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Chemotherapy-provoked thrombotic microangiopathy in ovarian cancer patient with APS

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Abstract

The article analyzes a clinical case of the development of thrombotic microangiopathy in a patient with ovarian cancer during chemotherapy, which manifested in the form of renal failure. An analysis of laboratory and biochemical findings is given, which were initially incorrectly interpreted and only a kidney biopsy made it possible to make a correct diagnosis and begin pathogenetic treatment. Cancer patients are at increased risk for developing secondary TMA, which requires increased attention to symptoms uncharacteristic of the underlying disease.

Keywords: Cancer; Thrombotic microangiopathy; secondary TMA; Chemotherapy-associated TMA; Antiphospholipid Syndrome; ADAMTS13; Mitomycin C; Gemcitabine.

Introduction

Thrombotic Microangiopathy (TMA) is a rarity and a severe pathology rooted in systemic microvascular thrombosis. Thrombocytopenia and indications of microangiopathic hemolytic anemia are characteristic to TMA. Thrombotic Microangiopathy (TMA) occurs in 6-15% of cancer patients, and the risk of this complication increases with red bone marrow stem cell transplantation in patients with hematologic malignancies [1,2]. The onset of TMA can range from a few days to 34 months from initial exposure. Secondary TMAs that occur against the background of a damaging factor are much more common than primary ones [3].

Clinical Case

Patient O.65 years old, was admitted to the emergency department with complaints of facial swelling, weakness, headaches and increased blood pressure to 160/100 mmHg. The above complaints have been bothering the patient for a month; she did not consult a doctor, did not receive antihypertensive therapy, and relieved pain with Ketoprofen 100 mg per day.

The patient is constantly monitored at the oncology clinic with a diagnosis ovarian cancer (C56) IIA T2aN0M0. By decision of the medical oncology conciliumn, after surgery: extirpation of the uterus and appendages, the patient was prescribed treatment with Mitomycin C. But due to a pronounced allergic reaction and the presence of residual tumor nodes more than 1 cm, a change in therapy was made: has been recommended combination of Gemcitabine/Bevacizumab at a dosage of 15 mg/kg IV with an interval of 3 weeks for a total of 18-22 courses.

An examination 3 weeks before the onset of complaints revealed an increase in the blood creatinine to 121 μmol/l, a general urine test revealed proteinuria up to 1 g/day. She was sent for an ultrasound examination of the kidneys and abdominal organs, but she miss the appointment for the procedure.

On examination: The patient has a normosthenic build (BMI 24.6 kg/m^2). The skin and mucous membranes are icteric, body temperature is 36.9^{o}C. The pulse on palpation on the radial artery is satisfactory, rhythmic, heart rate 70-78 b.p.m., blood pressure 165/100 mmHg. Auscultation of the heart is normal, there are no pathological murmurs. The chest excursion is symmetrical during breathing, the RR is 16 per minute. There are no distant wheezes.

On palpation of the abdominal cavity: The abdomen is soft, painless in all parts, intestinal motility is determined, the Shchetkin-Blumberg sign is negative. Pasternatsky's symptom is negative on both sides. Urination is spontaneous, there are no signs of dysuria. The stool is regular, normal consistency.

Lab test results:

- Serum creatinine 155 μmol/l;
- Lactate dehydrogenase 440 units/l;
- Indirect bilirubin 40 μmol/l, Coombs test negative.
- Total protein- 61 g/l;
- Albumin- 34 g/l;
- Hemoglobin 82 g/l;
- Platelet level 150 *109/l;
- In urine analysis, daily proteinuria is up to 1.8 g, haptoglobin is not detected.

Ultrasound of the kidneys: No pathology was detected. ECG: Sinus rhythm, heart rate 75 per minute.

Based on complaints, anamnesis, laboratory and instrumental studies, a decision was made to admit to the nephrology department for further treatment and monitoring the dynamics of the condition with a diagnosis of «Unspecified renal failure. N19».

Therapy was prescribed: Diet with salt restriction, ACE inhibitor - enalapril 2.5 mg per day, diuretic - hydrochlorothiazide 25 mg. Antitumor therapy in the same regimen.

