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Original Research Paper

Pathology

MULTIPLE MYELOMA COMPLICATED BY FATAL THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) – A CASE REPORT OF AUTOPSY FINDINGS IN A TERTIARY CARE CENTRE.

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ABSTRACT Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurological abnormalities, fever and renal dysfunction. Early clinical suspicion and presumptive diagnosis of TTP helps in timely initiation of treatment modalities specific for TTP which may prove to be lifesaving and thus augment in reducing the mortality rate of TTP which is estimated to be 80 – 90 % if left untreated. We report a case of a known case of multiple myeloma who developed TTP which proved fatal despite plasmapheresis. Significant autopsy findings of presence of microthrombi in the microvasculature of multiple organs is also highlighted.

KEYWORDS : Multiple myeloma, thrombotic thrombocytopenic purpura (TTP) , microthrombi .

INTRODUCTION

Thrombotic thrombocytopenia purpura (TTP) is a rare form of thrombotic microangiopathy (TMA) characterised by microangiopathic homolytic anemia (MAHA) , severe thrombocytopenia and ischaemic end organ damage resulting from formation of platelet rich thrombi in the microcirculation[1] .The estimated incidence of TTP is 2 per million per year[2] TTP refers to a thrombotic disorder due to the deficiency of ADAMTS13 which may be due to genetic mutation or due to the presence of inhibitory autoantibodies. ADAMTS13, a metalloprotease of the M12B subfamily, cleaves vWF at the Tyr 1605- Met 1606 bond in the central A2 domain of the VwF polypeptide whenever this normally cryptic bond is rendered accessible by circulatory shear stress or chaotropic agents. This cleavage progressively converts the endothelial vWF polymers to smaller multimers that are conformationally less flexible and less adhesive.

When ADAMTS13 is deficient, vWF multimers are conformationally unfolded but not cleaved, resulting in accumulation of hyperactive forms of vWF that cause platelet aggregation and microvascular thrombosis characteristic of TTP.[3]. For TTP, the full pentad of signs and symptoms (thrombocytopenia, schistocytic anemia, neurological impairment, and fever) are present in only 5% of patients[4]. The first two criteria – thrombocytopenia and schistocytic anemia- are enough to initiate treatment, especially since early mortality is high with about 50% of deaths occurring in the first 24 hours.[5] Multiple myeloma is a B- cell malignancy with a terminally differentiated plasma cell phenotype characterised by lytic bone lesions, renal insufficiency, anaemia, hypercalcemia, and humoral as well as cell mediated immunodeficiency [6].In this report , we discuss the short clinical history , laboratory findings and most importantly the autopsy findings of a case of TTP associated with multiple myeloma. It is also noteworthy that the said patient also had a previous history of autologous stem cell transplantation two years back and a history of Covid-19 vaccination two weeks prior to the development of her illness.

CASE STUDY

A 49-year-old previously healthy female presented with the chief complaint of generalized weakness, abdominal discomfort and appearance of multiple blackish spots over her feet and other parts of her body. She was a known and treated case of multiple myeloma (diagnosed in Jan 2019) and had also undergone autologous stem cell transplantation the same year in June and was on maintenance therapy with Thalidomide and Aspirin for the last two years. There was also a history of Covid -19 vaccination (batch no - 412Z003) two weeks prior to the development of her symptoms. The prominent findings of the hematological investigations performed in this patient were that of anemia, severe thrombocytopenia, elevated nucleated RBCs (nRBCs) and the presence of schistocytes (3.5 %) which were characteristic of TTP. Other associated findings included a raised level of red blood cell width (RDW) and a normal total leucocyte count. Coagulation profile was found to be in the normal range and there was an increase in the D-Dimer level and all the components of the liver function test. Enzyme linked immunosorbent assay (ELISA)performed to detect the presence of antibodies to the platelet 4 (Pf 4) in the form of Heparin Pf4 IgG (HIT) were found to be negative. Serum lactate dehydrogenase levels were raised and the only abnormal finding in the kidney function test was that of an elevated serum urea level During the course of the treatment, she developed headache and episodes of nausea, vomiting and irrelevant talk for which she underwent an NCCT brain which revealed a subdural hematoma over the cerebral convexity , along with evidence of sub arachnoid hemorrhage.

