Case report

Cancer-related microagiopathic hemolytic anemia in a patient with breast cancer – diagnostic difficulties

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ABSTRACT

Cancer-related microangiopathic hemolytic anemia is rarely recognized as a paraneoplastic syndrome with a very poor prognosis in cancer patients. The treatment and prognosis are significantly different from that in other thrombotic microangiopathies, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. The case of described patient demonstrates the diagnostic difficulties in diagnosing the causes of hemolytic anemia in patient with breast cancer and appropriate treatment.

Key words: cancer-related microangiopathic hemolytic anemia, CR-MAHA, breast cancer, thrombotic microangiopathy, thrombocytopenia

INTRODUCTION

In cancer patients, microangiopathic hemolytic anemia (CR-MAHA) is very rare type of anemia. So far, only a few dozen cases of hemolytic anemia accompanying breast cancer have been described in the literature. To the best of our knowledge, about 60 cases of CR-MAHA associated with breast cancer were found in the MEDLINE via PubMed database [1–7]. The survival in these cases from the diagnosis of MAHA did not exceed 3 years [1, 2].

CR-MAHA is manifested by hemolytic anemia with a negative direct antiglobulin test (DAT), the presence of schistiocytes in the peripheral blood smear and thrombocytopenia [1]. An accurate diagnosis is often difficult and delayed. The oncologist often considers complication of chemotherapeutic treatment as the cause of anemia and thrombocytopenia, which may lead to discontinuation of systemic treatment. If this type of anemia is suspected in an oncological patient, a bone marrow biopsy should be performed and treatment should be initiated immediately because the prognosis is extremely unfavorable. The treatment and prognosis in this cases are significantly different from the management of other thrombotic microangiopathies, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.

Due the rarity of this anemia, we would like to present a case of patient with breast cancer and difficulties in diagnosing the causes of hemolytic anemia as well as analyzing the effectiveness of the therapeutic methods.

CASE REPORT

Breast cancer, carcinoma invasive G2 mammae estrogen receptor (ER) positive, progesterone receptor (PgR) positive, human epidermal growth factor receptor 2 HER2 negative with the presence of multiple bone metastases was diagnosed in the patient aged 59, in 2014 in another oncology center based on a breast biopsy. The breast cancer was disseminated in stage T3N2M1, clinical stage IV, according to American Joint Committee on Cancer (AJCC).

The patient underwent radiotherapy to the area of the spine with a total dose of 1400 cGy and to the pelvic area to a total dose of 2000 cGy. Bisphosphonates in infusion were administered. Hormone therapy with tamoxifen 20 mg/24 h was initiated followed by an aromatase inhibitor – letrozole due to disease progression. From February 2017, anemia and thrombocytopenia worsened and the patient was hospitalized in a district hospital, where dexamethasone was administered. In March 2017, she was admitted to the Department of Hematology due to symptomatic macrocytic anemia and thrombocytopenia.

Peripheral blood count revealed anemia with hemoglobin (Hb) concentration of 7.55 g/dl, with mean corpuscular volume (MCV) of 104 fl, and the number of reticulocytes 407 × 10^9/l and also thrombocytopenia with platelet count of 82 × 10^9/l. Other results were: total bilirubin concentration 5.54 mg/dl, LDH activity 2477 U/l (N 135–225 U/l), AST 98 U/l (N < 40 IU/l), ALT 75 U/l (N < 40 IU/l), GGTP 266 U/l (N < 35 IU/l), alkaline phosphatase 188 U/l (N 38–126 U/l). Vitamin B_{12} and folic acid levels were normal. The results of the initial laboratory findings are presented in table 1.

TABLE 1.
Initial laboratory findings.