On the 2nd day of hospitalization, a deterioration in the patient's condition was noted - signs of acute kidney injury, increased jaundice of the skin, blood pressure readings 170/110 mm Hg, oliguria up to 750 ml of urine per day.

According to laboratory tests: hemoglobin level 75 g/l, hyperkalemia up to 5.9 μmol/l, acidosis - blood pH 5.9. General urine analysis: relative density 1.028, acanthocytes more than 5%, hyaline and granular casts, 5-10 red blood cells in the field of view.

Patient has been transferred to the intensive care unit. Therapy: Intravenous infusion of calcium gluconate 10% 20 ml, 20% glucose 500 ml + 40 IU of soluble human short-acting insulin IV drop 15-30 IU every 3 hours for 1-3 days, until the level of potassium in the blood normalizes. 5 mg enalapril to normalize blood pressure, furosemide 40-80 mg IV bolus, then 5-20 mg/hour IV through a perfuser (200-400 mg), transfusion of albumin, red blood cells and fresh frozen plasma.

On the 3rd day, there was an increase in creatinine in a biochemical blood test to 200 mmol/l, progression of proteinuria to 3.3 g per day and blood dysproteinemia, a decrease in the rate of hourly diuresis over the last 12 hours by 0.4 ml/kg/h, an increase metabolic acidosis, deterioration of condition - Glasgow scale 8 points. The amount of urine through the urinary catheter was 400 ml, a decision was made to carry out hemodialysis and artificial ventilation. Discontinue administration of furosemide.

On the 4th day, despite the therapy, a further increase in the level of creatinine, thrombocytopenia, and hemolytic jaundice was noted. A biopsy of renal tissue was taken with further histological examination: blood clots, mesangiolysis, edema of the glomerular vascular endothelium, and damage to the tubulo-interstitial apparatus of the kidney were visualized inside the glomeruli. ADAMTS13 metalloproteinase levels were found to decrease by up to 19% in the absence of anti-ADAMTS13 antibodies. VWF: Ag level was 193 IU/dL. Thus, the level of ADAMTS13 was reduced, and the level of vWF was at the upper limit of reference, which is typical for cancer patients receiving chemotherapy. The ratio of vWF and ADAMTS13 was shifted towards the persistence of ultra-large molecule of vWF, what could makes a significant contribution to the development of TMA.

The development of thrombotic microangiopathy was suspected, endothelial factors (endothelin, plasminogen activator inhibitor-1) were analyzed, and therefore a decision was made to perform pulse therapy: dexamethasone IV through a perfuser 56 mg per day and plasmapheresis. Maintenance therapy: antihypertensive, anticoagulant, etc. The antitumor drug Gemcitabine/Bevacizumab was discontinued.

On the 6th day, positive dynamics were noted, a decrease in acute kidney injury, normalization of

blood pressure, and stabilization of the patient's condition.

Taking into account the fact that TMA can also be associated with Antiphospholipid Syndrome (APS), the obstetric history was collected more carefully and it turned out that the patient had 2 episodes of pregnancy loss at 12 and 14 weeks. Then an analysis was carried out for the presence of circulating APA: Anticardiolipin, Anti-beta-2-glycoprotein-I antibodies and Lupus anticoagulants were found. That is, in addition to chemotherapy agents that could provoke the development of TMA, the patient also had a triple positive test for APS.

On the 10th day, the patient was transferred from the ICU to a multidisciplinary oncology center for further observation and treatment.

Discussion

Diagnosis of TMA is difficult, but indirectly suspecting this particular disease is helped by the patient's medical history with the presence of aggravating factors like cancer, especially mucinous adenocarcinoma, and taking medications, especially Mitomycin C, which, even after discontinuation, increases the body's sensitization to other antitumor drugs, such as Gemcitabine, Bleomycin, Cisplatin and other drugs used for malignant ovarian tumors [4].

