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Microangiopathic hemolytic anemia/Acquired Thrombotic Thrombocytopenic Purpura as a first presentation of pancreatic cancer

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening hematologic disorder. It is mainly characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, renal impairment and neurological abnormality. Plasmapheresis and steroids are the standard of care.

MAHA/TTP can be the initial presentation of solid organ malignancies especially gastrointestinal tumors. We report a 56-year-old female patient who presented with progressive back pain, tiredness, easy bruising, fever and weight loss. Laboratory results showed anemia, thrombocytopenia, and schistocytes in the peripheral smear. An initial diagnosis of thrombotic thrombocytopenic purpura (TTP) was made on the basis of clinical presentation and lab findings. She was treated with corticosteroids and plasma exchange but with no major response.

CT abdomen and PET CT were suggestive of pancreatic carcinoma with extensive lymph nodal, organs and bone metastases. Supraclavicular lymph node biopsy was compatible with metastatic adenocarcinoma. As a result, the diagnosis of pancreatic cancer was established and the decision was for palliative treatment.

This case highlights the need to consider malignancy in patients with MAHA/TTP especially if it does not respond to plasmapheresis. Hence, the treatment of MAHA/TTP could be directed to the underlying malignancy if available.

Keywords: TTP, pancreatic cancer, plasmapheresis

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Introduction:

Cancer-related Microangiopathic hemolytic anemia is a rare complication of disseminated malignancy caused by a non-immune mediated hemolytic process affecting the small vessels causing micro-thrombi formation that would lead to red blood cells and other blood cells injury. It can present alone or as part of thrombotic thrombocytopenic purpura-like syndrome which is characterized by a microangiopathic hemolytic anemia and thrombocytopenia caused by reduced activity of ADMATS13 (a von Willebrand factor-cleaving protease). The estimated incidence of cancer-related MAHA is about 0.25 to 0.45 patients per million per year [1].

Most commonly, it affects patient with advanced stage cancer with gastric, breast and prostate cancers being the most common [1.]

Although therapeutic plasma exchange is the standard therapy for acquired TTP with a success rate of up to 80-90% [2], it is rarely effective in patient with TTP secondary to malignancy meanwhile, Chemotherapy might have some benefits managing these cases.

In this case, we had a female patient who presented with TTP and was found later on to have a pancreatic cancer.

Case presentation:

A 56-year-old Filipino female known to have only essential hypertension presented to the hospital complaining of progressive back pain for two weeks associated with generalized body weakness. She has had a history of easy bruising over her arms for a few days prior to presentation. She mentioned history of subjective fevers associated with un intentional weight loss. She denied any symptoms of upper respiratory tract infection, any gastrointestinal or other neurological symptoms.

Vitally she had a fever of 38.3 and tachycardia with normal blood pressure and respiratory rate. On physical examination, she had severe pallor with multiple petechiae all over her body. her neurological examination however was completely unremarkable.

Her initial laboratory tests showed normocytic anemia with hemoglobin of 6.6 g/dl , thrombocytopenia of 33 x10^3/μL (normal range 150-400 x10^3/μL) and reticulocytes count of 4.1% (normal range 0.5–2.5%), Lactate Dehydrogenase > 1800 (normal range 135–225 U/L), Total bilirubin 33 (normal range 0–21 μmol/L), Haptoglobin <10 mg/dl (normal range 30–200 mg/dl), Creatinine 44 (normal range 44–80 μmol/L), ALT 71 (normal range 0–33 IU/l) , AST 57 (normal range 0–33 IU/l), PT 11.9 seconds (normal range 9.7–11.8) ,PTT 26.0 seconds (normal range 24.6–31.2 seconds) and the direct antiglobulin test was negative. Peripheral smear showed low erythrocytes and platelets count with features suggestive of microangiopathic hemolysis (basophilic stippling, many scattered macro-ovalocytes, some tear drop cells, spherocytes and prominent schistocytes).

An initial diagnosis of thrombotic thrombocytopenic purpura (TTP) was established although it could be considered as MAHA with thrombocytopenia apart from TTP. The patient was treated with steroids and plasmapheresis with insignificant improvement, as defined by persistent low platelets count and hemoglobin with the presence of schistocytes in peripheral smear.

Bone marrow biopsy showed signs of metastatic carcinoma. CT abdomen was done to rule out possible epidural abscess as she came with back pain and fever, however it showed Extensive retroperitoneal lymphadenopathy including the inguinal lymphadenopathy, possibly inflammatory/ neoplastic and apparently bulky pancreas. PET CT was more suggestive of pancreatic carcinoma with extensive lymph nodal, pulmonary, liver, pleural, peritoneal and bone metastases. Left supraclavicular lymph node biopsy was suggestive of metastatic adenocarcinoma, compatible with metastasis from pancreaticobiliary or upper gastrointestinal tract source. Multidisciplinary team discussion was held and the patient was deemed suitable only for best supportive and palliative care. The patient eventually developed Disseminated Intravascular

Coagulopathy (DIC) and passed away 24 days from admission to the hospital.

