Journal of Clinical Apheresis 26:152–155 (2011)

Case Report

Stroke in a Young Patient Treated by Alteplase Heralding an Acquired Thrombotic Thrombocytopenic Purpura

Amandine Sevy,[1]* Emilie Doche,[2] Christian Squarcioni,[2] Pascale Poullin,[3] Jacques Serratrice,[1] Francois Nicoli,[2] and Pierre-Jean Weiller[1]

[1]Department of Internal Medicine, CHU Timone, Marseille, France
[2]Stroke Center, CHU Timone, Marseille, France
[3]Department of Autotransfusion and Hemapheresis, CHU Timone, Marseille, France

Background and purpose: Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystem disorder characterized by thrombocytopenia and fluctuating neurological symptoms due to microinfarcts. In rare cases, large cerebral arteries can be occluded. **Summary of the case:** We report on a 30-year-old woman with a first-ever acute stroke related to a right proximal MCA M1 occlusion. Platelet count was normal at admission and progressively decreased 6 days after intravenous thrombolysis with the occurrence of a hemolytic anemia with schistocytes. Most biological anomalies reversed after plasma exchange. No hemorrhagic complication occurred. Diagnosis of initial TTP was confirmed by low ADAMTS13 activity and positivity of anti-ADAMTS13 antibody. **Conclusion:** This observation highlights the fact that even if platelet count and hemoglobin rate are normal in the beginning, an acute ischemic stroke in a young patient can be related to TTP. Faced with subsequent thrombopenia, practitioners should be aware of acquired TTP, and, thus, schistocytes, haptoglobin, and LDH assays should be performed. Early diagnosis is paramount to start the life-saving plasma exchanges. J. Clin. Apheresis 26:152–155, 2011.

Key words: stroke; middle cerebral artery; thrombotic thrombocytopenic purpura; thrombolysis

INTRODUCTION

We report a case of first-ever acute ischemic stroke in a young woman treated by intravenous thrombolysis (IVT) disclosing an autoimmune TTP.

CASE REPORT

A 30-year-old woman was referred to the Stroke Centre for a sudden left hemiplegia. She was an active smoker of 20 cigarettes a day and was taking an oral estroprogestin agent. She had no previous personal or familial history of stroke or thrombosis. She suddenly presented with a left global hemiplegia, associated with hemianopsia and right gaze deviation (National Institute of Health Stroke Score (NIHSS) = 14) while eating, and vomiting.

MRI performed in emergency revealed an acute ischemia in right mild cerebral artery (MCA) territory related to an M1 segment occlusion (Fig. 1). There was no other acute or old ischemic lesion. IVT using a standard dose of alteplase was performed 90 min after stroke onset. Patient's condition improved 1 h after procedure (visual and motor recovery) but worsened 3 h later (left faciobrachial hemiplegia). CT angiography performed 24 h later showed a complete MCA M1 recanalization without hemorrhage but a residual thrombus in an MCA M2 branch treated by unfractionated heparin. Standard biological data were normal: hemoglobin 14.3 g/dL, platelet 252,000/mm^3, lactate dehydrogenase (LDH) 217 UI/L ($125<N<248$), and WBC 16,000/mm^3.

Because of initial vomiting, an acute inhalation pneumonia occurred (hyperthermia, WBC 40,000/mm^3, CRP 177 mg/L, and blood PCR Streptococcus oralis positive, Fig. 2). Imipenem 500 mg/day and vancomycin 2 g/day were given intravenously for 6 days relayed by 10 days of IV piperacilline tazobactam 12 g/day and ciprofloxacin 400 mg/day.

On Day 4, platelet count was down to 131,000/mm^3, and hemoglobin was 13.6 g/dL (Fig. 3). Anti-PH4

*Correspondence to: Amandine Sevy, 264 rue Sainte Pierre, Marseille 13005, France. E-mail: amandine.sevy@ap-hm.fr

Received 27 July 2010; Accepted 20 October 2010

Published online 13 December 2010 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/jca.20276

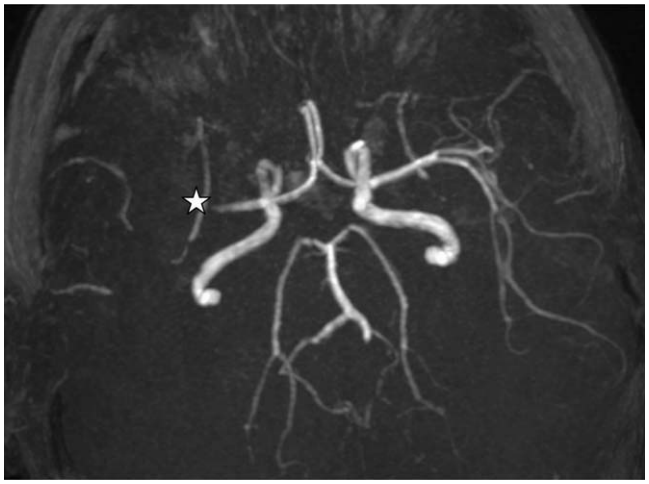

Fig. 1. Time-of-flight MR angiography: occlusion of the M1 segment of the right middle cerebral artery.

