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A RARE CASE OF THROMBOTIC THROMBOCYTOPENIC PURPURA COMPLICATED BY MACROVASCULAR EVENTS

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Abstract

Thrombotic thrombocytopenic purpura is a rare but serious disease with high rates of mortality. It is a thrombotic microangiopathy associated with fever, thrombocytopenia, haemolytic anaemia and can also present with neurological and renal dysfunctions. It is caused by the reduced activity of ADAMTS13, a metalloprotease which cleaves von Willebrand factor resulting in widespread microvascular occlusion due to platelet rich thrombi. Although small vessel infarcts are common in kidney and brain, large vessel occlusions are rarely seen in thrombotic thrombocytopenic purpura.

We present a case of a 56-year-old woman who presented with symptoms of urinary tract infection subsequently diagnosed with Thrombotic thrombocytopenic purpura. The initial treatment regimen consisted of plasma exchange therapy followed by steroids and cyclophosphamide. She was gradually improving, however her course of disease was complicated by a large cerebral infarct and bilateral pulmonary artery thrombosis resulting in intensive care unit admission and prolonged hospitalization. The patient was subsequently started on anti-coagulant therapy with fondaparinux and monitored continuously due to the increased risks of haemorrhage. The patient gradually improved over time with sustained improvement in laboratory reports. The outcomes of anti-coagulant therapy were favourable in our case and patient was discharged with rituximab therapy on subsequent follow ups.

This case report intends to highlight the macrovascular thrombotic events and the challenge it brings to physicians regarding thrombolysis.

Keywords *TTP, cerebral infarct, pulmonary artery thrombosis, macrovascular.*

Introduction

Thrombotic thrombocytopenic Purpura, a rare life-threatening hematological condition has significant morbidity and mortality unless diagnosed and treated promptly [*Balasubramaniyam N et al., 2021*]. The underlying pathogenesis of thrombotic thrombocytopenic purpura (TTP) is a severe deficiency in ADAMTS13 (A Disintegrin and Metalloprotease with ThromboSpondin type 1 motifs 13) activity, a metalloprotease that cleaves large von Willebrand factor multimers [*Fujikawa K et al. ,2001; Levy G et al., 2001*]. In the absence of ADAMTS13 activity vWF polymers accumulate and cause severe platelet clumping with resultant microthrombi formation. This deficiency is either autoantibody mediated (acquired TTP) or due to deleterious mutations in the gene encoding ADAMTS13 (congenital TTP). It is classically characterized by the pentad of microangiopathic hemo-

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lytic anemia, consumption thrombocytopenia, fever, neurological symptoms, and renal dysfunction [*Iqbal S et al., 2016*]. However, the clinical data now suggests that this pentad is neither sensitive nor specific, and most patients do not have all the five clinical features [*Scully M et al., 2008*]. Prompt differentiation of TTP from other causes of thrombotic microangiopathies is crucial for the initiation of an appropriate therapy in order to reduce morbidity and mortality. There exists a significant risk of suboptimal outcomes which are potentially avoidable. Here, we report on an atypical case of acquired TTP which was complicated by large cerebral artery infarct and pulmonary embolism. The macrovascular events are considered rare and presented as a challenge with thrombolysis in the setting of thrombocytopenia. This case report intends to provide a perspective on the management of a complicated TTP as performed in our institution highlighting the incidence of macrovascular complications, large cerebral infarct and bilateral pulmonary artery thrombosis.

Case Presentation

A 56-year-old woman, presented to the emergency department with complaints of burning urination, increased urinary frequency and fever for 15 days. She also complained of generalized fatigue and headaches over the past 15 days. Her only significant medical history consisted of diabetes mellitus diagnosed two years ago, under control with Oral hypoglycemic agents. On examination, Vital signs were normal and physical examination was unremarkable except for pallor. Her initial respiratory, cardiovascular, abdominal, and neurological assessments were unremarkable. The initial laboratory investigations are listed in table 1.

The patient was admitted in view of the above laboratory findings and further investigations were obtained. The peripheral smear was suggestive of microangiopathic hemolytic anemia with presence of schistocytes and microcytes. Post admission the patient was drowsy with intermittent focal deficit and her vitals remained stable. The differentials at the time of admission included TTP, hemolytic uremic syndrome and tropical fever. The patient developed one episode of generalized tonic clonic seizure with right side hemiparesis following which the patient was shifted to intensive care unit. Computed tomography (CT) of the brain was normal; however, plasma exchange therapy was initiated in view of high PLASMIC score [*Tufano A et al., 2022*]. Tropical fever was ruled out through detailed serological work-up, ADAMTS13 levels were significantly deficient at 1.2%, ADAMTS13 inhibitors screening was positive. Based on the laboratory parameters a diagnosis of immune TTP was established. The patient was started on intravenous corticosteroids and plasma exchange therapy every alternate day for a total of six cycles. Her platelets improved to $178x10^3$ /*cu.mm*, lactate dehydrogenase reduced to 255 *IU/L*, and she was shifted out of intensive care unit for further management.

