Atypical presentations of thrombotic thrombocytopenic purpura in young and middle-aged women with recurrent cerebral macrovascular thrombosis: a case report and review of the literature

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Abstract

We here report the case of a 42-year old woman diagnosed with acquired relapsing thrombotic thrombocytopenic purpura (TTP). The past medical history of the patient was characterized by recurrent macrovascular events with only slight haematological manifestations that did not support any clinical suspicion for TTP. Diagnosis of TTP was performed only after a new recurrent cerebral ischemic episode combined with frank haemolytic anaemia, thrombocytopenia and very low levels of ADAMTS-13 activity (6%). First-line management with plasma exchange and steroids led to a good initial response but the disease relapsed after few days. A second remission occurred after four weekly administrations of Rituximab but TTP exacerbated after two weeks. At the time of the second exacerbation, re-challenge with rituximab and maintenance treatment with azathioprine induced a persistent remission. We also revise similar cases of atypical TTP with recurrent macrovascular ischemic manifestations that have been reported in young and middle-aged women.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disease, commonly described as a pentad of clinical manifestations consisting of fever, thrombocytopenia, microangiopathic haemolytic anaemia, renal impairment and neurological abnormalities. The clinical features of TTP are generally secondary to microthromboses, with platelets and Von Willebrand Factor aggregates mainly located in small blood vessels. The onset of TTP is usually acute and it is related to an acquired deficiency of the metalloprotease ADAMTS-13, with an enzymatic activity of less than 5% [1]. In recent times, a growing number of reports are focusing on atypical presentations of TTP, generally characterised by recurrent and unusual macrovascular manifestations with less marked laboratory abnormalities.

The prevalence of the atypical disease is probably underestimated because it is often not suspected for a heterogeneous clinical course and symptoms common to other disorders.

TTP relapses are quite frequent (20%-50% of cases) and they are defined as the recurrence of acute TTP symptoms after 30 days from the first episode, while TTP exacerbations occur within 30days after the first episode. The likelihood of relapse is elevated in those patients who, despite entering remission, still have low detectable plasma ADAMTS13 activity (i.e., $\leq$10%) or persistent anti-ADAMTS13 antibodies. A slight reduction in ADAMTS13 Activity (>25%) can be observed in conditions like sepsis, cancer, acute inflammatory states. During remission persistently undetectable ADAMTS13 in plasma is highly predictive of recurrence [1, 2]. In a report from Ferrari et al 38% of severely deficient patients relapsed vs 5% of those with measurable ADAMTS13 activity [2] .Negative predictive values for relapse of measurable ADAMTS13 is high as 95% [3]. In the current clinical practice, minimal criteria required to define TTP are related to the presence of at least the signs of microangiopathic haemolytic

anaemia and low platelets count [4]. We here report on an atypical case of acquired TTP diagnosed in a young woman, with a past history of apparently idiopathic recurrent macrovascular ischemic events, only when all the pentad of symptoms appeared. We furthermore briefly revise similar cases previously reported in the literature.

Case report

A 42-year old Caucasian woman with a clinical history of coronary and cerebral ischemic events was admitted to the Internal Medicine Ward of our local hospital on June 2013, following a recurrent transient ischemic attack (TIA). From a haematological point of view, the patient had progressively developed severe anaemia and thrombocytopenia with laboratory signs of intravascular haemolysis and mild renal impairment. In the past medical history of the patient, recurrent neurological and myocardial ischemic events occurred from 2008 to 2013 in the absence of known risk factors, infections, use of toxic drugs and regardless of the oral anticoagulant and antiplatelet therapy administered. The patient was treated with acetyl salicylic acid at a dose of 100 mg daily after the first ischemic event plus anticoagulation with Coumadin from the time of the third stroke, with a good compliance to treatment and therapeutic INR values (range 2-3). Autoimmune disease screening, antiphospholipid antibodies and Lupus anticoagulant assays were normal. Screening for inherited thrombophilia, including Factor V Leiden and Factor II (G20210A) gene mutations, was performed with negative results. Ant thrombin, anticoagulant protein C and protein S plasma levels were within the normal range. Complete blood cell count (CBC) and peripheral blood smear did not show any significant abnormality during all the previous admissions, a slight decrease in platelets count (platelets= 92 x 10^9/L) was observed only once (in 2012), at that time ADAMTS13 was determined with normal results (ADAMTS13