Discussion:

Microangiopathic hemolytic anemia (MAHA) is a non-immune mediated hemolytic process caused by a physical blockage of the small blood vessels by fibrin micro-thrombi which affects the blood cells and lead to damage of red blood cells and formation of schistocytes (one of the main features of this disorder besides negative direct antiglobulin test (DAT) with laboratory features of intravascular hemolysis such as increased indirect bilirubin, high lactate dehydrogenase and low haptoglobin). This process might be associated with thrombocytopenia as part of a range of disorders which are commonly termed as “thrombotic microangiopathy” that includes thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and other disorders. TTP is classically described as a constellation of MAHA, thrombocytopenia, fever, renal injury and neurologic symptoms however this presentation is rare and most commonly TTP patients will present with MAHA and thrombocytopenia only [3]. The pathophysiology is lack of a protease that is responsible of cleavage of von Willebrand large multimers to prevent excessive thrombosis. The protease is called ADAMAT 13 and it could be absent congenitally or acquired. Severe deficiency of ADAMT 13 of less than 5 % is specific for idiopathic TTP. It affects 3 people per one million adults per year in the United States according to Oklahoma TTP-HUS Registry [4]. It might be associated with systemic disorders such as autoimmune diseases, bacterial infections, HIV, pancreatitis, cancers, some drugs or pregnancy. TTP is considered a life-threatening hematologic disorder and without treatment most of the patients will die within 10 to 14 days from the time of diagnosis [5].

Cancer-related microangiopathic hemolytic anemia is a rare complication of a disseminated malignancy. The pathogenesis is not well understood, some cases are related to the primary tumor while others might be an adverse event of cancer therapy. It might present as MAHA alone or as part of TTP/HUS-like syndrome [6]. In these cases, malignant cells are accused of causing small vessels obstruction with thrombosis and so lead to blood cell damage [7]. In a recent systematic review involving 168 patients with cancer related MAHA, gastric, breast, prostate, lung and cancer of unknown origin were the most common with 44, 36, 23, 16, 12 cases respectively. In this study, pancreatic cancer was found in only three cases. Only 11 cases presented with TTP-like clinical picture and 26 cases presented with HUS-like clinical picture [1].

The Oklahoma TTP-HUS registry followed 351 patients diagnosed with TTP or HUS and 10 patients were found later on to have malignancy with 2 cases of lung non-small cell carcinoma, 2 cases of breast cancer, 1 case of renal cell carcinoma, Kaposi's sarcoma, Non-Hodgkin lymphoma and 1 case of pancreatic carcinoma [8].

Upon searching the literature for pancreatic cancer associated MAHA/TTP, we found 3 cases [8,9,10]. The first case was for a 73-year-old male with no known history of malignancy who presented with generalized weakness and confusion, his hematocrit was 19%, platelet count was 17000/μL, managed as TTP with plasmapheresis before he was diagnosed with pancreatic cancer by bone marrow biopsy and he passed away 2 days after the diagnosis [8]. The second case is of a 39-year-old female with a known pancreatic cancer, she was admitted with normal hemoglobin of 13 g/dL and moderate thrombocytopenia of 44000/μl, then she developed a drop in hemoglobin and platelet count to 7000/μL, she was managed as TTP but they started chemotherapy (gemcitabine) immediately, she improved and after cycles of chemotherapy she was discharged home [9]. The 3 cases are summarized in the table below.

Conclusion:

Microangiopathic hemolytic anemia can be a first presentation of disseminated malignancy as MAHA alone or as part of thrombotic thrombocytopenic purpura. The standard therapy with plasmapheresis and steroids might not be effective but targeted therapy for the malignancy might

lead to complete resolution of the disorder. The main challenge is to find the primary source of the malignancy and apply the treatment which is usually delayed and the nature of these disorders necessitate a rapid response to avoid the poor outcome.

Year	Age	M/F	Known to have cancer	MAHA/TTP	Method of cancer diagnosis	Plasmapheresis	Chemotherapy	Clinical course
1998	73	M	No	TTP	Bone Marrow Biopsy	Yes	No	Death
2003	39	F	Yes	TTP	_	No	Gemcitabine	Discharged
2019	56	F	No	TTP/MAHA	Bone Marrow Biopsy	Yes	No	Death

Conflict of interest:

The authors declare that there was no conflict of interest with regard to the publication of this case report

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