Annals of Clinical Case Reports

Case Series
Published: 26 Aug, 2019

Thrombotic Microangiopathy Secondary to a Mucinous Cystic Neoplasm of the Pancreas

Podrug Kristian[1], Perko Zdravko[1,2], Rogosic Veljko M[1,3], Vedran Kovacic[1], Mikacic Marijana[1], Alicic Damir[1], Martinic Roko[1] and Nincevic Zeljko[1,4]*

[1]Department of Internal Medicine, University of Split, Croatia

[2]Department of Surgery, University Hospital Center Split, Croatia

[3]Department of Ophthalmology, University Hospital Center Split, Croatia

[4]Department of Anesthesiology and Intensive Care, University Hospital Center Split, Croatia

Abstract

Thrombotic Microangiopathy (TMA) is a group of disorders characterized by disseminated occlusive microvascular thrombosis, microangiopathic hemolytic anemia and thrombocytopenia. Classic TMA is Thrombotic Thrombocytopenic Purpura (TTP), but TMA in some cases could be associated with malignancy. Tumor associated TMA was infrequent correlated with benignant proliferation. We report a case a 27-year-old woman with thrombotic microangiopathia syndrome associated with noninvasive mucinous cyst of the pancreas. After surgical removal of the cyst, repeated laboratory evaluations were completely normal. We concluded that mucinous cyst of the pancreas was source of endothelial damage with presented as microangiopathic hemolytic anemia and thrombocytopenia. S lower and more variable response to the therapeutic plasmapheresis emphasizes this presumption. Despite reported cases of TMA in malignant pancreatic lesions, this case report is very first published case of benignant pancreatic cystic tumor connected with some type of thrombotic microangiopathy. Treatment for the underlying tumor is treatment of choice for tumor-associated TMA.

Keywords: Microangiopathic hemolytic anemia; Thrombocytopenia; Pancreatic cyst

Key Points

1. Thrombotic microangiopathy could be associated with tumor.
2. Treatment for the underlying tumor is treatment of choice for tumor-associated thrombotic microangiopathy.

Introduction

Thrombotic Microangiopathy (TMA) is a descriptive term for the characteristic pathological findings in a group of disorders characterized by disseminated occlusive microvascular thrombosis, thrombocytopenia, and ischemic end-organ damage, most commonly in kidneys and brain. TMA represents a final common pathway of a multitude of clinical syndromes. Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP) are the two main clinical entities including in TMA syndromes [1]. Despite of TTP and HUS, TMA could be induced by many other possible factors, as drugs, collagen vascular diseases, infections, stem cell transplantation, and malignancies. Common clinical features of TMA syndromes (including TTP, Shiga toxin-mediated HUS or complement-mediated HUS) are microangiopathic hemolytic anemia and thrombocytopenia [2], with classic clinical findings as fever, neurologic and renal dysfunction [3]. Typical clinical feature of HUS is renal failure, but in TTP renal involvement is milder, while neurological symptoms predominate. A consequence of erythrocytes fragmentation during passing through clogged arterioles with reduced lumen to 'pin-point size', is mechanical red cell destruction by intra-luminal shearing, presented as a Coombs-negative hemolytic anemia with an elevated schistocyte count. The pathological features include microvascular thrombi with obstruction and endothelial swelling. Typical TTP is idiopathic condition; also in some rare of thrombotic microangiopathy was demonstrated in association with malignant proliferation, and well recognized at the terminal stage of cancer, considered pivotally caused by mechanical obstruction of the vascular lumen by tumor cell emboli [4]. This cancer-associated TMA is a paraneoplastic

OPEN ACCESS

Correspondence:
Vedran Kovacic, Department of Internal Medicine, Intensive Care Unit, University of Split, Spinciceva 1, 21220 Split, Croatia, Tel: 38521557458; Fax: 38521557266;
E-mail: vedran.kovacic.split@gmail.com

Received Date: *27 Jul 2019*
Accepted Date: *21 Aug 2019*
Published Date: *26 Aug 2019*

Citation:
Kristian P, Zdravko P, Rogosic Veljko M, Kovacic V, Marijana M, Damir A, et al. Thrombotic Microangiopathy Secondary to a Mucinous Cystic Neoplasm of the Pancreas. Ann Clin Case Rep. 2019; 4: 1707.