Activity =65%).During the last hospital admission, atypical TTP was strongly suspected. ADAMTS-13 activity was measured, identifying a value of 6%. ADAMTS-13 inhibitors were also detected at high titre (2 Bethesda Units, BU). ADAMTS-13 activity and inhibitor tests were performed with an ELISA technique (Technozym,Technoclone®). A genetic test for Upshaw-Schülman syndrome was also performed, revealing the absence of ADAMTS-13 gene abnormalities. Table 1 details the main clinical and laboratory features at the current and previous hospitalizations of the patient. Therapeutic plasma exchange (TPE) and corticosteroid (prednisone, given at a dose of 1mg/kg body weight) treatment were thus commenced and maintained until clinical and haematological remission was achieved [5]. TPE (Gambro®, Italy) was performed daily for three weeks with a good response and an increase of ADAMTS13 activity to 50%. The patient experienced exacerbation of TTP after ten days, she was well controlled with the administration of Rituximab, given at a weekly dose of 375 mg/m^2 body surface, for a total of 4 doses [6]. Following the first exacerbation, a relapse occurred after 37 days when the patient presented seizures; ADAMTS-13 activity, whose values were 54 % after the last treatment with Rituximab decreased to 6% at relapse. A second course of weekly Rituximab, followed by maintenance with azathioprine (50 mg twice daily for the first ten days, then 50 mg once daily) determined clinical and haematological remission. The decision to administer a second course of treatment with Rituximab was taken based on the previous rapid response to the drug and the need to prevent further serious clinical complications [7]. The patient is alive and free form recurrences from 18 months, maintenance treatment with azathioprine is still on course.ADAMTS-13 activity levels are monitored every four months after the last remission and they range from 45 to 51%; inhibitors are no longer

detectable. Reviewing accurately results of previous laboratory tests, we noticed that only at the time of last admission for stroke (2012) a mild thrombocytopenia was detected (Table1), thus, we hypothesize that the disease had its onset at the time of the first ischemic event, in 2008, with a chronic relapsing behaviour, a more acute phase occurred only during the patient's last hospitalization. The patient gave her informed consent to the treatment and divulgation of data related to her case.

Materials and methods

An electronic literature search on atypical cases of TTP in young and middle aged women, reported from 1st January 1990 to 31st December 2014, was performed on PubMed MEDLINE, EMBASE, SCOPUS and OVID. The main inclusion criteria adopted were a diagnosis of TTP, acute, recurrence or exacerbation in the context of macrovascular ischemic events with or without laboratory and hematological criteria for TTP. Different combinations of the following search terms were adopted for this systematic review: "atypical", "acute", "recurrence", "exacerbation","TTP", "stroke", "infarction", "cerebrovascular accident", "cardiac ischemic event", "recurrent", "women", "ADAMTS-13 activity" , "ADAMTS-13 inhibitor" and "treatment". Only articles with a full text in English were considered. The main exclusion criteria was the lack of clinical and laboratory information in the available reports.

Results

Overall, ten cases were found mainly in the format of single report and small case series. Clinical and laboratory findings related to each case are reported in Table II and discussed in the following section. Data refer to African-American and Caucasian young adult and middle aged women with a median age of 42 years (range: 25-68). All

the patients had similar characteristics with a history of recurrent arterial thrombosis (stroke, transient ischemic attacks, myocardial infarction) and no significant cardiovascular risk factors, presenting at their TTP onset with mild thrombocytopenia or minimal microangiopathic haemolytic anaemia. ADAMTS-13 activity was > 5% in 40% of these cases. First line treatment was based on plasma exchange, alone or in combination with steroids and Rituximab, in all cases.

Discussion

The demonstration of large vessel thrombosis in TTP has been only rarely shown, ten similar cases of atypical TTP recurrence with only slight laboratory abnormalities have been reported by other authors [8-13], and (Table 2) .In atypical cases with a known diagnosis of TTP, symptoms mainly guide treatment at the time of recurrence. Interestingly, in our report at first symptoms onset, even minimal criteria for the diagnosis of TTP were not satisfied and only during the last two admissions for apparently idiopathic macrovascular ischemic events, the clinical suspicion of TTP increased.

One case from Imanirad [8] reported on a 25 year old woman presenting during her 25th week of pregnancy with intermittent paraesthesia of the left arm and face with normal haemoglobin and platelet values, initially treated with Low Molecular Weight Heparin, the woman experienced recurrent post partum ischemic events, always with a normal CBC count and only symptoms supported at this point the suspicion for TTP.

Idowu [9] reported the case of a 48 years old woman with an atypical TTP recurrence characterized by the occlusion of the mean cerebral artery and only slight laboratory abnormalities, the peripheral blood smear did not show schistocytes. Downes [11]

reported two cases of relapsed atypical TTP with stroke, increased LDH serum levels, only slight decrease in haemoglobin levels and rare schistocytes, and one occurred in a Caucasian 42 years old woman and the other in a 40 years old African American woman. At the time of recurrence, ADAMTS13 activity was > 10% and inhibitors were not detectable. Tsai [12] also described a similar case in 27 years-old African American woman presenting at her first relapse with neurological symptoms but normal platelets count, LDH levels and blood smear. O'Brien [13] already reported two cases of delayed diagnosis of TTP where neurological abnormalities preceded from weeks haematological manifestations. Sarode [10] reported in his revision the atypical cases, from Downes [11] and Tsai [12].

In the current case, recurrent cardiovascular and cerebrovascular events with normal laboratory findings occurred years before TTP became manifest and a previous determination of ADAMTS13 activity resulted normal. Thus, in all these reports the classic pentad of symptoms was never observed. All the subjects showed a tendency to exacerbation and relapses, the majority of them recovered after the administration of rituximab or other immunosuppressive agents; one patient subsequently underwent a splenectomy [8]. ADATMS-13 Activity of less than 10% is usually considered associated with a typical TTP clinical course and its presenting features [14].