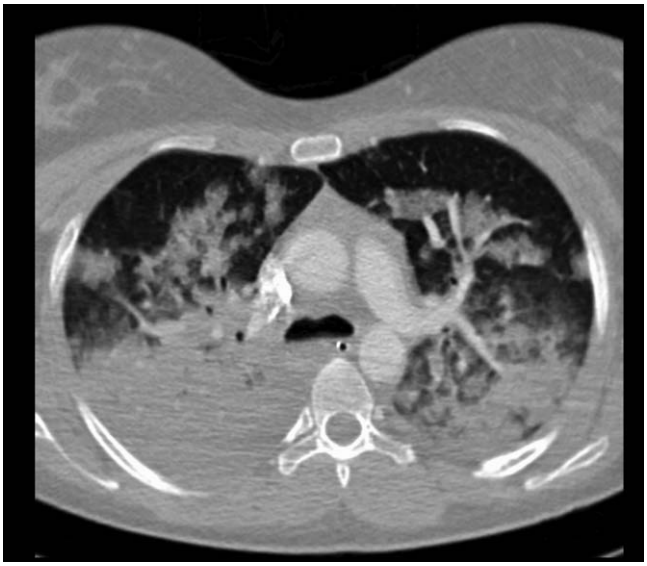

Fig. 2. Chest CT scan at 24 h: bilateral pneumonia.

ELISA assay was first positive but with a low level (0.36 UI). Heparin-induced thrombocytopenia was evoked and danaparoid was introduced. Five days later, we observed no plasma proaggregating activity. Danaparoid was continued for 10 days as anticoagulant after alteplase because of residual thrombus in M2 branch.

On Day 8, platelet count was 25×10^9/L, and hemoglobin was 8.2 g/dL. Reticulocytes were 168,000/mm^3. Serum haptoglobin was under 0.08 g/L ($0.57<N<1.52$); LDH was 1505 UI/L. Peripheral blood smear showed 6% schistocytes. Faced with thrombocytopenia and hemolytic anemia with schistocytes, we entertained the diagnosis of thrombotic thrombocytopenic purpura (TTP). It was confirmed retrospectively by the low ADAMTS13 activity (<5%) and the positive anti-ADAMTS13 antibody test in the third-day-plasma (>150 UI/mL). ADAMTS13 activity was determined based on the positive correlation between VWF multimeric size and ristocetin cofactor activity (VWF:RCo) as described by Böhm et al. [1]. Antibody assay was performed with Western blot analysis according to Klaus et al. [2]. Daily plasma exchange with methylene blue-photoinactivated plasma (1.5 plasma volume) was started for 4 days (Days 9–12) until the platelet count was $>150 \times 10^9$/L for longer than 48 h while danaparoid was continued. Renal function remained normal, and hemoglobin and platelet count gradually improved. Protease activity was decreased and antibody tests were positive for all studied plasma.

There was no genetic or acquired thrombophilia. There were no antinuclear antibodies. Beta human chorionic gonadotrophin (HCG) was negative. There was no heart conduction block, no arrhythmia, and no carotid dissection on the angio-CT scan. Thoracoabdominopelvic CT scan and echocardiography results were normal. No other clinical manifestation occurred. One month after admission, the patient was discharged to a rehabilitation center. She was able to walk alone in spite of persisting left arm weakness (modified Rankin scale = 3 at 3 months). Three months later, ADAMTS 13 activity remained <5% and antibody tests remained positive. Result of typing human leukocyte antigen (HLA) class II type was DRB1*11*/DRB1*15. Because of a high-relapsing probability, a multidisciplinary decision was made to treat with rituximab.