ISSN: 2474-1655

syndrome characterized by Coombs-negative hemolytic anemia with schistocytes and thrombocytopenia. One report [5] demonstrated only 35% patients and other report [6] demonstrated 78% patients initially diagnosed with TTP before systemic malignancy was subsequently discovered. As opposed to classical idiopathic TTP, patients with TMA and disseminated malignancy had a longer duration of symptoms, higher lactate dehydrogenase levels, and more often failed to respond to plasma exchange treatment [7]. Despite clear correlation between malignant processes and TMA, TMA was infrequent correlated with benignant proliferation. We report a first described case of TMA associated with noninvasive mucinous cyst of the pancreas.

Case Presentation

We report a case of a 27-year-old woman with thrombotic microangiopathia syndrome presented at hospital admission with jaundice, pallor, dark urine output, tiredness, weakness, and bilateral lumbal pain without fever. She complained on those signs for the last few days before admission. She was taking the medication for epilepsy chronically (lamotrigine). In her family a case of malignant lymphoma was recorded (father of the patient). Clinical examination revealed only weakness, pallor and jaundice, without purpura-like skin efflorescence and without any neurologic disturbances. Laboratory evaluation at admission showed slight hemolytic anemia (hemoglobin level 111 g/L, reticulocyte count was 14.0%), thrombocytopenia (platelet count 69×10^9/L) and normal blood nitrogen compounds. Other laboratory findings were: serum haptoglobin <0.12 g/l, lactate dehydrogenase 1993 UI/l, total bilirubin 116 μmol/L (direct 94 μmol/L), Aspartate Aminotransferase (AST) 95 U/L, Alanine Aminotransferase (ALT) 29 U/L and Alkaline Phosphatase 66 UI/L. Activated partial thromboplastin time and prothrombin time were normal. Plasma electrolytes levels were normal. Direct and indirect Coombs' tests were negative. A peripheral blood smear study demonstrated the presence of schistocytes. As a pattern of microangiopathic hemolytic anemia and thrombocytopenia was established, diagnosis of TTP was presumed, so immediately plasma exchange therapy on daily bases *via* central line was started concomitant with systemic steroid therapy. Totally, 17 sessions of plasma exchanges was conducted, and subsequently, with variable success, platelet count and LDH were restored at the normal ranges, meanwhile process of hemolysis was partially stopped with consequently normalization of hemoglobin concentration. Despite good response, a serial of peripheral blood smear revealed constant presence of schistocytes. Concomitantly, set of laboratory and imaging investigations were performed to potentially reveal secondary etiology of microangiopathic hemolytic anemia and thrombocytopenia, as in our institution ADAMTS 13 plasma activity cannot be determined. Chest X-ray, laboratory panel for viruses (HBV, HCV, HIV), panel for immune system serology (ANA, anti-dsDNA, SS-A/Ro, Anti SS-B/La, ACA-CentB, aCL-IgM, aCL-IgG, PR3-ANCA, MPO-ANCA), oncomarkers (beta HCG, CA15-3, CA125, CEA, CIFRA 21-1), electrophoresis of serum proteins, serum light chains kappa and lambda, IHA for Echinococcus antigen were at the normal ranges. Investigations of serum oncomarkers CA19-9 and NSE demonstrated higher values. Finally, ultrasound scan of the abdomen find out a cyst sized about 80 mm in diameter with dense content within, placed in region of pancreatic trunk. Computed Tomography (MSCT) abdominal scan confirmed this finding and revealed in region of pancreatic trunk and tail a cystic formation (sized 88 mm × 82 mm × 65 mm) with just slight opacification of blood vessels. Finally, Magnetic Resonance Imaging (MRI) abdominal scan demonstrated the septated cystic formation with irregular cyst wall. Despite presence of schistocytes, we stopped plasma exchange sessions, and the patient was referred to abdominal surgeon and subsequently distal pancreatotomy with splenectomy was performed. There was no evidence of involvement of other abdominal organs. Finally, pathohistological examination of received material proved noninvasive mucinous cyst of the pancreas with moderate grade cell dysplasia (Neoplasma cysticum mucinosum pancreatis). After surgical removal of the cyst, repeated laboratory evaluations of her blood in next 3 months were completely normal, with no detectable presence of schistocytes in blood smears. We concluded that mucinous cyst of the pancreas was source of endothelial damage with consecutively Thrombotic Microangiopathy (TMA) presented as microangiopathic hemolytic anemia and thrombocytopenia, with no evidence of ischemic end-organ damage. Slower and more variable response to the therapeutic plasmapheresis emphasizes this presumption.

