epstein-Barr virus (EBV), while serological tests for parvovirus B19 infection were negative.

The diagnosis of primary autoimmune thrombocytopaenia was finally established, and the patient was discharged. Within a week, a control blood count revealed normal platelet count (200 G/l), leukocytosis (10.65 G/l, N: 4–10.5 G/l), red blood cells at a level of 3.05 T/l (N: 4.2–5.6 T/l), with Hb concentration of 9.6 g/dl (N: 12.5–16.1 g/dl), and increased CRP (92.2 mg/l). Due to a suspicion of an ongoing infection, the general physician (GP) prescribed cefuroxime in a dose of 500 mg twice a day and a control blood test. The following day, the platelet count dropped to 10 G/l; consequently, the patient was re-admitted to the department.

On admission she was in overall good condition, with no fever or signs of infection, only reporting periodic headaches in the frontal area. Physical examination revealed petechiae on the back, abdomen, buttocks, hips, and – after blood sampling – in the elbow bends.

Due to a life-threatening thrombocytopaenia as well as anaemia, platelet and red cell concentrate transfusions were immediately performed. Laboratory tests revealed increased levels of total bilirubin, ferritin, and LDH activity. Moreover, bone marrow trephine biopsy was conducted, and the outcome excluded the presence of neoplastic metastases, substance deposits, or proliferative disease. Due to a further decrease in the platelet count, it was decided to start (from the 5th day after admission) oral steroid therapy (prednisone in a dose of 3 × 40 mg). Within the next 6 days, the platelet count remained in a range of 8–26 G/l. Biochemical tests revealed slightly decreased renal function (serum creatinine 85 µmol/l, urea 10.9 mmol/l, N: 2.76–8.07 mmol/l, uric acid 395 µmol/l, N: 202.3–416.5 µmol/l) and hyperphosphataemia.

TABLE 1. Selected diagnostic parameters during the first hospitalization

Selected diagnostic parameters	Days of hospitalization				
	1	2	3	7	8
Reticulocytes (%) (N: 0.5–2.5)	–	–	2.49	–	8.26
Lactate dehydrogenase activity [IU/l] (N: 120–300)	744	683	–	–	–
Serum creatinine [µmol/l] (N: 46–70)	78	67	–	69	–
Total bilirubin [µmol/l] (N: 3.4–22)	40.60	26.30	18.90	–	17.40
Indirect bilirubin [µmol/l]	–	17.50	–	–	11.30
Direct bilirubin [µmol/l] (N: 0–3.4)	–	8.80	–	–	6.10

TABLE 2. Values for ADAMTS-13 and its inhibitor throughout the case

Parameters	Initial outcome	23 days later	2-month follow-up	9-month follow up	21-month follow-up
ADAMTS-13 (%) N: 40 –130	1	< 1	2	3	39
ADAMTS-13 inhibitor [U/ml] N: <12	142	161	39	34	0.57

On the 12th day of hospitalization, the patient showed symptoms of jaundice accompanied by hyperbilirubinaemia (40.7 μmol/l), decreased fibrinogen concentration (1.69 g/l, N: 2–4 g/l), increased concentration of d-dimers (3.36 μg/ml, N: 0–0.5 μg/ml), reticulocytosis (17.17%, N: 0.5–2.5%), persisting renal function deterioration (creatinine concentration – 83 μmol/l, urea – 11.7 mmol/l, uric acid 440 μmol/l), with decreased epidermal growth factor receptor (67.92 ml/min/1.73 m^2), and increased LDH activity (1012 U/l). The control red blood cell smear confirmed anisocytosis and the presence of 3–5% of schistocytes. Suspicion of atypical haemolytic uraemic syndrome (aHUS) was raised (increasing parameters of renal insufficiency, anaemia, and thrombocytopaenia); therefore, the patient was transferred to the Department of Paediatric Nephrology for further treatment.

Decreased ADAMTS-13 activity at the level of 1% (N: 40–130%) with the presence of the ADAMTS-13 inhibitor (142 U/ml, N: < 12 U/ml) were determined (Department of Haemostasis and Metabolic Diseases, Institute of Haematology and Transfusiology in Warsaw) and comparable results were obtained after 23 days. Therefore, excluding aHUS, the diagnosis of iTTP was confirmed. Additional tests revealed no pathogenic intestinal bacilli in stool sample, borderline Ro-52 and AMA-M2 antibodies in the ANA profile, MPO breakpoints in the ANCA profile, and negative Coombs tests, both direct and indirect.