DISCUSSION

We report the case of an autoimmune TTP revealed by an MCA M1 occlusion in a 30-year-old woman. TTP syndrome is a thrombotic microangiopathic disease characterized by microangiopathic hemolytic anemia and thrombocytopenia. Platelet microthrombi form in the microcirculation and cause vessel occlusions. TTP can be an acquired or be a congenital autosomic recessive disease. Acquired TTP can be triggered by many factors like cancers, infection, autoimmune disease, and medications, or it can be idiopathic. Plasma exchange is the first-line therapy for acquired TTP, whereas plasma infusion is preferred for congenital deficiency. Physiologically, various sizes of Willebrand factor multimers are secreted when endothelium is injured. The largest form, ultralarge von Willebrand factor (ULVWF) multimers, is considered as the major pathogenic factor in TTP due to platelet clumping. A disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) is an enzyme that reduces the ULVWF to its normal size. It is either absent in congenital TTP, or neutralized by IgG auto-antibodies in acquired TTP.

On our patient on Day 3, high titers of anti-ADAMTS13 antibodies (>150 UI/mL) and severe deficiency of ADAMTS13 (<5%) confirmed the diagnosis

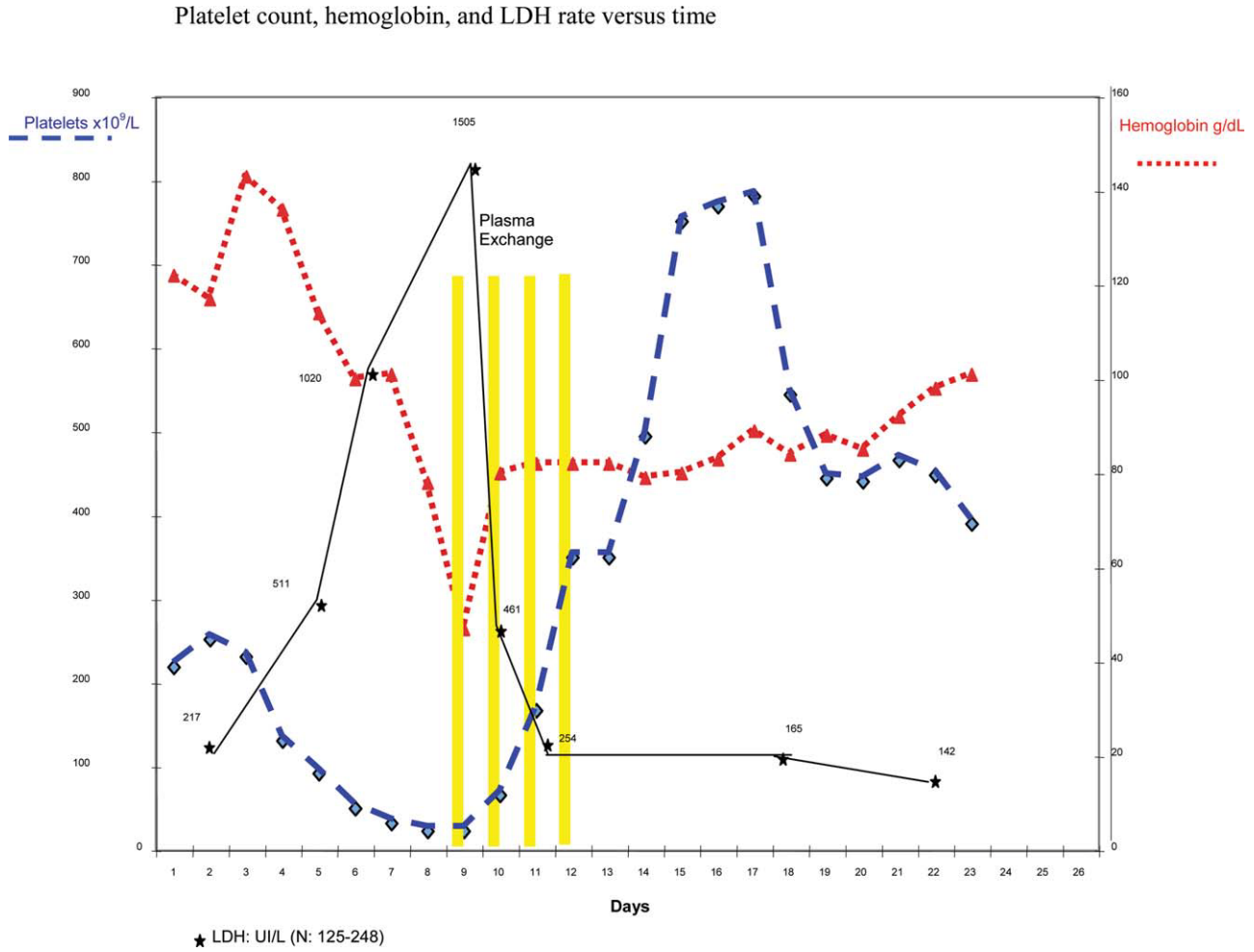

Fig. 3. Platelet count, hemoglobin, and LDH rate versus time. ★, LDH: UI/L (*N*: 125–248). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of acquired TTP. We checked that protease activity after IVT was normal in three other patients.