Discussion

We reported interesting case of TMA correlated with benignant mucinous cystic lesion of the pancreas. Benignant tumors correlated with TMA were extremely rarely reported. Despite few previously reported cases of TMA in malignant pancreatic lesions, this case report is very first published case of benignant pancreatic cystic tumor connected with some type of thrombotic microangiopathy.

Generally, Thrombotic Microangiopathy (TMA) is kind of microvascular thrombosis with intraluminal platelet thrombi leading to some degree of the vessel lumen occlusion. Possible clinical manifestations of thrombotic microangiopathy are TTP, HUS (Hemolytic Uremic Syndrome), and HELLP Syndrome (Hemolysis with Elevated Liver Enzyme Levels and Low Platelets), consecutively with multiorgan disease, and typical with neurologic, kidney and cardiac symptoms. For diagnosis of TTP and other types of thrombotic microangiopathes, essential features are thrombocytopenia with nonimmune (Negative Antiglobulin Test) microangiopathic hemolytic anemia (occurrence of schistocytes as red blood fragments, high reticulocyte count, elevated LDH, indirect bilirubin, and low haptoglobin blood concentration) [8].

Pivotal role of Von Willebrand factor (VWF) in pathogenesis of idiopathic TTP is well recognized. VWF is synthesized in endothelial cells and in blood is typically present as large multimers cleaved in the circulation into smaller multimers of VWF by a VWF cleaving protease (metalloproteinase called ADAMTS13). TTP is caused by the deficiency of ADAMTS13, which results in the accumulation of unusually large VWF multimers, which then causes platelet agglutination and microvascular thrombi [9]. In congenital type of TTP are recognized inborn ADAMTS13 changes, resulting in incapability of cleaving large VWF multimers which are consecutively accumulated and lead to the platelet aggregation with microthrombosis. Acquired kind of ADAMTS13 deficiency are correlated with malignancies (and cancer therapy), liver failure, chronic inflammation, pregnancy, and disseminated intravascular coagulation. If TTP could be demonstrated, nevertheless ADAMTS13 deficiency is acquired or congenital; the ADAMTS13 activity is typically less of 5% normal activity [5]. This severe deficiency of ADAMTS13 (<5% of normal) has been proposed as the key pathogenetic factor for idiopathic TTP [10]. In malignant patients is reported higher ADAMTS13 activity (Median value was 50%, range, 13% to 100%) [7].

Cancer-Induced TMA

Cancer-associated thrombotic microangiopathy refers to a group of disorders characterized by microvascular thrombosis, thrombocytopenia, and possible ischemic end-organ damage. Systemic metastatic cancer can cause severe microangiopathic hemolytic anemia and thrombocytopenia that may be indistinguishable from TTP, with the exception of prostate cancer, where aHUS was a common presentation [11].