TABLE 1

Initial laboratory investigations

Initial Laboratory investigations	Patient Values	Reference Values (Adult Female)
Haemoglobin (*g/dL*)	9.0	12.0-16.0
Haematocrit (%)	25.20	37-47
Platelets ($x10^3$ /*cu.mm*)	29	1.5-4.5
White Blood Cells (*cu.mm*)	9200	4500-11,000
Erythrocyte Sedimentation Rate (*mm/hr*)	69	0-20
Urea (*mg/dL*)	42	8-20
Creatinine (*mg/dL)*	1.56	0.5-1.1
Total Bilirubin (*mg/dL*)	1.15	0.3-1.0
Aspartate Transaminase (*IU/L*)	29	10-40
Alanine Transaminase (*IU/L*)	17.6	10-40
Alkaline Phosphatase (*IU/L*)	66	30-120
Lactate Dehydrogenase (*IU/L*)	>1000	80-225
Coombs	Negative	
Prothrombin time (*sec*)	11.4	11-13
International normalized ratio	1.01	0.8-1.1

The patient was further started on cyclophosphamide and her lab parameters were found to be improving. However, on the second day following her time in the intensive care unit, she experienced a sudden loss of consciousness along with left-sided hemiparesis. Her vital signs were unstable: Pulse-56/*min*, Blood pressure-70/40 *mmHg*, SpO2 of 56% following which she was intubated and mechanically ventilated in intensive care unit. Her

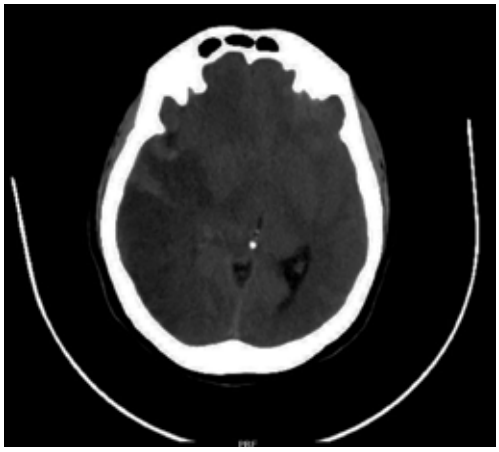

Figure 1*. CT Brain showing an acute cerebral infarct with haemorrhagic transformation involving the right parietal, temporal and occipital lobes*

CT Brain showed a large infarct in the right parietal, temporal and occipital region with M2 segment thrombosis (Fig. 1).

In view of hypoxia and elevated d-dimer levels, CT pulmonary angiogram was performed which was suggestive of bilateral pulmonary thrombosis in distal main pulmonary arteries (Fig. 2).

Laboratory investigations revealed a platelet count of 84x10^3 /*cu.mm*, lactate dehydrogenase at 450 *IU/L*, ADAMTS13 activity at 1.56%. She was again treated with five cycles of plasma exchange therapy on alternate days, intravenous steroids and fondaparinux with acceptable risk of hemorrhage. She gradually improved and her laboratory investigations showed sustained improvement as shown in table 2. At the time of discharge, her ADAMTS13 was 9.6% and she was initiated on rituximab injection weekly for six weeks. She was discharged on tapering doses of steroids, anti-coagulants and advised to follow up for rituximab therapy. During the last follow up platelet count was 238x10^3 /*cu.mm*, lactate dehydrogenase at 291 *IU/L* and she showed significant neurological recovery.

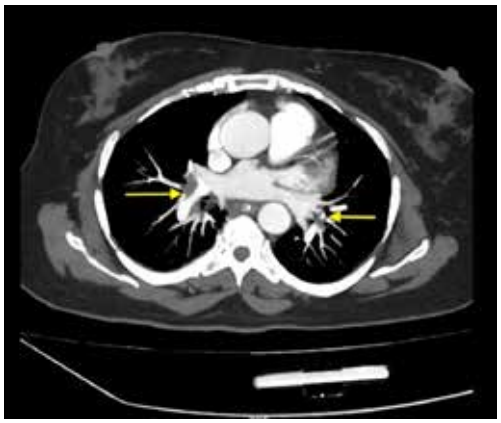

Figure 2. *Axial view of computed tomography pulmonary angiography showing non-enhancing fillings defects in distal most part of right and left main pulmonary arteries (yellow arrow)*

Discussion

Thrombotic thrombocytopenic purpura remains a life-threatening disease which requires rapid intervention in the form of early diagnosis and treatment. The diagnosis is primarily based on clinical features, lab parameters, peripheral smear and ADAMTS13 activity levels [*Blombery P, Scully M, 2014*]. The most common complaints were recurrent fever (19.1 %), followed by fatigue (16.2 %) and headache (14.7 %) [*Jiang H et al., 2014*]. In our case, the patient presented with complaints of burning micturition and fever. Initially, there were no neurological symptoms in our case, but the patient developed a seizure episode with right-sided hemiparesis within 3 days of admission. In view of the laboratory findings, peripheral smear examinations and onset of neurological symptoms, clinical suspicion of TTP were high and low levels of ADAMTS13 confirmed the diagnosis. Initial treatment with plasma exchange therapy and corticosteroids was initiated. Although microvascular complications are common, macrovascular complications in our case such as a massive cerebral infarct and pulmonary thrombosis are considered rare [*Sugarman R et al., 2018*]. This presented as a dilemma whether to perform thrombolysis or not as platelet levels were still low and risks of hemorrhage were high. Idowu M. and Reddy P. (2013) described a similar case of TTP who presented with an acute M2 right middle cerebral artery oc-