In our patient, thrombocytopenia appeared on Day 5, and was associated with a weak anti-PF4 assay. A heparin-induced thrombocytopenia was first considered. Sensitivity and specificity of anti-PF4 assay are debated [3], particularly with such a low level. This hypothesis was further ruled out by the absence of plasma proaggregating activity and negative serotonin release assay in our patient. Finally, hemolytic anemia appeared (Fig. 3) and protease activity was already decreased at the third-day-serum assay. Thus, thrombocytopenia should be considered as being the first biological sign of TTP. As this is an acquired TTP; revealed concomitantly with MCA occlusion exact chronological order is difficult to establish.

On one hand, stroke can be considered as a consequence of TTP, with an atypical presentation as it usually presents with microangiopathic thrombi. Indeed, no peripheral vascular involvement was seen on MRI at admission. This does not rule out the above hypothesis because thrombosis of large-diameter arteries has already been reported in congenital TTP [4]. This physiopathology could be related to direct endothelial cell apoptosis caused by autoantibodies, exposing the subendothelium and leading to thrombus formation. However, this has never been proven.

Normal initial biological data is also atypical (hemoglobin, platelet count, and LDH levels). Two other acquired cases of relapsed TTP presented as MCA M1 occlusion with normal initial biological data [5]. Thus, the normality of initial biological data does not exclude that TTP can be a rare cause of stroke.

On the other hand, as 40% of ischemic strokes in young patients are idiopathic [6], one wonders if stroke itself can be a triggering factor heralding a latent acquired TTP. Even after treatment, ADAMTS 13 activity remained $<5\%$ and antibody tests remained highly positive, so a severe autoimmune ADAMST13 deficiency was likely pre-existing. Thus, a susceptibility to microangiopathic disease could be evoked, triggered by several factors. As infectious diseases have been related to TTP [7], in our case pneumonia must be considered as a precipitating factor.

HLA class II typing was of interest: it has been reported that DRB1*11/DRB1*15 types are associated with susceptibility of developing an acute acquired TTP in European patients [8]. Moreover, it could be useful to determine the exact antibody type against ADAMTS 13 and exact genotyping of ADAMTS 13 to help understand the exact mechanism implicated in this case and help in prognosis.

CONCLUSIONS

In conclusion, this is a rare case of acute MCA M1 occlusion heralding a latent acquired TTP, probably revealed by pneumonia. Early diagnosis of TTP is paramount to start the life-saving plasma exchanges. Initial sampling for anti-ADAMTS13 antibodies and ADAMTS13 activity performed at admission could help to retrospectively elucidate idiopathic ischemic stroke.

REFERENCES

1. Böhm M, Vigh T, Scharrer I. Evaluation and clinical application of a new method for measuring activity of von Willebrand factor-cleaving metalloprotease (ADAMTS13). Ann Hematol 2002; 81:430–435.
2. Klaus C, Plaimauer B, Studt JD, Dorner F, Lämmle B, Mannucci PM, Scheiflinger F. Epitope mapping of ADAMTS13 autoantibodies in acquired thrombotic thrombocytopenic purpura. Blood 2004;103:4514–4519.
3. Schneiter S, Colucci G, Sulzer I, Barizzi G, Lämmle B, Alberio L. Variability of anti-PF4/heparin antibody results obtained by the rapid testing system ID-H/PF4-PaGIA. J Thromb Haemost 2009;7:1649–1655.
4. Downes KA, Yomtovian R, Tsai HM, Silver B, Rutherford C, Sarode R. Relapsed thrombotic thrombocytopenic purpura as an acute cerebrovascular accident. J Clin Apher 2004;19:86–89.
5. Kelly PJ, McDonald CT, Neill GO, Thomas C, Niles J, Rodorf G. Middle cerebral artery main stem thrombosis in two siblings with familial thrombotic thrombocytopenic purpura. Neurology 1998;50:1157–1160.
6. Woimant F. Ischemic stroke in young adults. Presse Med 2007; 36:1S59–1S64.
7. Douglas KW, Pollock KGJ, Young D, Catlow J, Green R. Infection frequently triggers thrombotic microangiopathy in patients with preexisting risk factors: a single-institution experience. J Clin Apher 2010;25:47–53.
8. Scully M, Brown J, Patel R, McDonald V, Brown CJ, Machin S. Human leukocyte antigen association in idiopathic thrombotic thrombocytopenic purpura: evidence for an immunogenetic link. J Clin Apher 2010;8:257–262.