Steroid therapy was continued, and 5 plasmapheresis sessions were performed until the platelet count reached over 150 G/l. Due to anaemia, the patient had red blood cell transfusions, and treatment with fresh frozen plasma was continued (34 units in total).

The patient was discharged and instructed to continue steroid therapy, perform weekly blood count tests, and contact the Department in the event of a platelet count drop below 150 G/l, as well as to follow a low-calorie diet and hydration in an amount of about 2 litres per day.

An additional test of ADAMTS-13 activity (2%) and the level of ADAMTS-13 inhibitor (39 U/ml), performed at a 2-month follow-up, correlated with the improvement of the patient's clinical condition. The prednisone dose was gradually reduced to be completely discontinued after 5 months.

Nine months later the girl was admitted for a routine check-up. She presented good general condition, without any complaints or disturbing symptoms, while laboratory tests showed no significant deviations and confirmed the iTTP remission. The ADAMTS-13 activity (3%) and the concentration of the ADAMTS-13 inhibitor (34 U/ml) were determined, and ANA and ANCA panels were performed (the presence of autoantibodies against: u1-nRNP, Sm, SS-A/Ro, SS-B/La, Scl-70, Jo-1, PCNA phospholipids, dsDNA, nucleosomes, histones, ribosomal-RNP, cANCA, and pANCA were excluded). A follow-up abdomen ultrasound revealed no pathologies, previously described gallstones were not visualized.

The patient remained under regular observation of Haematology and Nephrology Clinic for Children until she became 18 years old. Last ADAMTS-13 activity and the concentration of the ADAMTS-13 inhibitor were determined at the 21st month of observation, and the results were, respectively, 39% and 0.57 U/ml. Table 2 presents the values for ADAMTS-13 and its inhibitor throughout the case.

DISCUSSION

The symptoms of iTTP, which are the consequence of generalized thrombosis, are essentially the sequel of an ischaemia of different organs. Most frequently patients suffer from symptoms affecting the central nervous system, including headache, personality changes, cognitive impairment, transient ischaemic attacks, paresis, aphasia, dysarthria, amblyopia, encephalopathy, and disturbance of consciousness (together with coma) among others. Such problems did not appear in the presented case; therefore, initially we encountered some difficulties establishing a proper diagnosis. Moreover, intestinal ischaemia may cause abdominal pain [3, 4]. Whereas renal ischaemia may lead to a kidney damage manifested by proteinuria and haematuria, haemodialysis in iTTP is quite rare and rather indicates haemolytic uremic syndrome as the possible aetiology of TMA. Due to the accompanying thrombocytopaenia, symptoms such as epistaxis, bruising, ecchymosis, gingival bleeding, prolonged menses or menorrhagia, gastrointestinal and retinal haemorrhage, and haemoptysis may occur. Chest pain, heart failure, and hypotension are main characteristics of myocardial ischaemia. Jaundice can also be observed due to MAHA [3, 4]. However, a group of symptoms, including fever, thrombocytopaenia, hemolytic anaemia, renal dysfunction, and neurological disorders, described as the classic pentad of TTP, cannot lead to the final diagnosis, because these symptoms appear in only 50% of cases [8]. A summary of the characteristic symptoms of iTTP and their comparison with the clinical features of the described patient is presented in Table 3.