Table 2

Platelet count and Lactate Dehydrogenase values over time

Timeline	Platelet Count (x10^3/cu.mm)	LDH (IU/L)
Day 0	29	>1000
Day 14 (After six cycles of therapeutic plasma exchange)	178	255
Day 16 (Post thrombotic event)	84	450
Day 26 (At discharge)	220	245
At 3 month (follow up)	238	291

Notes: LDH -Lactate Dehydrogenase

clusion and underwent thrombolysis. Her neurological symptoms did not improve, and new right middle cerebral artery ischemic areas with haemorrhagic change were detected on brain MRI. On the contrary, in another case thrombolysis proved to be effective in large cerebral infarct [*Boattini M, Procaccianti G, 2013*]. Our patient was treated with Fondaparinux, repeated cycles of plasma exchange therapy and showed improvement. She was later discharged on oral tapering dose of steroids, oral anticoagulants and advised to follow up for further Rituximab therapy.

CONCLUSION

Transient neurologic deficits due to small vessel occlusion are well described in thrombotic thrombocytopenic purpura. Large vessel infarcts are rare in thrombotic thrombocytopenic purpura and can be seen as in our case. Thrombotic thrombocytopenic purpura is a rare differential for a large vessel occlusion such as in cerebral or pulmonary infarcts. Early identification based on clinical and laboratory parameters, rapid initiation of therapy and continuous monitoring can lower mortality. Further studies are also required to understand the efficacy and safety of thrombolytic therapy in patients with thrombotic thrombocytopenic purpura.

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REFERENCES

1. *Balasubramaniyam N, Yandrapalli S, Kolte D, Pemmasani G, Janakiram M, Frishman WH (2021).* Cardiovascular Complications and Their Association with Mortality in Patients with Thrombotic Thrombocytopenic Purpura. Am J Med. 134: 89-97 DOI: 10.1016/j.amjmed.2020.06.020
2. *Blombery P, Scully M (2014).* Management of thrombotic thrombocytopenic purpura: current perspectives. J Blood Med. 5:15-23 DOI: 10.2147/JBM.S46458
3. *Boattini M, Procaccianti G (2013).* Stroke due to typical thrombotic thrombocytopenic purpura treated successfully with intravenous thrombolysis and therapeutic plasma exchange. BMJ Case Rep. 28: 2012008426 DOI: 10.1136/bcr-2012-008426
4. *Fujikawa K, Suzuki H, McMullen B, Chung D (2001).* Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. Blood. 98: 1662-1666 DOI: 10.1182/blood.v98.6.1662
5. *Idowu M, Reddy P (2013).* Atypical thrombotic thrombocytopenic purpura in a middle-aged woman who presented with a recurrent stroke. Am J Hematol. 88: 237-239 DOI: 10.1002/ajh.23249.
6. *Iqbal S, Zaidi SZ, Motabi IH, Alshehry NF, Al-Ghamdi MS, Tailor IK (2016).* Thrombotic thrombocytopenic purpura - analysis of clinical features, laboratory characteristics and therapeutic outcome of 24 patients treated at a Tertiary Care Center in Saudi Arabia. Pak J Med Sci. 32: 1494-1499 DOI: 10.12669/pjms.326.11274.
7. *Jiang H, An X, Li Y, Sun Y, Shen G, Tu Y, Tao J (2014).* Clinical features and prognostic factors of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus: a literature review of 105 cases from 1999 to 2011. Clin Rheumatol. 33: 419-42. DOI: 10.1007/s10067-013-2312-5
8. *Levy GG, Nichols WC, Lian EC, Foroud T, McClinitic JN., et al (2001).* Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 413: 488-494 DOI: 10.1038/35097008
9. *Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B., et al (2008).* Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. Br J Haematol. 142: 819-826 DOI: 10.1111/j.1365-2141.2008.07276.x
10. *Sugarman R, Tufano AM, Liu JM (2018).* Large vessel stroke as initial presentation of thrombotic thrombocytopenic purpura. BMJ Case Rep. 5: 2017221857 DOI: 10.1136/bcr-2017-221857.
11. *Tufano A, Polimeno M, Matani B, Cardiollo G, Capasso F., et a (2022).* Validation of PLASMIC score in a cohort of patients with suspected thrombotic microangiopathy in an academic medical centre. Blood Transfus. 9: 10-2450 DOI: 10.2450/2022.0082-22

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