CMI Clinical Management Issues

Emergency Plasmapheresis in a case of Thrombotic Thrombocytopenic Purpura (TTP)

Maria Serena Pioli Di Marco[1], Francesco Guercini[1], Chiara Busti[1], Olivia Minelli[2]

Abstract

An 84 year-old female was admitted to our Department of Vascular Internal Medicine after a sudden onset of weakness on her right side and aphasia along with signs of myocardial ischemia from Electrocardiogram (EKG). Clinical and blood exams led to a suspicion of Moschcowitz syndrome, which was reinforced by the presence of numerous schistocytes on a peripheral blood smear.

Due to a rapid deterioration of vital signs as well as alertness, the patient underwent an emergency transfusion and plasmapheresis treatment as recommended by American Society of Apheresis (ASFA) guidelines: one plasma volume was replaced with fresh frozen plasma (FFP) every 24 hours, for the first eight days, in order to reach at least a level of 150,000 platelets/mm3 over three consecutive days accompanied by a decrease in LDH until to 670 UI/l.

After this therapy, the clinical picture significantly improved with a complete recovery of consciousness and the disappearance of neurological defects.

Examinations to determine the etiology made us hypothesize a secondary status of thrombotic thrombocytopenic purpura due to an autoimmune disorder compatible with Sjogren's syndrome.

The patient was discharged and prescribed prednisone.

Currently the patient is in good clinical condition and continues the therapy with prednisone (5 mg/die).

Keywords: Plasmapheresis; Thrombotic Thrombocytopenic Purpura (TTP); Emergency

Plasmaferesi di emergenza in un caso di porpora trombotica trombocitopenica (TTP)

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[1] Struttura complessa di Medicina Interna Vascolare e Stroke Unit, Azienda Ospedaliera di Perugia

[2] Servizio di Immunoematologia e Trasfusionale, Azienda Ospedaliera di Perugia

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) typically occurs with a pentad of signs: thrombocytopenia, anemia, neurological symptoms, fever and renal involvement. TTP is a rare disease, with an incidence of 5-10 cases per year per million. The incidence is 2-3 times higher in females, though it affects both males and females [1-3].

TTP occurs in two forms: a congenital form and an acquired form. The congenital form is due to mutations in the *ADAMTS13* gene (which is located on chromosome 9q34 and codes for the metalloprotease) and it is inherited as an autosomal recessive con-

Why we describe this case

To highlight the importance of treating suspected cases of TTP even before laboratory confirmation. In fact, various studies in literature[3] have confirmed a reduction in 30-day mortality and a significant increase in platelet count after apheretic therapy in combination with corticosteroids and/or immunosuppressive drugs. Moreover, mortality associated with thrombotic thrombocytopenic purpura is generally high, if it is not carried out with plasmapheresis. Plasma exchange has decreased the overall mortality rate to 10%

Corresponding author
Dott. Francesco Guercini,
fguercini@libero.it

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dition. Usually, but not always, it occurs at birth or in childhood [4-6].

Furthermore, there are two main types of acquired TTP: immune-mediated forms, due to autoantibodies against ADAMTS13 [7-11], and those probably secondary to massive endothelial stimulation, with consequent release of ULVWF multimers in amounts exceeding the system's ability to degrade them, despite the presence of normal or only slightly reduced levels of ADAMTS13 [12]. Both these pathogenic situations are usually triggered by concomitant factors which cause widespread endothelial activation.

The most common physiological or pathological conditions present in the immune-mediated forms, which are often associated with very low or undetectable levels of ADAMTS13 (less than 10% of the normal), are pregnancy, infections, autoimmune diseases, and the use of drugs such as ticlopidine and clopidogrel. In most cases TTP occurs as a single, sporadic acute episode, but there are chronic recurrent forms (20- 30% of the cases). The chronic recurrent forms may have a genetic basis or be associated with the formation of autoantibodies, whereas the forms associated with malignancy or transplantation present as acute episodes with a low propensity to recur (in part because of the high mortality rate) [13].

Plasma exchange with plasma replacement has significantly improved clinical outcome. No other intervention has had such a significant impact on the efficacy of treatment [14].

CASE REPORT

An 84 year-old female was admitted to our Department of Vascular Internal Medicine after a sudden onset of weakness on right side of her body and aphasia.

The patient reported a medical history including: an abdominal infrarenal aortic aneurysm that required the positioning of an endoprothesis many years before, a slight iron anemia and a chronic erythematous gastritis. Over the past few months, the patient had presented an erythematous, edematous, crusted dermatitis at the level of her forearms and trunk, in the absence of pruritus, associated with worsening asthenia. One month prior to admission, she had a bout of diarrhea and fever that lasted for about a week and then regressed spontaneously.

