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Thrombotic microangiopathy as a presentation of undifferentiated metastatic carcinoma, a case report

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Summary. Thrombotic microangiopathy (TMA) is a group of hereditary or acquired syndromes that shared clinical and pathological characteristics: microvascular thrombosis, thrombocytopenia and ischaemic end-organ damage. Thrombotic microangiopathy can be a manifestation of a subjacent disease as cancer, infection, auto-immune disease and others. Patients presenting cancer-related TMA have an extremely poor prognosis. We report a case of a 61-year-old man who was admitted for persistent lumbar pain. Results from imagiological exams showed multiple retroperitoneal lymph nodes suggestive of metastatic cancer. A sudden clinical episode with changes in mental and behavioral status and laboratory alterations consistent with TMA, were observed. A first strategy including plasma exchange and steroids was performed with no clinical response. The retroperitoneal lymph node biopsy revealed undifferentiated carcinoma of unknown primary and then, chemotherapy was started.

Key words: thrombotic microangiopathy, thrombotic thrombocytopenic purpura, cancer

Introduction

Thrombotic microangiopathy (TMA) is a group of hereditary or acquired syndromes that share clinical and pathological characteristics: microvascular thrombosis, thrombocytopenia and ischaemic end-organ damage (1). Haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura (TTP) are the two major subtypes. TTP is described by a pentad with thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), neurologic deficits, renal failure, and fever. This classic pentad is rarely observed and the two first symptoms are essential to diagnosis (2). TMA can be a manifestation of a subjacent disease as cancer, infection, auto-immune disease and others (1-3). TMA cancer-related is different to another causes: ADAMTS13 activity is normal and sparse response to plasma exchange occurs (1, 3).

Patients with cancer-related TMA need an urgent treatment to directed to cancer because the prognosis among these cases is extremely poor (3).

Case report

We present the case of a 61-year-old man, Caucasian, with an history of mesangioproliferative glomerulonephritis, arterial hypertension and obstructive sleep apnea, that was admitted for intense lumbar pain with 1 month of evolution and urinary symptoms, dyspepsia, night sweats and weight loss (4 kgs/1 month). Physical examination showed pain only in the lower quadrant of the abdomen. No alterations on blood analysis except reactive protein-C 11.7 mg/L (<3 mg/L). Urinalysis showed leukocyturia and proteinuria (1g/L). After, urinary culture revealed Enterobacter cloacae, ciprofloxacin-sensitive and antibiotherapy was started in a first approach. To characterize the pain, an abdominal computerized tomography (CT) was realized and showed "numerous retroperitoneal, retrocrural and celiac lymphadenopathies, being the largest with 22x17 mm". A biopsy of one lymphadenopathy was done. An upper and lower gastrointestinal endoscopy, thoracic CT, lumbar X-ray, scrotal, pelvic and prostatic ultra-

sound were performed, and no alterations were found. PSA total result was 0.240 ng/mL (<4). We excluded auto immune disease, sarcoidosis, tuberculosis, hepatitis B and C, Human Immunodeficiency Virus and other infectious diseases. Despite the treatment, the patient maintained lumbar pain. At day-19 he started with neurologic alterations (confusion, prostration and dysarthria), pallor of skin and mucous membranes. No alterations were reported in a head CT Scan. . Blood analysis showed the presence of anemia (hemoglobin 7.3 g/dL (reference values 13-18)); thrombocytopenia (platelets 88000 (150000-400000)); liver function alterations (Aspartate transaminase 75 U/L (10-37); alanine aminotransferase 97 U/L (10-37); gama glutamil transferase 84 U/L (10-49); total bilirubin 2.28 mg/dL (<1.2), direct bilirubin 0.45 mg/dL (<0.4); lactate dehydrogenase (LDH) 583 U/L (135-225); presence of schistocytes, haptoglobin <8 mg/dL (50-320), direct Coombs test negative. Therefore, a clinical diagnosis of TMA (microangiopathic hemolytic anemia, thrombocytopenia and neurologic disfunction) was stated. Plasma exchange and steroids were started. A neurological improvement with a hematological worsening was seen after 4 days of treatment. At this time, we had the result of biopsy that showed "morphological and immunohistochemical features compatible with metastasis of undifferentiated carcinoma". The discussion of the case was presented in a multidisciplinary team and it was decided to start chemotherapy with paclixel and carboplatin. The patient maintained worsening and best supportive care was performed. The patient passed away after 28 days.

Discussion

Thrombotic microangiopathy (TMA) is a group of different syndromes, hereditary or acquired, secondary to various systemic diseases, including cancer; with sudden or gradual onset; but with common clinical and pathological features. Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) are included. TTP is a syndrome consisting of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage secondary to microvascular thrombi. Classical pentad (MAHA, thrombocytopenia, fever, neurological and renal changes) are rarely present (5-40%) (1-3). MAHA and thrombocytopenia are universal and according to the new diagnostic criteria are those necessary for the diagnosis of PTT (3). Other situations have been reported where TMA is a manifestation of the underlying disease, such as cancer, infections, transplants, autoimmune diseases and severe hypertension (3, 4). Among the secondary causes, in the cancer-related TMA there are at least two entities: one induced by chemotherapy and another induced directly by cancer. The latter has a pathophysiology still largely unknown but different from the others TMA: tumor invasion, endothelial damage caused by abnormal growth and tumor angiogenesis. The response to plasma exchange in TMA related to cancer is sparse. The most frequently associated cancer are adenocarcinomas, essentially gastric, breast and lung. Although it may arise at an early stage, most of described cases are diagnosis in an advanced stage (4, 5).

There are no laboratory findings that confirm the TMA, and its diagnosis encompasses clinical history, physical examination and blood analyses with a peripheral blood smear (1-3). Symptoms related to thrombocytopenia such as hemorrhage and ecchymosis; neurological changes, fever and nonspecific symptoms may be present (pallor, myalgias, jaundice, fatigue; proteinuria and hematuria, abdominal pain, chest pain…). Thrombocytopenia is caused by the consumption of platelets in platelet-rich thrombi. Mechanical fragmentation of erythrocytes occurs when they pass into a partially occluded vessel, causing non-immune hemolytic anemia (presence of schistocytes in peripheral blood, decreased haptoglobin, reticulocytosis, and negative direct coombs test). The observed increase in LDH is explained by hemolysis and tissue ischemia. Coagulation tests presented normal values (1-5). In the case we report, patient was admitted for retroperitoneal adenopathies, probably as a result of metastases of an occult cancer. After the entire inconclusive study for the diagnosis of unknown cancer, and while waiting for the histological diagnosis, the patient presented a sudden onset of pallor with neurological alterations with no alterations in head CT, but with MAHA and thrombocytopenia. Given the absence of another clinical entity associated with TMA and a

diagnosis of metastatic carcinoma of unknown origin, the diagnosis of cancer-related MAT was the most probable diagnosis.

Cancer-related TMA is poorly responsive to plasma exchange and immunosuppression (less than 20% response), but this treatment is still recommended. In this entity, the treatment is essentially based on the treatment of the underlying cancer. In this clinical report, treatment with plasma exchange and steroids was started as a life-saving therapy, pending the definitive histological diagnosis. After the histological diagnosis, with no definitive characterization and a progressive clinical and analytical worsening, palliative chemotherapy was initiated, with no response. Cancer-related TMA is associated with a high mortality rate, so it is considered a medical emergency. With no treatment, the mortality associated is greater than 90%. The prognosis for these cases is extremely poor, with most patients passed away within a few weeks after diagnosis (4, 5). In the Lechner et al study nearly half of the 168 patients died within 1 month with or without treatment (4).

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