A presumptive diagnosis of TTP was agreed upon and she received multiple sessions of plasmapheresis. However, no significant improvement was noted in her general condition, and she was declared dead at the intensive care unit after 22 days of hospital admission. Autopsy was performed to find out the cause of death and the major findings in the gross examination included areas of petechial hemorrhage in multiple organs including the brain, kidney, heart, liver and the urinary bladder. A summary of the microscopic findings is listed below.

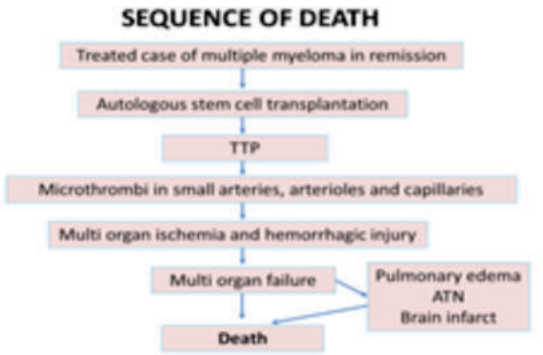
Summary of findings in major organs

Microscopic :
1) Microthrombi in multiple organs including
- Lungs
- Kidney
- Cerebrum and meninges

2) Haemorrhages in multiple organs including
- Lungs
- Kidney
- Liver
- Heart (Rt atrial wall and papillary muscle)
- Cerebrum and cerebellum(subdural)
- Meninges
- Urinary bladder

3) Infarction of cerebrum and cerebellum
4) Other associated findings of liver necrosis and red pulp hyperplasia of spleen

The probable sequence of events which might have led to the death of the patient is depicted below



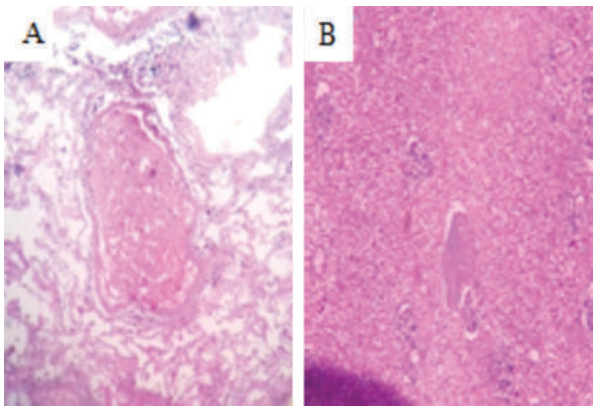


Fig-1(A) Microthrombi in alveolar capillaries(B) Microthrombi in renal arteries. (H&E stain, 10 x)

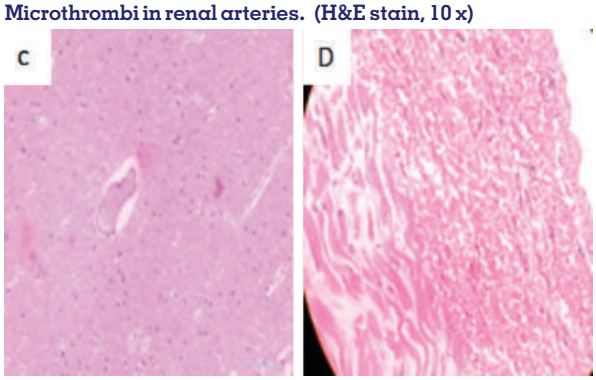


Fig-2(C)Microthrombi in cerebral arteries (D) Hemorrhage in papillary muscle of the heart. (H&E stain, 10 x)

