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CASE REPORT

Risk of diagnostic delay in congenital thrombotic thrombocytopenic purpura

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Essentials

- Congenital thrombotic thrombocytopenic purpura (cTTP) is a very rare thrombotic microangiopathy.
- Its rarity and great phenotype heterogeneity may account for misdiagnosis.
- We report the history of a middle-aged woman with cTTP, misdiagnosed until adulthood.
- Accurate clinical history is crucial for early diagnosis to prevent long-term sequelae.

Summary. Thrombotic thrombocytopenic purpura (TTP) is an acute life-threatening disorder characterized by multiple organ ischemia due to disseminated thrombus formation in the microvasculature. The congenital form of the disease (Upshaw-Schulman syndrome) is related to *ADAMTS13* mutations. Adulthood-onset of TTP does not exclude the congenital form of the disease and a diagnostic delay may account for a great morbidity burden in these patients. We describe the case of a middle-aged woman who presented to our attention with a clinical diagnosis of a chronic relapsing form of TTP. The medical history of the patient raised the suspicion of a congenital form of TTP. Phenotype and genotype tests were performed, and clinical diagnosis was confirmed. Upshaw-Schulman syndrome is a rare congenital disease with a great phenotype heterogeneity that can be diagnosed also in adulthood. Accurate clinical history is crucial. Early diagnosis can prevent recurrences and long-term organ damage with long-term sequelae.

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Introduction

Congenital thrombotic thrombocytopenic purpura (cTTP), also known as Upshaw-Schulman syndrome [1,2], is a rare life-threatening autosomal recessive disorder caused by biallelic mutations on the gene encoding for ADAMTS13 (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), responsible for von Willebrand factor (VWF) cleavage. *ADAMTS13* mutations result in enzyme deficiency, with subsequent accumulation of ultralarge VWF (ULVWF) multimers in the microcirculation, leading to consumptive thrombocytopenia and microangiopathic hemolytic anemia.

The clinical phenotype of cTTP is variable, ranging from isolated recurrent thrombocytopenia to catastrophic widespread ischemic organ damage. The onset of disease is variable, too, with the first manifestations occurring in the neonatal period up to adulthood. The age of onset and recurrence rate are determined by genetic background [3,4] and by the exposure to environmental risk factors acting as triggers, such as pregnancy [5] and certain drugs [6]. The rarity of cTTP and its variable phenotype may often delay the correct diagnosis.

We report the clinical history of a challenging case of cTTP, diagnosed with a homozygous missense mutation in a non-consanguineous family and only at adulthood after multiple misdiagnosed episodes of TTP.

Case presentation

In November 2009, a 55-year-old female was hospitalized for dysarthria and right arm hemiplegia. Blood

examination revealed severe thrombocytopenia and microangiopathic hemolytic anemia. Acute TTP was suspected and the patient was treated with plasma infusions followed by plasma exchange (PEX) and steroids, with complete blood count normalization after three PEX procedures only. Blood samples at diagnosis were not available for ADAMTS13 testing, and analyses performed while the patient was already on treatment showed mild decrease of ADAMTS13 activity levels with negative anti-ADAMTS13 antibodies. The patient was discharged with antiplatelet therapy. On October 2011 the patient experienced a new ischemic event, characterized by dysarthria and dysphagia for liquids, associated with thrombocytopenia and normal hemoglobin level. With the suspicion of TTP relapse she was treated with five PEX procedures with prompt improvement. The patient was referred to our center for further evaluation. At the time of the visit the patient was dysarthric, with mild expression aphasia and memory loss, associated with mild sensorimotor impairment of the right side of her body. A thorough anamnesis and further laboratory tests (assay of ADAMTS13 activity, antigen and anti-ADAMTS13 antibodies, ADAMTS13 gene analysis, *in vitro* expression study) were performed [7–12].