Many cases of cancer-related microangiopathic hemolytic anemia are reported (mostly breast, lung, and stomach cancer) [12], especially in metastatic disease [13,14], and in metastatic disease of mucin-producing adenocarcinomas [15,16]. Various types of malignant disease were reported associated with TMA: gastric cancer, colon cancer, squamous cell carcinoma of anal canal, metastatic appendiceal carcinoma, breast cancer, lung cancer (adenocarcinoma, squamous cell carcinoma, and small cell lung cancer), prostate cancer, ovarian cancer, renal cell carcinoma, seminal vesicle tumor, hepatobiliary cancers, hepatocellular carcinoma, pancreatic cancer, cholangiocarcinoma, multiple endocrine neoplasia type 1, pheochromocytoma, neuroendocrine tumor, prolactin producing pituitary adenoma, Kaposi sarcoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia, myelodysplastic syndrome, Hodgkin lymphoma, and multiple myeloma [17]. Lechner et al. [11] demonstrated 154 cases of TMA associated with solid cancer (gastric, breast, prostate, and lung) and 14 with lymphoma (Hodgkin disease, angiotropic lymphoma, diffuse large cell lymphoma, and myeloma). Adenocarcinoma was the most common histopathological subtype in patients with cancer-associated TMA, 91.8% of cancers were metastatic, and in 19.4% solid cancers, and gastric carcinoma was the most common type (26.2%), followed by breast (21.4%), prostate (13.7%), and lung cancer (9.5%). In the vast majority (81.1%) of evaluable cases, bone marrow infiltration with cancer cells was documented by bone marrow biopsy or at autopsy. Bone marrow infiltration was sometimes associated with bone marrow necrosis or fibrosis. In the vast majority of cancer patients, ADAMTS 13 was above 20%.

Most cases of cancer-associated TMA have been reported in patients with mucin-producing adenocarcinoma and in those with disseminated malignancies. Cancer-associated TMA was also been described in cases with tumor invasion of the bone marrow [18]. Lohrmann et al. [18] determined that 5.7% of patients with metastatic carcinoma have TMA. A case with TTP and multiple endocrine neoplasia type I, with two islet cell tumors, adrenal adenoma, pituitary adenoma, and bronchial carcinoid with liver metastasis also was demonstrated [19].

The pathogenesis of cancer-associated TMA is poorly understood [20], and different from the mechanism of idiopathic TTP. Two main possible group of cancer-associated TMA is chemotherapy and cancer itself (especially in cases with bone marrow invasion or secondary myelofibrosis) [21]. Mechanisms proposed in development of cancer-associated TMA include angiogenesis, systemic microvascular metastases, tumor growth, bone marrow metastasis or necrosis, secondary myelofibrosis and endothelial damage as a complication of chemotherapy [22]. Chemotherapy-induced TMA in malignant patients could be antibody mediated or dose dependent. The occurrence of TMA with bone marrow necrosis (necrosis of myeloid tissue and medullary stroma with preservation of bone) associated with lung cancer has also been reported as the first manifestations of a lung cancer [23] or as the first manifestation of disseminated colon cancer [24]. Aggregates of cancer cells, which may cause mechanical obstruction, could be found in bone marrow necrosis in metastatic carcinoma [25]. Generally, cancer-associated TMA occurs most often in patients with known metastatic cancer, but TMA is possible also in nonmetastatic malignant disease or be the presenting features of occult cancer. Although occult malignancy associated with TMA is uncommon, it is an important consideration in the evaluation of patients with TMA. If cancer-induced TMA is considered, a bone marrow biopsy is appropriate. Documentation of malignant cells in the marrow provides the diagnosis.