TABLE 3. A summary of immune-mediated thrombotic thrombocytopaenic purpura symptoms in comparison with those occurring in the described patient

Selected symptoms of iTTP	Presence in the described case
Fever	Yes
Hemolytic anaemia	Yes
Thrombocytopenia	Yes
Central nervous system ischemic symptoms – Headache	Yes
Central nervous system ischemic symptoms – transient focal symptoms (visual disturbances, paraesthesia, aphasia)	No
Jaundice	Yes
Symptoms of thrombocytopenic bleeding disorder	Yes
Increase in the concentration of indirect bilirubin and urobilinogen in the urine	No
Intestinal ischemic symptoms – abdominal pain, diarrhoea, nausea, vomiting	Yes
Chest pain	No
Acute kidney injury	Yes
Current schistocytes usually more than 10%	No
Increased number of reticulocytes	Yes
Significantly increased LDH activity	Yes
Increased level of serum creatinine	Yes
Hyperbilirubinaemia	Yes
Normal fibrinogen concentration	Initially correct, then lowered

iTTP – immune-mediated haematological disease, LDH – lactate dehydrogenase

Initial diagnosis of TMA is usually established from the medical history of the patient, physical examination, and routine laboratory tests. A characteristic feature of the peripheral blood smear is the presence of schistocytes (fragmented erythrocytes) with a threshold value of 1% (usually more than 10%), alongside hypochromic erythrocytes and anaemia [1, 2, 4]. Laboratory tests also reveal increased activity of LDH (due to haemolysis and tissue ischaemia), decreased concentration of haptoglobin, thrombocytopaenia, increased number of reticulocytes, and usually normal parameters of blood coagulation [1, 2, 4]. Elevated LDH is non-specific marker. It can reflect different situations where tissue damage occurs. In our patient, decreased haemoglobin, with concomitant elevated bilirubin, LDH concentrations, and increased reticulocyte count reflected haemolysis in the acute phase of disease presentation. We observed rapid improvement of the patient's condition and suppression of haemolysis after intravenous immunoglobulin infusion. The diagnosis of iTTP should be confirmed (and distinguished from other MAHA causes) by a significant decrease in ADAMTS-13 activity (< 10%) and the presence of IgG anti-ADAMTS-13 autoantibodies [11, 12]. The mainstay of treatment is a high-dose plasma exchange transfusion (PEX), which should be initiated as soon as possible in any patient with hemolytic anaemia of unknown cause and thrombocytopaenia with normal prothrombin time, international normalized ratio, and partial thromboplastin time. The aim of this procedure is to remove antibodies against ADAMTS-13 and ULvWF from the circulation [2, 8]. It has also been proven that immunosuppressant therapy reduces the frequency of relapses, due to the autoimmune background of iTTP [8, 11]. Vincristine and rituximab are commonly used in PEX-refractory iTTP cases [8]. Studies on the effectiveness of rituximab treatment of iTTP have shown that it reduces the relapse rate from 57% to 10% [9, 11]. Rituximab eliminates IgG-producing CD20 lymphocytes through several mechanisms, including antibody- or complement-dependent cellular cytotoxicity and apoptosis [13]. In some cases, abnormalities, both clinically and in laboratory outcome, might require concentrated red blood cell transfusions [8]. Platelet transfusions may be performed regarding massive bleeding or scheduled invasive procedures in patients with severe thrombocytopaenia [2, 8]. Treatment response monitoring is a major key to determine the duration of PEX. Most often, haemolysis rates are checked daily and PEX treatment is terminated when the platelet count has been maintained at 150 G/l for at least 48 hours [8]. Research on innovative methods of TTP treatment including gene therapies (recombinant ADAMTS-13 in the treatment of hereditary TTP), anfibatide, N-acetylcysteine, and caplacizumab indicate a significant improvement in the response to treatment in patients with acquired TTP and acceleration in the normalization of the platelet count [2, 14]. Caplacizumab is a single variable chain humanized nanoparticle/antibody directed against the A1 domain of vWF. It inhibits the interaction between platelets and VWF, which limits the formation of microclots [15].

Dutt *et al*. described 4 cases of children treated with caplacizumab in addition to plasmapheresis, steroids, and rituximab. In all presented cases the platelet count was stabilized, and after 30-day therapy with caplacizumab after plasmapheresis they maintained remission for an average of 92 days [16].

CONCLUSIONS

This case presents a rare, oligosymptomatic course of iTTP in a child with a successful use of fresh frozen plasma (plasmapheresis and repeated infusions) and corticosteroids, which resulted in a permanent remission of the disease in childhood. The authors would like to raise awareness of iTTP, especially in cases such as the one presented herein, where, despite less characteristic features, the differential diagnosis was continued and the patient received proper treatment.

DISCLOSURE

The authors declare no conflict of interest.

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