The past clinical history of the patient was relevant for multiple events of bleeding, hemolytic anemia, and thrombocytopenia. The first clinical event occurred at the age of 18 months, when the patient required blood transfusion for mouth bleeding and epistaxis; no blood tests regarding that event were available. At the age of 19 years, the first pregnancy was complicated in the second trimester by neurological impairment, characterized by paresthesia and headache, followed by coma, lasting almost 36 h. Since her complete blood count showed severe anemia with thrombocytopenia, a sternal puncture was performed and the result was normal. Despite the presence of schistocytes and signs of hemolysis, she was treated with blood transfusions. During the following months she remained asymptomatic in the absence of mucocutaneous bleeding, despite low hemoglobin levels and low platelet count, with persistent signs of Coomb's negative hemolysis. She was treated with supportive therapy and, at the 32nd week of gestation, delivery was induced and a healthy baby male was born. Two days after delivery hemoglobin and platelets dropped again and the patient received transfusions.

Further relevant clinical events occurred during two courses of antiviral therapy for chronic hepatitis C, developed as a consequence of previous blood transfusions. At the age of 44 years the patient was treated with interferon. Before treatment hemoglobin level was normal with low platelets. Despite an initial good drug tolerability and transaminase decrease, at the fifth month of therapy the patient developed a drop in platelet count, leading to antiviral therapy interruption for suspected interferon toxicity. Despite drug withdrawal, hemoglobin and platelet levels further decreased, with Coomb's negative hemolysis. The patient received blood transfusions. Two years later a new course of interferon therapy plus ribavirin was administered for 1 year, until interruption for development of hematomas on her limbs associated with hemolytic anemia and thrombocytopenia. Blood transfusions were performed again. A diagnosis of Fisher-Evans syndrome was postulated. Subsequent laboratory tests showed a sustained virologic response to antiviral therapy, with complete normalization of transaminases and absence of cryoglobulins. In the following years platelet count remained about 80 x 10^9/L, without overt anemia.

At the time of the visit to our center, the overall history of the patient (Table 1) raised the suspicion of unrecognized multiple previous TTP events. Laboratory tests revealed minimal ADAMTS13 residual activity (0.92%) and severe reduction of ADAMTS13 antigen levels (1.7%). Western Blotting analysis result was negative with undetectable inhibitor activity against ADAMTS13 (<1 U mL^{-1}). The genetic analysis performed using Sanger sequencing [10] revealed the presence of a homozygous missense mutation, p.Ile143Phe (c.427A>T), located at exon 5 within the metalloprotease domain. *In vitro* expression study was performed using human embryonic kidney (HEK) 293 cells transiently transfected with wild-type or p.Ile143Phe mutant *ADAMTS13* expression vector, as previously described [11]. Antigen and activity levels of recombinant ADAMTS13 (rADAMTS13) secreted in the conditioned medium and concentrated 30-fold were analyzed using ELISA [9] and FRETS-VWF73 assays [7,12], respectively. The results of mutant rADAMTS13 were reported as percentage of wild-type rADAMTS13, set as 100%. The antigen and activity levels of p.Ile143Phe rADAMTS13 were severely reduced (2% ± 1 standard deviation and <3%, respectively).

A diagnosis of congenital TTP based on clinical history and laboratory results was made. Periodic prophylactic plasma infusion was started at the age of 57 years with clinical and biochemical improvement and is still ongoing.

Discussion

Thrombotic thrombocytopenic purpura may be difficult to diagnose, both for its rarity and for its clinical variability. This is utterly true for congenital TTP, which is much more rare and often atypical in its presentation. To reduce the risk of misdiagnosis, a high index of suspicion should be kept in mind for all patients presenting with an acute thrombotic microangiopathy, regardless of their age. Specific clinical clues may also help clinicians to get the correct diagnosis. In this case report an accurate clinical evaluation highlighted many clues, although most of them had received an alternative but plausible explanation. In early infancy the patient had an unexplained

Table 1 Main clinical events in the patient's history, with the available laboratory data