One of considered hypotheses in cancer-associated TMA is injury to the endothelial cells of vessels in bone marrow by direct tumor invasion. Mechanisms of endothelial injury in the bone marrow could be correlated with abnormal angiogenesis, aggressive tumor growth and secondary myelofibrosis [26]. Above mentioned mechanisms can cause accumulation of large VWF, this could result in release of ultra large VWF multimers, and together with a possible decrease of ADAMTS13 (possible because formation of autoantibodies against ADAMTS13 in advanced cancer), may contribute to the aggregation of platelets [27]. Despite proposed mechanisms, in most cancer-associated TTP, ADAMTS13 activity and the multimers of vWf are mostly normal (the median value of ADAMTS13 activity is 50% in those with cancer-associated TMA) [28]. Only three of eight cases of TTP related to disseminate cancer have a suboptimal level of ADAMTS13 [29]. Another possible mechanism of cancer-associated TMA is endothelial damage generated by tumor cell emboli with an enhanced release of ultra-large von Willebrand factor (VWF) multimers from endothelial cells and consecutively platelet aggregation and red blood cell fragmentation due to contact with intraluminal thrombi [30]. This has been observed with diffuse microscopic pulmonary involvement [31]. Visceral microthrombi involved arterioles and capillaries of the heart were demonstrated in some cases [19]. A case with metastatic breast cancer and carcinocythemia with thrombotic microangiopathy was demonstrated, and proposed mechanisms of TMA was direct contact between erythrocytes and circulating carcinoma cells found at blood smear examination as well as tumor emboli with fibrin thrombi in small blood vessels observed at autopsy [32]. Microangiopathic hemolytic anemia and thrombocytopenia with microvascular clusters of breast cancer cells in lungs and in other organs, including the bone marrow also was demonstrated [33]. Proposed mechanisms of TMA in these cases are systemic arteriolar and capillary obstructions by tumor cells, so high shear rates of blood passing through obstructions result in fragmentation of the red cells with possible platelet consumption in the tumor emboli [34]. Some cases of lymphoma-associated TMA are immune mediated, and ADAMTS 13 antibodies were detected [11].

The effect of mucin on endothelial dysfunction has also been proposed as a mechanism for the development of cancer-TMA. Cancer-associated TTP has been mostly observed in mucin-producing adenocarcinomas (stomach, breast, colon, and lung), so mucin is proposed to have effect on the endothelial cells causing them to change their function and increases the production of large VWF multimers [35].

Despite well documented association of malignant tumors with TMA, extremely rare occurrence of TMA with nonmalignant lesions was recognized. A report of prolactin-secreting pituitary adenoma accompanied with thrombotic thrombocytopenic purpura (revealed as PAS-positive and von Willebrand factor-positive microthrombi

in the arterioles and capillaries of many organs, mainly in the heart and brain) was demonstrated [36]. High prolactin levels may be a risk factor for TMA [37]. A case of microangiopathic hemolytic anemia without thrombocytopenia associated with recurrent pulmonary emboli and benign pelvic tumors also was described [38]. A case of microangiopathic hemolytic anemia and thrombocytopenia was reported in woman with ovarian borderline serous tumor [39].

Our reported patient belongs to the very small group of TMA correlated with benignant tumors, and is the first reported case of benignant cystic lesion of the pancreas associated with TMA. Malignant tumors of pancreas were well documented factors for TMA development. Also, there were few reports of TMA connected with acute pancreatitis (pancreatitis may occur from TTP or, in a few cases, may trigger TMA) [40].

In accordance with previously reported mucin-producing adenocarcinomas associated with TMA and assumed role of mucin in endothelial damage, we hypothesized that mucinous structure of the cyst of our patient was the pivotal risk factor for TMA development.

In previously reported plenty of cases of TMA associated with solid cancer, majority of patients did not show clinical features of TTP or HUS, only mild signs of cerebral dysfunction and/or renal abnormalities could be demonstrated [11]. Similarly, our case also was without any signs of renal or cerebral dysfunction.

