Haemolytic Anaemia in a Patient with Progressive Breast Cancer: Consider Thrombotic Microangiopathies and Treat the Cancer

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Abstract

Background: Haemolytic anaemia secondary to cancer is a rare and potentially fatal cancer complication belonging to the Thrombotic Microangiopathies (TMAs), which include the better known Thrombotic Thrombocytopenic Purpura (TTP) and Haemolytic-Uremic Syndrome (HUS). Making the diagnosis is important, as there is generally no response to classic TMA treatment, including plasma therapy, plasmapheresis, and rituximab. Yet, in current practice, diagnosis is often made late. Survival can be improved by administering chemotherapy early. Few cases have been described in the literature, and no other cases of TMA secondary to breast cancer with proof of response to a targeted treatment, such as everolimus combined with exemestane, have been reported.

Case Presentation: A 76-year-old Caucasian woman with metastatic breast cancer was treated with aromatase inhibitors but presented with tumour progression and deterioration of her general condition. An evaluation revealed haemolytic anaemia with thrombocytopenia in combination with organ damage (brain and heart). She did not respond to classic TMA treatment, but to an anti-tumour treatment of exemestane combined with everolimus.

Conclusion: This case demonstrates the need for and efficacy of a specific treatment for TMA secondary to cancer, as well as the efficacy of everolimus and exemestane in the management of TMA associated with progressive breast cancer.

Keywords: Secondary thrombotic microangiopathy; Everolimus; Breast cancer

Abbreviations

TMA: Thrombotic Microangiopathy; TTP: Thrombotic Thrombocytopenic Purpura; HUS: Haemolytic-Uremic Syndrome; PET: Positron Emission Tomography; WHO: World Health Organization

Background

Haemolytic anaemia with Thrombotic Microangiopathy (TMA) is a rare cancer complication. The diagnosis is often made late and prognosis remains poor. Because this pathological entity does not respond to classic treatments, such as plasma exchanges or rituximab, a complete evaluation is necessary in order to administer adequate therapy. Secondary TMAs differ from classic Thrombotic Thrombocytopenic Purpura (TTP) and Haemolytic-Uremic Syndrome (HUS) in their clinical presentation and the lack of response to classic treatment. They may be secondary to certain drugs, surgery, bone marrow transplant, metastatic cancer, chemotherapy, severe antiphospholipid syndrome, or sepsis, among others [1]. In cancer patients, the TMA can be secondary to chemotherapy (mitomycin, bleomycin, cisplatin, gemcitabine) [2-4] or to the tumour itself [5-10]. TMAs secondary to cancer are often described as a paraneoplastic syndrome. The treatment is chemotherapy against the cancer.

We present the case of a patient with haemolytic anaemia due to TMA secondary to breast cancer who responded to treatment with everolimus and exemestane.

Case Presentation

A 76-year-old female patient was followed for 2 years for grade III invasive ductal carcinoma

Figure 1: Progress of the various blood parameters.

		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Platelets	(/µl)	66	74	87	39	66	72	143	282
Haemoglobin	(g/dl)	6,9	10,9	8,8	9,6	10	9	8,3	8,3
Schizocytes	(%)	1,6	1,5	2	5,9	7,2	5,9		
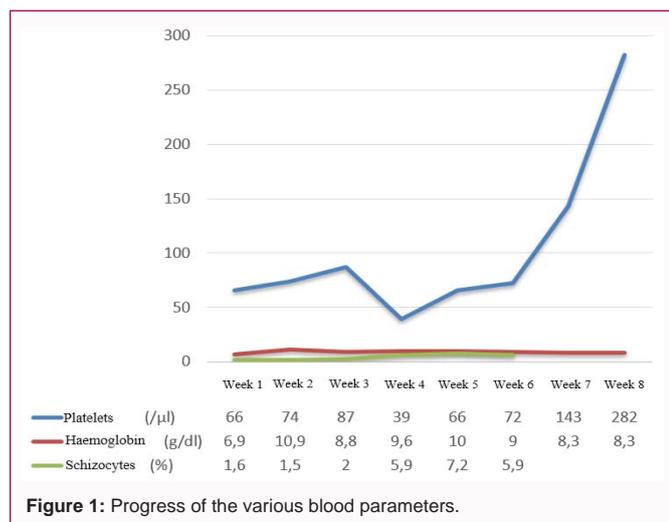
according to the Scarff-Bloom and Richardson (SBR) classification. The initial stage was pT2N2M1 according to the TNM classification. She was upfront metastatic with lymph node and bone metastases. The tumour was positive for progesterone and oestrogen hormone receptors and FISH negative for cerb2.

The patient initially underwent a right mastectomy and axillary node dissection, followed by treatment with tamoxifen and denosumab, which was replaced with zoledronic acid due to the development of bone pain. After the first progression and occurrence of pulmonary embolism 8 months after diagnosis, the treatment was changed to second-line hormone therapy with an aromatase inhibitor (letrozole).