	First pregnancy (2nd T)	Post-partum	First course of IFN, start	First course of IFN, on therapy (fifth month)	First course of IFN, at withdrawal	Second course of IFN (+RBV), on therapy	TTP diagnosis (11/2009)	TTP relapse (10/2011)
Platelet n.v. 130–400 × 10^9 L^{-1}	46	30	90	32	12	11	12	83
Hb n.v. 13.5–17.5 g dL^{-1}	3.6	5	13	n.a.	6.8	5.6	7.4	13.4
LDH n.v. 140–250 U L^{-1}	n.a.	n.a.	n.a.	n.a.	1558	1912	1548	n.a.
Total bilirubin n.v. 0.1–1.1 mg dL^{-1}	1.25	n.a.	n.a.	n.a.	2.2	1.98	2.56	n.a.
RET n.v. 0.8%–3%	15	n.a.	n.a.	n.a.	13.5	15		n.a.
Other lab data	Schistocytes	n.a.	n.a.	n.a.	Negative Coomb's test	n.a.	Schistocytes, negative Coomb's test	n.a.
Neurologic signs	Present	–	–	–	–	–	Present	–

IFN, interferon; lab, laboratory; n.a., not available;n.v., normal value; RBV, ribavirin; RET, reticulocytes;. T, trimester.

hemorrhagic diathesis probably due to thrombocytopenia, and cTTP may onset early, triggered by even mild infections, which are frequent during infancy. The patient's first pregnancy and puerperium were complicated by microangiopathic bouts, and pregnancy indeed represents a well-known challenge in cTTP since almost all women affected with cTTP do develop the clinical phenotype during pregnancy [4]. Interferon treatment triggered TTP recurrence twice in our patient, and this therapy has been reported as a potential trigger for TTP by enhancing endothelial ULVWF release [5]. Nevertheless, to our knowledge, this is the first report of interferon-induced acute TTP in a congenital patient. Mild thrombocytopenia was almost persistent at routine blood analyses of our patient, even in the absence of hemolysis, which is another clue of cTTP.

In addition to environmental factors, the clinical phenotype of cTTP is strictly related to the type of gene abnormalities since different *ADAMTS13* mutations cause different amounts of residual ADAMTS13 activity. Low residual activity correlates with early-onset disease and high annual recurrence rate, since even a mild increase of circulating ULVWF multimers may exceed a low residual ADAMTS13 proteolytic activity, leading more readily to an acute TTP event [3,4]. The homozygous missense mutation (p.Ile143Phe) identified in our patient causes a severe secretion defect with very low residual ADAMTS13 levels, which well correlates with the early TTP onset in this patient and her relapsing course. The same homozygous mutation has been recently reported in two cTTP siblings from a consanguineous family [13], showing similar *in vitro* expression levels (i.e. severe deficiency in both antigen and activity levels). Similar to our patient, they experienced many relapses (four events in an 8-year follow-up and six events in a 15-year follow-up, respectively) triggered by infections and/or pregnancy; unlike our patient, they had a later disease onset (at 18 and 21 years, respectively) [13]. We speculate this discrepancy may be due to different exposures to triggers or even to different estimation of previous events (i.e. hemorrhagic unexplained diathesis in childhood). Similar to our case, another cTTP patient carrying a homozygous missense mutation at the same exon (p.Ile143Thr, c.428T>C) leading to low residual ADAMTS13 activity showed an early onset (at 7 years) but a detailed medical history revealed easy bruising and anemia since birth [13,14].

In conclusion, we describe a congenital case of TTP, misdiagnosed until adulthood, caused by a homozygous missense mutation on *ADAMTS13*. In the era of technological progress, an old clinical tool such as anamnesis was indeed crucial to make the correct diagnosis.

Since this disease can manifest at any age and lead to medical attention in extremely different clinical settings, not only pediatricians should be aware of this rare condition, but also gynecologists, neurologists, specialists in internal and emergency medicine, in order to recognize the disease promptly and reduce its burden. Early diagnosis and appropriate treatment can prevent recurrences and organ damage with long-term sequelae.

Addendum

B. Ferrari designed the study and wrote the manuscript; A. Cairo and M. T. Pagliari carried out laboratory tests,

collected experimental data, and contributed to writing the manuscript; I. Mancini and S. Arcudi wrote and critically reviewed the manuscript; F. Peyvandi designed the study and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Disclosure of Conflict of Interest

F. Peyvandi has received honoraria for participating as a speaker at satellite symposia and educational meetings organized by Ablynx, Grifols, Novo Nordisk, Roche, Shire, and Sobi. She has received consulting fees from Kedrion and is a member of the scientific advisory board of Ablynx. The other authors state that they do not have any conflict of interest.

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