Type of laboratory test	Patient's test result	Reference range
WBC	10.81 × 109/l	4–11 × 109/l
Hb	7.55 g/dl	12–16 g/dl
Plt	82 × 109/l	150–450 × 109/l
MCV	104 fl	80–96 fl
MCH	32.0 pg	27–31.2 pg
MCHC	32 g/dl	30–36 g/dl
Reticulocyte	18.81% (0.4 × 106/µl)	0,5–2.5% (0.02–0.14 × 106 µl)
Total bilirubin Indirect bilirubin Direct bilirubin	5.54 mg/dl 4.21 mg/dl 1.33 mg/dl	0.2–1.20 mg/dl 0.2–1 mg/dl 0.0–0.2 mg/dl
Alkaline phosphatase	188 U/l	38–126 U/l
Haptoglobin	0 g/l	0.5–2.2 g/l
GGTP	266 U/l	< 35U/l
LDH	2477 U/L	135–225 U/l
AST	98 U/l	< 40 U/l
ALT	75 U/l	< 40 U/l
Ferritin	1268 ng/ml	13–150 ng/ml
Transferrin	174 mg/dl	250–320 mg/dl
TIBC	218 ug/dl	149–504 µg/dl
%Sat. transferrin	53%	15–50%
Iron	116 µg/dl	37–158 µg/dl
Vitamin B12	291 pg/ml	187–771 pg/ml
Folic acid	2.52 µg/ml	3.9–26.8 µg/ml
Creatinine eGFR	0.64 mg/dl > 60 ml/min/1,73 m^2	0.5–1.10 mg/dl > 60 ml/min/1,73 m^2
Copper	162 µg/dl	85–155 µg/dl
APTT	23 s	25–37 s
INR	1.17	0.9–1.3
Prothrombin index	83%	80–120%
Prothrombin time	13.5 s	12–16 s
Erytroblasts, schistiocytes	8–10%	< 1% on a peripheral blood smear (PBS)

Abdominal ultrasound showed numerous hyperechoic lesions in the liver and splenomegaly. During hospitalization the patient underwent a bone marrow biopsy, dexamethasone was

discontinued, resulting in normalization of leukocytosis. As autoimmune anemia was suspected, methylprednisolone was introduced, followed by prednisone. Treatment was discontinued due to the lack of clinical effectiveness of glucocorticosteroids. Infusion of polyclonal immunoglobulins of 2 g/kg body weight was used, but without improvement. The patient required frequent transfusions of red blood cells and platelets concentrate.

Laboratory tests of the causes of thrombocytopenia did not reveal the presence of anti-platelet antibodies. Both direct and indirect antiglobulin tests were negative, haptoglobin concentration was decreased to 0 g/l (N 0.5–2.2 g/l). In the eluate, no antibodies against red blood cells were found. Nocturnal paroxysmal hemoglobinuria clone was excluded as the cause of hemolysis. No antinuclear antibodies were found in the serum. Numerous erythroblasts and schistocytes (8–10%) were present in the peripheral blood microscopic smears. Thrombotic thrombocytopenic purpura was initially suspected, but the activity of metalloproteinase ADAMTS-13 was normal, i.e. 60% (N 40–130%), anti-ADAMTS-13 antibody titre was 21 U/ml (N < 12 U/ml). The patient was qualified for treatment plasmapheresis, which did not bring positive clinical results. Follow-up studies showed an increase in ADAMTS-13 activity to 73% and a reduction in ADAMTS13-inhibitor to five units. Due to elevated copper concentration in the peripheral blood, ceruloplasmin concentration was checked ceruloplasmin concentration was normal, so Wilson's disease was excluded. In order to find the cause of splenomegaly, molecular tests were performed for the detection of myeloproliferative neoplasms. The V617F mutation in *JAK2* gene and CALR mutation exon 9 were negative. At this stage of the diagnosis, the result of a histopathological examination was obtained, which showed the presence of adenocarcinoma cells that might correspond to breast cancer: CKAE1/AE3 +, CK7-, progesteron receptor negative, estrogen receptor negative, CK20-, CK7, CDX2-, TTF1. Full body computed tomography was performed and showed enlarged axillary lymph nodes, numerous metastases in bones and three hypodense lesions in the liver. A 20 × 15 mm nodule in the external quadrant of the right breast and an acoustic shadow and a 9 × 5 mm lesion in the left breast were detected by ultrasound. After obtaining the result of trepanobiopsy with the confirmation of the infiltration of hormone-insensitive cancer cells in the marrow, aromatase inhibitor therapy was finished and decided to introduce systemic therapy according to the FEC protocol (fluorouracil 500 mg/m^2 iv. on day 1st; epirubicin 37.5 mg/m^2 iv. on day 1st and cyclophosphamide 500 mg/m^2 on day 1st) was implemented. In the first cycle, the epirubicin dose was reduced by 50% due to hyperbilirubinemia, subsequent cycles were given in full doses. The patient received a total of eight cycles of chemotherapy, achieving disease stabilization (SD) according to RECIST (Response Evaluation Criteria In Solid Tumors) 1.1 criteria. As early as after first cycle of chemotherapy, there was a reduction in the severity of hemolytic anemia and a decrease in need for transfusion of blood components. Later, blood count parameters improved. The patient did not require red blood cell transfusions and her platelet count was normal. The markers of hemolysis also decreased. Two months after the end of treatment, an increase in hemolytic markers was again observed: total bilirubin concentration was 5.98 mg/dl (direct bilirubin 4.68 mg/dl), in the complete blood count, thrombocytopenia (57 G/l platelets) and anemia Hb 6.9 g/dl reappeared. On CT scans, new metastases to the liver were consistent with disease progression. Docetaxel treatment was initiated at 75% of the recommended dose due to thrombocytopenia.