At ER, a brain CT scan was performed to rule out for the presence of acute ischemic lesions and / or hemorrhagic lesions. An EKG evidenced a sinus tachycardia with signs of myocardial ischemia in the lateral leads. On admission to our department, the patient appeared agitated and disoriented. Neurologic examination showed right sided hemineglect and hemiplegia. No relevant signs were detected on physical examination of the chest, abdomen and heart. Erythematous papular patches, slightly hypopigmented in the middle, and pink at the edge, were detected on the skin, on both forearms.

Blood tests resulted: anemia with 9.2 g/dl Hb, RBC 3340 x 10^3/mm^3, erythrocyte indices within standard values, thrombocytopenia with 10,000/mm^3 confirmed during the control blood sample, LDH 1619 UI/l (n.v.: up to 450 UI/l), total bilirubin 1.60 mg/dl with a value on indirect bilirubin 1.13 mg/dl, reticulocytes 33 ‰, haptoglobin 7 mg/dl (n.v.: 30-200 mg/dl), INR 1.11, a PTT-Ratio 1.03, fibrinogen 351 mg/dl, BUN 60 mg/dl, creatinine 0.80 mg/dl. During the first hours after admission, the patient developed fever along with an increase in the miocardiolysis index (troponin: 6.33 ng/ml), deterioration of vital signs (PA 90/60 mmHg, RR 30/min, oxygen saturation 88% in air) and alertness (Glasgow Coma Scale 4). A further Hb reduction reaching 7.8 g/dl, was also documented, as well as a reduction in platelet levels: 6000/mm^3.

Clinical and laboratory findings suggested TTP (Moschcowitz syndrome). Furthermore, a Coombs'test was performed (resulted negative) and a peripheral blood smear showed the presence of numerous schistocytes per field. For this reason, the patient underwent an emergency transfusion with packed red blood cells and plasmapheresis treatment with COBE- SPECTRA. Specifically, one plasma volume was replaced with fresh frozen plasma (FFP) having a balance of 100%, delivered by an Arrow type central venous catheter. According to ASFA guidelines [14], treatment was administered every 24 hours, for the first eight days, in order to reach at least a level of 150,000 platelets/ mm^3 over three consecutive days, accompanied by a decrease in LDH until to 670 UI/l (Table I). Following this, the clinical picture improved with a recovery of consciousness and a complete disappearance of neurological defects.

After the therapy, the patient showed the presence of multiple positive predictive

Session	Hb (g/dl)	Plateletes (x10³/ul)	LDH (UI/l)
1	10.6	7	1984
2	10.2	16	1052
3	10.31	39	/
4	10.7	80	711
5	11.6	136	711
6	11.5	166	/
7	11.6	181	671
8	10.9	190	/

Table I. *Laboratory trend after plasma exchange (PEX)*

factors such as increase of platelet count, decrease in levels of LDH and a survival of nine days after the onset of the disease. This regimen was then performed every day for three weeks, achieving a constant platelet level of around 150,000/mm^3, until discharge. During the sessions, adverse effects related to plasmapheresis such as allergic reactions to plasma, systemic infections, catheter obstruction or venous thrombosis were never reported [15].

Furthermore, examinations were carried out to determine the etiology:

- Activity assay of ADAMTS13, carried out before plasmapheresis: <6% (range 50-150%);
- Screening for infectious diseases, resulted negative: blood cultures, urine cultures, coprocultures, parassitolological examination of stools, search for antigen enterohaemorrhagic E. coli pathogenic VTEC O.157, serology for hepatotropic viruses, Toxoplasmosis, rubella, CMV, HSV, Coxiella Burnetii, Adenovirus, Mycoplasma;
- Screenings for autoimmunities, resulted positive: ANA 194.2 UI/ml (n.v. < 5UI/ml), Anti-DNA Ab negative, confirmed in a further control, anti-ENA positive with positivity Anti-SSA/Ro 52 Ab 66.43 UI/L and Anti SSA/Ro 60 Ab 12.28 UI/L (n.v. <7 UI/ml negative; 7-10 UI/ml borderline; >10 UI/ml positive).

The patient refused to undergo a sore biopsy.

Given the above, we hypothesized a secondary status of TTP due to an autoimmune disorder compatible with Sjogren's syndrome. The patient was discharged and was prescribed prednisone at a dosage of 75 mg for the first two weeks, followed by 50 mg for another two weeks. After ten months of progressively decrease in therapy, currently the patient takes prednisone 5 mg/die. Currently, the general clinical condition remains good, and she is able to walk alone with minimal support. The platelet level remains steady at around 144,000/mm^3 with Hb 11.4 g/dl.