DISCUSSION

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disease. It is characterized by severe deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) which cleaves the Von Willebrand factor from its polymeric form to small multimers thus preventing the formation of thrombus. Inability to cleave the Von Willebrand factor in a scenario of severe ADAMTS13 deficiency leads to formation of platelet rich thrombi. ADAMPTS13 activity of < 10 % is considered to be confirmatory of TTP. However, these assays are not available in house in many situations and due to logistic reasons, the result may also take days to reach the physician as was the case in our situation. Therefore, a presumptive diagnosis of TTP considering the clinical and laboratory assessment plays a major role in initiating treatment modalities which may prove to be life saving for the patient in the absence of the ADAMTS13 assays. Recently, the diagnostic value of schistocytes was standardized by the International Council for Standardization in Hematology (ICSH) Schistocyte Working Group. The ICSH Schistocyte Working Group agreed that a schistocyte percentage above 1% in a peripheral blood smear in adults is a robust cytomorphological indication in favor of a diagnosis of TMA, when additional features suggesting an alternative diagnosis are absent [7] . We also encountered elevated levels of lactate dehydrogenase (LDH), liver enzymes, serum urea and D-DIMER levels with a normal coagulation profile which are all associated with TTP. Various severity scores have been proposed for TTP. Benhamou et al [8] found that a score that included age, an elevated lactate dehydrogenase (LDH) level higher than 10-fold of the normal and cerebral involvement, was highly accurate in predicting the risk of death in TTP patients. Multiple myeloma is a malignant disease of plasma cells with a worldwide incidence of 6-7 cases per 100000 persons per year [9]. Patients with multiple myeloma (MM) are susceptible to developing thrombotic microangiopathies (TMAs) , an etiologically diverse group of syndromes which includes atypical hemolytic uremic syndrome (a HUS) and thrombotic thrombocytopenia purpura (TTP) .In MM patients , TMAs maybe triggered by specific chemotherapies, bone marrow transplantation (BMT), and progression of underlying disease.[10] It is noteworthy here that our patient was also a known case of multiple myeloma who had undergone autologous stem cell transplantation 2 years back and this could have played a role in the development of TTP. The concept of TTP post-vaccination is not new. These were usually seen with vaccines against viral agents. It is especially important within two weeks of vaccination. Cases of immune mediated TTP following the administration of vaccines have been previously described and recently reviewed [11]. However, the exact mechanism remains unclear. In the literature, there is evidence of vaccine-induced autoimmunity, adjuvant-induced autoimmunity and antibody cross-reaction in both experimental models as well as human patients [12] . A lot of attention has recently been given to the thrombotic risk of Covid 19 vaccination, in particular, a new syndrome called vaccine- induced immune thrombotic thrombocytopenia (VITT) following administration of adenovirus based vaccine AstraZeneca has been described. This syndrome is characterized by thrombosis at unusual sites, thrombocytopenia, and the presence of high levels of antibodies to platelet factor 4 (PF4) in the absence of heparin treatment [13]. This situation also arose in this case as she also had a history of vaccination with the Covishield vaccine two weeks prior to the development of symptoms. However, the diagnosis of VIIT could easily be refuted as enzyme linked immunosorbent assay (ELISA) for the Pf 4 antibodies were found to be negative in our case, a positive result of which is considered to be confirmatory for VITT. Major autopsy findings of this case were that of multiple petechial hemorrhages on the brain, kidney, liver, heart and the urinary bladder. Striking microscopic findings included presence of microthrombi and hemorrhage in the lungs, kidney, cerebrum, cerebellum and meninges. Hemorrhage was also a prominent finding in the sections from the heart (atrial wall and the papillary muscle), liver, and the urinary bladder. Other associated findings included evidence of liver necrosis and red pulp hyperplasia of the spleen. Similar findings have been extensively documented by several authors. The most common TTP related findings at autopsy were thrombi/emboli in heart (9), lung (11), brain (3), kidney (7), followed by hemorrhage in heart (7), lung (4), brain (6), and kidney (3). The most common immediate cause of death were cardiac arrest and myocardial infarction.[14] . Patients with TTP are at high risk of severe organ failure and ICU admission should always be considered as soon as the diagnosis of TTP is suspected. The brain, heart and kidney are the main organs that may suffer from micro thrombosis [15]. The sequence of events leading to death in our case seems to be multifactorial. Some of the comorbid conditions which could have attributed to the development TTP included – multiple myeloma under treatment, h/o autologous stem cell transplantation and a

coincident history of Covid 19 vaccination. All these could have played a role in the development of TTP which consecutively lead to the development of microthrombi in various organs thus leading to shock and multiorgan failure which resulted in death of our patient.

CONCLUSION

Patients with TTP with or without any other co morbidities are at a higher risk of suffering from multiorgan dysfunction and failure. Micro thrombosis occurring in TTP affects mainly the brain, heart and the kidney which may prove fatal. Therefore an early diagnosis of TTP may have a positive impact on reducing the mortality and morbidities associated with TTP.

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