Again, the patient required transfusions of blood products. After bilirubin decrease to 2.2 mg/dl, normalization of LDH activity and increase of platelet values to 90 × 10^9/l, treatment with docetaxel was continued at 100% doses. After four cycles a partial response (PR) by CT scan was confirmed according to RECIST 1.1. However ascites and fluid in the pleural cavities were found. Thoracocentesis was performed. No cancerous cells were found in the cytological examination of the peritoneal fluid. Treatment with docetaxel was continued for up to six cycles. In March 2018, on the CT scan, the stabilization of the disease (SD) according to RECIST 1.1 was observed. Three months after the end of the treatment, metastatic lesions in the liver were found. In laboratory tests, a slight increase in bilirubin and AST was present.

As part of next line of treatment, the patient received gemcitabine in monotherapy. Gemcitabine chemotherapy was complicated by thrombocytopenia second grade according to CTCAE (Version 5.0) requiring postponement of subsequent treatments. Although a partial response (PR) according to RECIST 1.1 criteria was obtained after two cycles, disease progression was diagnosed after fifth cycle. Results of complete blood count parameters and hemolysis during treatment of the patient are presented in table 2.

From October 2018, the patient's general condition deteriorated (ECOG-3), which required discontinuation of systemic treatment. In November, blood counts showed an increase in leukocytosis and inflammatory markers (CRP), empirically antibiotic therapy was started. Ascites reappeared, therefore diuretics were administered. The patient died of a generalized refractory neoplastic disease, without symptoms of CR-MAHA.

TABLE 2.
Complete blood count and hemolysis parameters during treatment.

Parameters	Before FEC	After six FEC cycles	Before docetaxel	After six docetaxel cycles	Before gemcitabine	After five gemcitabine cycles
Hb g/dl	8.7	10.6	7.0	11.6	12.0	10.0
Platelets 109 /l	52	181	48	146	278	112
LDH U/l	2,796	321	1,088	277	272	448
Bilirubin mg/dl	7.53	0.9	5.93	0.84	1.34	1.68

DISCUSSION

Acquired hemolytic anemia may occur unexpectedly in a cancer patient, especially in an advanced stage of the disease [1, 7]. It should be an warning sign for the oncologist because of an unfavorable prognosis and special requirements of the management. It can also occur in patients with hematological neoplasms [8]. The cause of cancer-related hemolytic anemia is mechanical damage of red blood cells in a patient with disseminated neoplastic process. Some authors hypothesize that an increased number of circulating tumor cells (CTCs) and microbubbles derived from tumor cells may be involved in CA-MAHA initiation [9]. The tissue factor present on the tumor fragments and microbubbles activates the coagulation cascade and induces changes in the vessels, which contribute to erythrocyte damage [9, 10].