According to the French study over 7 years, including 564 patients, 94% were diagnosed with secondary TMA: in 19% of cases, malignant neoplasms were the main cause, and in 26%, TMA was caused by drugs [5]. The greatest influence on the development of TMA was exerted by drugs such as calcineurin inhibitors, Gemcitabine (which was used as a component of antitumor therapy for the treatment of ovarian malignancy in our case) and a vascular endothelial growth factor inhibitor. In this study, 61% of those observed were diagnosed with TMA due to the combined effects of damaging factors in the form of malignancy and antitumor therapy.

In our case, several clinical features indicate the development of secondary TMA during the use of chemotherapy: the close temporal relationship between the use of antitumor drugs and the onset of symptoms suggests that chemotherapy was a trigger for the development of TMA.

It is worth noting that chronic renal failure associated with TMA has no diagnostic criteria and has been poorly studied to date. It is likely that the use of several treatment regimens for malignant processes is a prerequisite for the occurrence of TMA, leading not only to chronic, but also to acute kidney injury [6].

Clinical manifestations are nonspecific for a particular disease, but the main pathologies are identified in the form of hemolytic anemia, thrombocytopenia, thrombus formation in the microvascular stream and failure of any organ, most often the kidneys and heart [7,8]. In connection with the clinical manifestations listed above, it is worth focusing on such laboratory indicators as the level of creatinine, indirect bilirubin, lactate dehydrogenase and Coombs test, as well as daily proteinuria in a general urine test. Ultrasound examination is informative in case of chronic renal failure; in case of acute kidney damage, no pathology may be observed.

Reduced levels or activity of ADAMTS13, possibly through the formation of anti-ADAMTS13 autoantibodies, also contributes to the development of TMA in cancer patients. Cancer patients have been shown to have higher levels of vWF and lower levels of ADAMTS13 than the general population, often also depending on the stage of cancer. Patients with a history of thrombotic complications or TMA have repeatedly demonstrated higher vWF levels [9].

There is a supposed connection between APS and TMA that can potentially be explained by the 2-hit hypothesis. This was concluded from various in vivo studies [10]. APS appears to enhance an already active coagulation cascade. The first 'hit' being represented by instances like chemotherapy causing endothelial injury. Antiphospholipid antibodies might have the capacity to instigate complement activation, thus worsening the inflammation and procoagulant environment. The precise mechanisms are yet to be fully understood though. An in vivo study demonstrated that in the presence of bacterial lipopolysaccharide, patients with APS anti-beta2-glycoprotein I antibodies can stimulate clotting through the terminal complement complex [11].

Also, an important role is played biopsy of the affected organ with histological examination; in acute TMA, it is possible to see microthrombi and other lesions of the renal parenchyma in the field of view, which will lead to a diagnosis [12].

Biomarkers may be useful as diagnostics, especially in drug-induced TMA associated with gemcitabine and mitomycin C. Increases in thrombomodulin, tissue plasmin activator, and plasminogen activator inhibitor-1 have been reported [13]. The usefulness of endothelial biomarkers for the diagnosis of other types of TMA requires further study.

Treatment of TMA requires an integrated approach due to the variety of lesions in the body. In addition to symptomatic therapy (antihypertensive, anticoagulant, replenishing the deficiency of blood cells, etc.), the use of pathogenetic drugs that promote regression of TMA is noteworthy. Discontinuation of the drug that leads to the occurrence of TMA is not a treatment method, since it does not lead to restoration of the kidneys and hemostasis components [14]. Choosing treatment is an important problem for the doctor, so a multimodal approach to therapy is used in the form of plasmapheresis, protein-A immunoadsorption, the use of rutuximab, inhibition of complement factors, sodium-glucose cotransporter-2 inhibitor and others [15].

Conclusion

It is important to carry out specific laboratory tests in a timely manner for the correct differential diagnosis of TMA. If TMA is confirmed, treatment should be immediately adjusted by discontinuing potentially causative agents. It should be remembered that secondary TMA can recur even after the removal of the damaging factor, so careful monitoring of the patient is necessary both at the inpatient and outpatient stages. Patients with cancer require special attention due to the higher risk of developing TMA and associated disorders.

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