The utility of ADAMTS13 assay is well known as a valuable tool in diagnosis of TTP but the role of this assay in predicting or monitoring treatment response is still object of debate.

In an adult patient with no cardiovascular risk factors, the occurrence of stroke and thrombocytopenia requires an accurate differential diagnosis that includes antiphospholipid syndrome, autoimmune vasculitis, systemic infectious processes or

unusual thrombophilic states. When symptoms are not accompanied by frank anaemia or thrombocytopenia, the diagnosis of TTP is rarely taken into account.

However, given the growing number of reports in the literature, when dealing with this subset of patients characterised by recurrent thrombosis in the absence of known risk factors, the hypothesis of TTP should be taken into account even with only slight laboratory and haematological abnormalities. When a low to very low ADAMTS-13 activity is detected, the recurrence of thrombosis and resistance to treatment could motivate the request for a genetic test to exclude the Upshaw-Schülman syndrome [15]. The administration of rituximab [16, 17] in the early phase of TTP seems to offer a high rate of prolonged remissions. In the reported case, the good response to rituximab is maintained by the administration of azathioprine.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1 . Clinical and laboratory history of the patient

Admission	June 2008	September 2009	May 2010	September 2012	January 2013
Macrovascular ischemic event	Stroke	TIA	ACS	Stroke	TIA
Hemoglobin level (g/dl)	14.7	14.7	13.9	12.9	7.6
(NR: 12-15)					
Platelet Count ($x10^9$/l)	160	185	175	93	26
(NR: 150-450)					
LDH (U/L)	ND	ND	194	275	362
(NR: 135-214)					
Creatinine (mg/dl)	0.82	0.86	0.96	1.17	1.29
(NR: 0.5-1.0)					
Schystocytes	N	N	N	N	Y
ADAMTS13 activity (%)	ND	ND	ND	65	6
(NR:45-120)					
Treatment	ASA	ASA+C	ASA + OAC	ASA + OAC	DEX + TPE

MI=Myocardial Infarction, TIA=Transient Ischemic Attack, ACS= Acute Coronary Syndrome, Y=Yes, =No, ND= Not Determined, NR= Normal Range ,ASA= Acetylsalicilic Acid, C= Clopidogrel, OAC= Oral Anticoagulants, TPE= Therapeutic Plasma Exchange, DEX= Dexamethasone

Table 2 Clinical features at presentation of atypical TTP in young and middle aged women

Publication	Age	Relapse	Clinical features	Hb g/dL	Plt x 1000/mmc	ADAMTS-13	Schistocytes	Creatinine mg/dL	Treatment
Lucchesi et al.	42	2	Stroke (Seizure)	7.5 (10.9-11.7)	24 (107-120)	6%	present	1.3 (1.1)	PEX, CS (PEX, RTX, AZA)
Imanirad et al.[8]	40	1	MI, Stroke	11.7 (14.4)	34 (49)	<5%	rare	1.4 (1.2)	PEX, CS (PEX, CS, RTX)
Imanirad et al.[8]	25	1	Stroke (Vague neurol. sympt.)	9.4 (12)	27 (40)	<5%	rare	1.2 (1.1)	PEX (PEX, RTX)
Imanirad et al.[8]	68	9	Seizure (Stroke, seizure)	7.4 (9.3-14.4)	27 (61-130)	NA (<5%)	rare/present	0.9 (0.6)	PEX, CS (PEX, CS, Splenectomy, RTX)
Imanirad et	58	1	Seizure	8 (14)	14 (180)	NA (<5%,	present/rare	1.3 (1)	PEX, CS, RTX

al.[8]			(Stroke)			6%)			
Idowu et al.[9]	48	2	Stroke (Stroke)	8 (13.2)	20 (113)	16%	no	NA (0.8)	PEX (PEX)
Downes [11]	42	Multiple	Stroke (Stroke)	10(NA)	207(NA)	12%	no	NA	PEX
Downes [11]	40	4	Stroke (MAHA)	9.3	239	NA	rare	NA	PEX
Tsai [12]	36	Multiple	Stroke (Stroke)	Normal	Normal	<0.1*	no	NA	PEX+CS+RTX
O'Brien [13]	28	1	TIA (Ecchymoses)	Normal	71	NA	present	0.7	PEX
O Brien [13]	44	2	TIA(Stroke)	12.4	205	NA	NA	1.0	PEX+CS

Legend: Clinical feature and treatment columns:Brackets report information related to symptoms and treatment at relapse, PEX, plasma exchange; CS, corticosteroid; RTX, rituximab; AZA, azathioprine; MAHA: Microangyopatic Haemolytic Anemia MI, myocardial infarction; NA, not available; Neurol=Neurological;TIA=Transiente Ischemic Attack;* Tsai reports ADAMTS13 activity =<0.1U/mL