Unlike other forms of microangiopathic anemia, thrombotic thrombocytopenic purpura (TTP) in CR-MAHA has not significant metalloproteinase ADAMTS-13 deficiency, ADAMTS-13 inhibitor titer in CR-MAHA may be found, but not as high titer as in the case of TTP [7, 10]. Contrary to TTP, plasmapheresis procedures performed in CR-MAHA are not very effective [7, 10]. On the other hand, the basic diagnostic test in the diagnosis of anemia in CR-MAHA is a histopathological examination of the bone marrow. The bone marrow image shows an infiltration of metastatic neoplastic cells and secondary myelofibrosis [8]. The obstruction of small vessels blocked by cancer cells causes fragmentation of erythrocytes and platelets [7].

In our patient, it was very difficult to diagnose the causes of anemia. **Differential diagnosis of anemia included:**

- Deficiency anemia was excluded because concentrations of vitamin B_{12}, folic acid and iron metabolism were within normal range.
- Autoimmune hemolytic anemia was excluded because direct and indirect antiglobulin tests were negative and treatment with glucocorticosteroids was ineffective.
- Classic thrombotic thrombocytopenic purpura (TTP) was excluded due to a small titer of ADAMTS-13 inhibitor and a slight decrease in concentration of the ADAMTS-13 enzyme, as well as the lack of effectiveness of plasmapheresis procedures.
- Hemolytic uremic syndrome was excluded because the patient's renal parameters were normal.
- Disseminated intravascular coagulation was excluded because no changes in the coagulation system were observed.

Microangiopathic anemia was confirmed by the presence of schistocytes > 1% in the peripheral blood smear, increased erythropoiesis confirmed the presence of erythroblasts and an increased percentage of reticulocytes in the peripheral blood. The diagnosis was made on the basis of the symptoms of microangiopathic hemolytic anemia with confirmed bone marrow involvement by breast cancer cells, excluding other causes of anemia.

Therapeutic options for the patients were:

- Plasmapheresis with plasma exchange proved to be ineffective.
- Glucocorticosteroids proved ineffective.
- Hormone therapy was no longer effective due to the alteration of receptors in the tumor.
- Systemic chemotherapy seemed to be the only effective therapeutic option, which allowed to achieve clinical response.

The treatment for CR-MAHA involves hormone or chemotherapy. In our patient, the bone marrow biopsy revealing the presence of adenocarcinoma cells, which did not have estrogen and progesterone receptors on their surface, changed the patient's treatment, leading to discontinuation of the aromatase inhibitor-letrozole and initiation of appropriate chemotherapeutic treatment. The change of the tumor phenotype from ER(+), PgR(+) to ER(-), PgR(-) observed in the patient is associated with a worse prognosis; the so-called tumor escape with a different phenotype is observed in the disease progression in more than 20% of patients with breast cancer, as well as in the course of many other cancers [11, 12]. In our patient, this change in disease progression resulted in the ineffectiveness of the previously used hormone therapy. Chemotherapy allowed the patient to become independent from transfusions. The problem in the treatment of this patient was the use of gemcitabine, which, according to some authors, can induce drug-induced thrombotic microangiopathy (HUS) caused by formation of drug-dependent antibod-

ies [7, 8]. Some authors confirm the effectiveness of eculizumab, a monoclonal antibody against the complement component C5, in the treatment of patients with complement-mediated thrombotic microangiopathy, e.g. in the case of TMA associated with the use of chemotherapy with symptoms resembling atypical hemolytic uremic syndrome (aHUS) [4, 7]. The treatment of the patient with gemcitabine is controversial, which, according to some authors, can induce HUS. No deterioration of renal parameters was observed in our patient, but negative effects of gemcitabine in this patient cannot be ruled out.

The prognosis in CR-MAHA is extremely unfavorable, with the survival from the diagnosis of MAHA did not exceeding 3 years. The reappearance of anemia and thrombocytopenia accompanied disease progressions and the tumor remained sensitive to subsequent lines of chemotherapy. Unfortunately, after the 4th disease progression, the patient died.

CONCLUSION

In some cases, the treatment of cancer patients is stopped temporarily or terminated when peripheral blood counts show thrombocytopenia or anemia. It is worthwhile to perform a complete differential diagnosis of these symptoms each time during the treatment, including bone marrow biopsy. The diagnosis of CR-MAHA is crucial for changing the management of patients with such an unfavorable prognosis. The use of appropriate chemotherapy can extend the life of these patients. The overall survival of our patient from the diagnosis of CR-MAHA was 21 months with appropriate treatment.

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