The treatment of choice for classic TTP remains plasma exchange therapy to remove the multimers of VWf and possible autoantibodies on ADAMTS13. Despite absence of organ dysfunction in our case, the presence of thrombocytopenia and microangiopathic anemia are accepted as sufficient to establish an initial diagnosis of TTP to introduce plasma exchange as an effective treatment modality [41], so plasma therapy with variable success was immediately started. Despite good results of plasma exchange in treatment of idiopathic TTP, in cancer-associated TMA the role of plasma exchange should be re-evaluated [42]. TMA associated with tumor generally fails to respond to plasma therapy. Plasma exchange and immunosuppression therapy is not helpful in cancer-associated TTP, possible because of the lack of deficiency of ADAMTS13 which may explain the poor response to the plasma exchange. An exception is TMA associated with prostate cancer, where it is demonstrated good response to plasma exchange. On contrary, classic TTP demonstrates excellent respond with rapid reversal of neurologic symptoms, with reduction of LDH levels over 1 to 2 days and rise in platelet counts over 3 to 4 days. Our case need 17 plasma exchange sessions in to normalize platelets number, despite constant presence of schistocytes in blood smears. Only surgical removal of tumor completely resolved ominous laboratory findings of microangiopathic anemia. Effective treatment of the underlying tumor can be crucial in the management of cancer-associated TMA. Early institution of appropriate chemotherapy for systemic malignancy and avoidance of drugs associated with TMA are the most important management principles [43].

Platelet transfusion should generally be avoided in patients with any kind of TTP (platelet transfusion can cause severe exacerbations secondary to increased microvascular thrombi formation), and consecutively platelet transfusion is not reasonable treatment choice neither in tumor associated TTP [44].

Conclusion

Patients with TTP/TMA who do not initially respond to plasma exchange must be scrutinized suspecting an underlying tumor, so clinical and radiological work-up should be initiated despite introduction of plasma exchange therapy. As plasma exchange is associated with major complications, deferral of plasma exchange for additional diagnostic evaluation is appropriate in cases with previously known malignancy [45].

Normal plasma ADAMTS13 activity could be marker of secondary TTP or TMA. A severe ADAMTS13 deficiency (activity <10%) defines TTP. The higher LDH values, coagulation abnormalities and abnormal liver function suggest cancer-associated TMA rather than TTP.

Treatment of underlying disease in TMA, especially in tumor associated TMA should improve sinister clinical course of TMA. Cancer-induced TMA have an extremely poor prognosis, a report of median survival was only 3 days [46], but rare case of noninvasive tumors associated with TMA could be completely resolved surgically.

In a patient with TMA, despite early initiation of plasma exchange treatment, search for malignancy (including bone marrow biopsy) is mandatory, especially when patient presumed as TTP have atypical clinical features (no clear organ dysfunctions) or week respond to plasma exchange. In patient with microangiopathic hemolytic anemia and thrombocytopenia, poor respond to plasma therapy could be an evidence of possibility of some neoplasm existence. Ultimate treatment for the underlying tumor that resulted in TMA is surgical treatment or chemotherapy.

References

1. Moake JL. Thrombotic microangiopathies. N Eng J Med. 2002;347(8):589-600.
2. Corrigan JJ, Boineau FG. Hemolytic-uremic syndrome. Pediatr Rev. 2001;22(11):365-9.
3. Rock GA. Management of thrombotic thrombocytopenic purpura. Br J Haematol. 2000;109(3):496-507.
4. Antman KH, Skarin AT, Mayer RJ, Hargreaves HK, Canellos GP. Microangiopathic hemolytic anemia and cancer: A review. Medicine. 1979;58(5):377-84.
5. Vesely SK, George JN, Lammle B, Studt JD, Alberio L, El-Harake MA, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood. 2003;102(1):60-8.
6. Levandovsky M, Harvey D, Lara P, Wun T. Thrombotic thrombocytopenic purpura hemolytic uremic syndrome (TTP-HUS): a 24-year clinical experience with 178 patients. J Hematol Oncol. 2008;1:23.
7. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. Oncologist. 2007;12(1):11-9.
8. Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int. 2001;60(3):831-46.
9. George JN. The role of ADAMTS 13 in the pathogenesis of thrombocytopenic purpura-hemolytic uremic syndrome. Clin Adv Hematol Oncol. 2005;3(8):627-32.
10. Bianchi V, Robles R, Alberio L, Furlan M, Lämmle B. Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura. Blood. 2002;100(2):710-3.

11. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore). 2012;91(4):195-205.

12. Chang JC, Naqvi T. Thrombotic thrombocytopenic purpura associated with bone marrow metastasis and secondary myelofibrosis in cancer. The Oncologist. 2003;8(4):375-80.

13. Perkovic V, Came NA, Grigg AP, Becker GJ. Haemolytic uraemic syndrome and prostatic cancer. N Z J Med. 1999;29:383-4.

14. Arkenau HT, Mussig O, Buhr T, Jend HH, Porschen R. Microangiopathic hemolytic anemia (MAHA) as paraneoplastic syndrome in metastasized signet ring cell carcinomas: Case reports and review of the literature. Z Gastroenterol. 2005;43(8):719-22.

15. Pirrotta MT, Bucalossi A, Forconi F, Bocchia M, Mazzotta S, Sammassimo S, et al. Thrombotic thrombocytopenic purpura secondary to an occult adenocarcinoma. Oncologist. 2005;10(4):299-300.

16. von Bubnoff N, Sandherr M, Schneller F, Peschel C. Thrombotic thrombocytopenic purpura in metastatic carcinoma of the breast. Am J Clin Oncol. 2000;23(1):74-7.

17. Govind Babu K, Bhat GR. Cancer-associated thrombotic microangiopathy. Ecancermedicalscience. 2016;10:649.

18. Lohrmann HP, Adam W, Heymer B, Kubanek B. Microangiopathic hemolytic anemia in metastatic carcinoma. Report of eight cases. Ann Intern Med. 1973;79(3):368-75.

19. Kouides PA, Phatak PD, Cramer SF. Fatal thrombotic thrombocytopenic purpura (TTP) presenting concurrently with metastatic endocrine neoplasia (MEN) type I. Hematopathol Mol Hematol. 1996;10(3):161–70.

20. Forman RB, Benkel SA, Novik Y, Tsai HM. Presence of ADAMST13 activity in a patient with metastatic cancer and thrombotic microangiopathy. Acta Haematol. 2003;109(3):150-2.

21. Spoormans I, Altintas S, Van den Brande J, Luijks A, Vermorken JB. Purpura in a patient with disseminated breast cancer:a rapidly progressive cancer-related thrombotic thrombocytopenic purpura. Ann Oncol. 2008;19(6):1204-7.

22. Raife TJ, Lager DJ. Chronic thrombotic microangiopathy associated with antineoplastic therapy with minimal hematologic effects. Mayo Clin Proc. 2002;77(4):323-8.

23. Sevinc A, Kalender ME, Pehlivan Y, Sari I, Camci C. Thrombotic thrombocytopenic purpura and bone marrow necrosis as the initial presentation of lung cancer. Clin Appl Thromb Hemost. 2007;13(4):449-52.

24. Lee JL, Lee JH, Kim MK, Cho HS, Bae YK, Cho KH, et al. A case of bone marrow necrosis with thrombotic thrombocytopenic purpura as a manifestation of occult colon cancer. Jpn J Clin Oncol. 2004;34(8):476-80.

25. Janssens AM, Offner FC, Van Hove WZ. Bone marrow necrosis. Cancer. 2000;88(8):1769-80.

26. Gonzalez N, Rios E, Martin-Noya A, Rodríguez JM. Thrombotic thrombocytopenic purpura and bone marrow necrosis as a complication of gastric neoplasm. Haematologica. 2002;87(1):ECR01.

27. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med. 1998;339(22):1585-94.

28. Fontana S, Gerritsen HE, Kremer Hovinga J, Furlan M, Lämmle B. Microangiopathic haemolytic anaemia in metastasizing malignant tumours is not associated with a severe deficiency of the von Willebrand factor-cleaving protease. Br J Haematol. 2001;113(1):100-2.

29. Forman RB, Benkel SA, Novik Y, Tsai HM. Presence of ADAMTS13 activity in a patient with metastatic cancer and thrombotic microangiopathy. Acta Haematol. 2003;109(3):150-2.

30. Loreto MF, De Martinis M, Corsi MP, Modesti M, Ginaldi L. Coagulation and cancer: Implications for diagnosis and management Pathol Oncol Res. 2000;6(4):301-12.

31. Kane RD, Hawkins HK, Miller JA, Noce PS. Microscopic pulmonary tumor emboli associated with dyspnea. Cancer. 1975;36(4):1473-82.

32. Robier C, Neubauer M, Beham-Schmid C, Sill H. Thrombotic microangiopathy and disseminated intravascular coagulation associated with carcinocythemia in a patient with breast cancer. J Clin Oncol. 2011;29(34):e825-6.

33. Morton JM, George JN. Microangiopathic Hemolytic Anemia and Thrombocytopenia in Patients With Cancer. J Oncol Pract. 2016;12(6):523-30.

34. George JN. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. Oncology (Williston Park). 2011;25(10):908-14.

35. Brain MC, Azzopardi JG, Baker LR, Pineo GF, Roberts PD, Dacie JV. Microangiopathic haemolytic anaemia and mucin forming adenocarcinoma. Br J Haematol. 1970;18(2):183-93.

36. Kovacs K, Garvey MB. Thrombotic thrombocytopenic purpura associated with a prolactin-producing pituitary adenoma. Am J Hematol. 2003;74(1):55-9.

37. Mannucci PM, Canciani MT, Forza I, Lussana F, Lattuada A, Rossi E. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. Blood. 2001;98(9):2730-5.

38. Blau A, Kaplinsky N. Microangiopathic haemolytic anaemia associated with recurrent pulmonary emboli and benign pelvic tumours. Postgrad Med J. 1982;58(680):362-3.

39. Morris GJ, Yaeger HC, Hamm F, Irwin S, Scialla SJ. Microangiopathic Hemolytic Anemia in 57-year old Woman with Borderline Serous Tumor of the Ovary: Real Time Management of Common Pathways of Hemostatic Failure. Mediterr J Hematol Infect Dis. 2012;4(1):e2012030.

40. Muñiz AE, Barbee RW. Thrombotic thrombocytopenic purpura (TTP) presenting as pancreatitis. J Emerg Med. 2003;24(4):407-11.

41. George JN. How I treat patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. Blood. 2000;96(4):1223-9.

42. Werner T, Agarwal N, Carney H, Rodgers GM. Management of cancer accociated thrombotic microangiopathy: what is the right approach? Am J Hematol. 2007;82(4):295-8.

43. Arkenau HT, Müssig O, Buhr T, Jend HH, Porschen R. Microangiopathic hemolytic anemia (MAHA) as paraneoplastic syndrome in metastasized signet ring cell carcinomas: case reports and review of the literature. Z Gastroenterol. 2005;43(8):719-22.

44. de la Rubia J, Plumé G, Arriaga F, Carpio N, Sanz MA, Marty ML. Platelet transfusion and thrombotic thrombocytopenic purpura. Transfusion. 2002;42(10):1384-5.

45. McClain RS, Terrell DR, Vesely SK, George JN. Plasma exchange complications in patients treated for thrombotic thrombocytopenia purpura-hemolytic uremic syndrome. Transfusion. 2014;54(12):3257-9.

46. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. Oncologist. 2007;12(1):11-9.