DISCUSSION

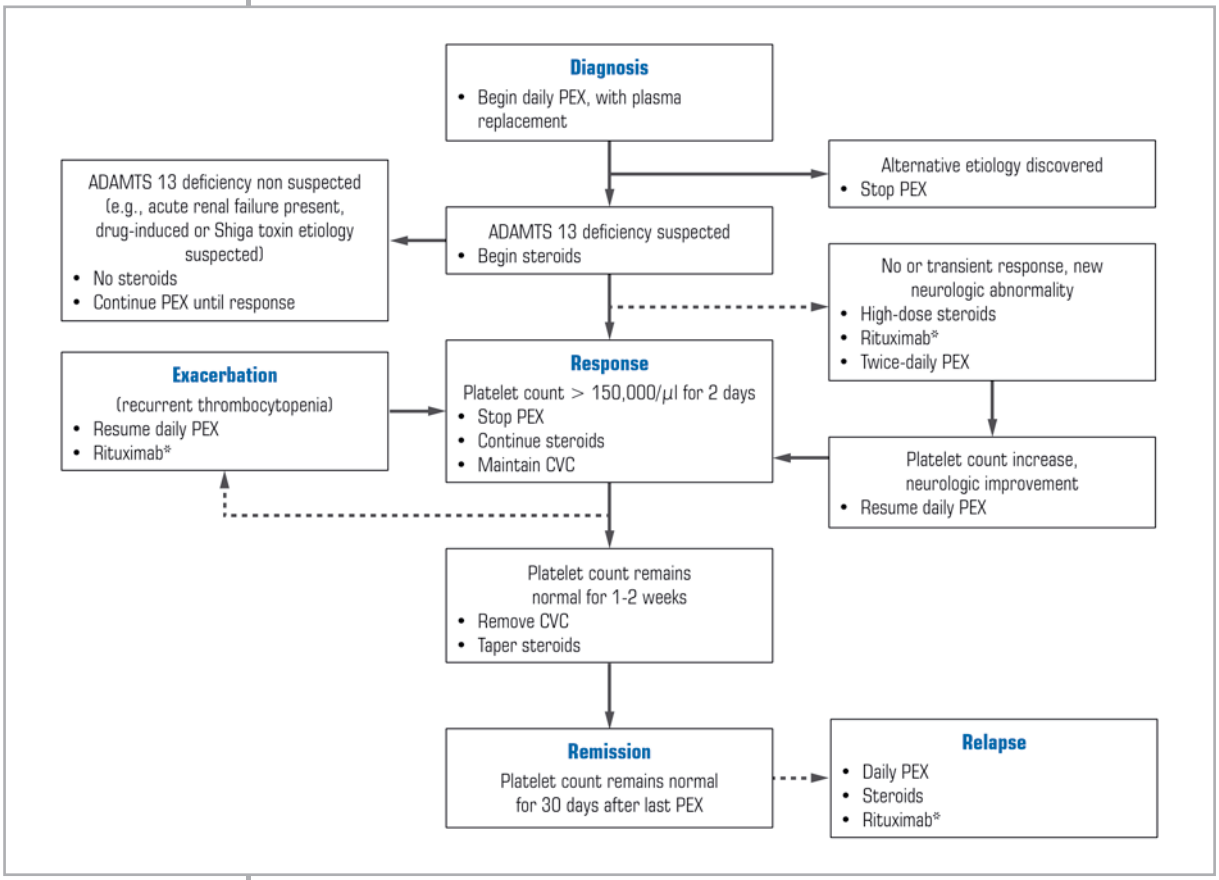
The acquired form of TTP, secondary to autoimmune disease, accounts for approximately 50% of all cases of TTPs, but in many cases their pathophysiology is still uncertain. As well, the recurrence rate of all TTPs is above 35% with an excessively high mortality rate. Today the only treatment that has proven to be effective in changing the prognosis of these patients is apheresis with plasma exchange. Before the plasma exchange (PEX) era, only 10% of patients survived [16]: initials report of PEX from 1981 to 1991 already described an increase in the survival rates of up to 70-79% [17-19].

According to the proponents of the infusion of plasma, the benefit would be related to the administration of a deficient substance in patients with TPP. On the other side, the proponents of PEX argue that the advantage of this therapeutic option consists not only in the administration of a deficient factor, but also in the elimination of toxic substances, which occurs during the procedure PEX [19].

This treatment should be promptly taken into consideration also in the only suspect of TTP, even before laboratory confirmations. Various studies in literature [20] have confirmed a reduction in 30-day mortality and a significant increase in platelet count after apheretic therapy in combination with corticosteroids and/or immunosuppressive drugs. Corticosteroids in combination with plasmapheresis increase the complete re-

mission rate and decrease the relapse rates. This latter result is due to the removal of the Unusually Large Von Willebrand Factor (ULVWF) and anti ADAMTS 13 Antibodies, while steroids reduce anti- ADAMTS 13 Antibodies production [21].

ALGORITHM FOR MANAGEMENT OF TTP PATIENTS [15]



Broken lines represent complications that occur in a minority of patients

PEX = Plasma exchange; CVC = Central venous catheter

* Although rituximab may be appropriate for 3 different situations illustrated in this algorithm, Authors have never used more than a single course of rituximab for any patient

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