The patient was stable with letrozole for 17 months, after which she was hospitalised for deterioration of her general condition with repeated falls and major asthenia. The evaluation revealed WHO grade 3 macrocytic anaemia (haemoglobin 6.9 g/dL), WHO grade 2 thrombocytopenia ($66 \times 10^3/\mu$L). Leucocytes were normal. Schizocytes were present on the blood smear (1.6%) and an increased number of reticulocytes (202.3/µL) were observed in the peripheral blood. We also noticed abnormal liver tests with lactate dehydrogenase (LDH) 7-times the normal value (4,246 IU/L), total alkaline phosphatases 1.2-times the normal value (162 IU/L), aspartate transaminase (SGOT) 3-times the normal value (111 IU/L), alanine transaminase (SGPT) normal (48 IU/L), gamma-GT 3-times the normal value (143 IU/L), and slightly increased total bilirubin (1.32 mg/dL; direct bilirubin 0.58 mg/dL). Haptoglobin was decreased to 3.6 mg/dL (RR: 34-200). C-reactive protein was increased to 33-times the normal value (167.14 mg/L). Coagulation tests were normal Figure 1. We also noted an increase in Creatine Phosphokinase (CPK) 70-times the normal value (7,608 IU/L).

The day following admission, the patient developed neurological symptoms with left hemiparesis. Cerebral CT without iodinated contrast was normal [10-15]. Her troponin values were also high (2,100 ng/mL; RR: <0.013), without precordial pain. As this context suggested TTP with cardiac and neurological complications, the ADAMTS13 activity was tested. The result was 52%, which is normal. The Coombs test was not performed. Several medullary puncture attempts were also made and turned out to be white.

Given the diagnostic hypothesis of TTP, plasma therapy (three fresh frozen plasma per day) was started in combination with corticosteroid therapy (methylprednisolone 64 mg/d) that continued for 11 days. Despite this treatment, thrombocytopenia continued at ~80,000/µL. Therefore, the fresh frozen plasma was stopped and daily plasmapheresis started. This was stopped after 8 days due to deterioration of the thrombocytopenia to ~40,000/µL and the persistence of haemolytic anaemia.

At this stage, the hypothesis of purpura secondary to neoplastic progression was put forward and a PET scan performed. It confirmed progression of the breast cancer with metastatic spread at the medullary, bone, and hepatic level. Due to the major deterioration of the patient's general condition and abnormal blood values, we opted for anticancer treatment with the combination of everolimus and exemestane rather than classic chemotherapy. This treatment led to the progressive normalization of blood platelets from 39,000 to 68,000 in 4 days, to 72,000 in 14 days. They returned to normal after 1 month. Haptoglobin increased after 10 days.

The final diagnosis was TMA secondary to cancer progression based on biological markers, the clinical presentation, and the oncological context. This occurs in the presence of a very significant cancer progression, confirmed by the PET scan, after chemotherapy known to cause TMA, and without typical symptoms of TTP or HUS. The related organ damage (neurological and cardiac damage) is probably related to the severity of the TMA. Unfortunately, we do not have an idea of the potential medullary invasion of the disease; therefore, a medullary biopsy should always be performed whenever technically possible.

Unfortunately, the patient died 3 months after the first symptoms and 2 months after the initiation of treatment. She was in palliative care for 3 days due to global alteration and repetition of thrombopenia.

Discussion

TMA is related to the dissemination of microthrombi consisting of platelets agglutinated in the arterioles and capillaries, which cause partial or complete occlusion of the vessel lumen [1]. The disorder is characterized by severe thrombocytopenia and macroangiopathic haemolytic anaemia and is generally related to organ damage [1]. Haemolytic anaemia and is characterised by a negative Coombs test, high LDH, indirect bilirubin, reticulocytes, and schizocytes, and low haptoglobin [5]. The most commonly described TMAs are TTP and HUS [1,3,5].

TTP generally manifests as renal or neurological impairment and fever. It may be secondary to a congenital mutation of ADAMTS13 or acquired by the development of ADAMTS13 antibodies. In both cases, the result is a severe decrease in its activity [1,3]. Normally, the activity of ADAMTS13 is between 50% and 178% [5].

ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motifs, is a metalloproteinase that divides the multimeric proteins of von Willebrand Factor (vWF). vWF is produced by endothelial cells and released in the local circulation secondary to various stimuli, including epinephrine. It may also be activated by hypoxia, interleukins, or TNF-alpha. In the circulation, the large vWF multimers are normally reduced quickly by ADAMTS13 into smaller multimers [5]. After inhibition of ADAMTS13, the large released vWF multimers are no longer cleaved. These large forms of vWF cannot interact with the platelet Glycoprotein Ib (GP1b), which leads to platelet activation.

The clinical picture presented by our patient may have

corresponded to a case of classic TTP. However, this diagnosis was not retained given a quasi-normal level of ADAMTS13 and the absence of response to the classic treatment.

Typical HUS is secondary to an *E. coli* infection producing Shiga toxin and generally manifests as renal insufficiency and diarrhoea. An atypical congenital HUS entity has also been described related to a mutation or polymorphism that decreases the regulation of complement proteins or acquired secondary to the production of antibodies involved in the regulation of the complement. A specific treatment, eculizumab, has proven efficacy in this type of TMA [9]. This diagnosis was unlikely because of the lack of diarrhoea. However, we did not dose the complement. We retained the possibility of TMA secondary to drug or to the cancer itself. The result of the PET scan confirmed the hypothesis of progressive breast cancer.

A literature review made it possible to analyse 168 cases of TMA of tumour origin, the first of which was described in 1979 [3]. Of the cases analysed, 154 were secondary to a solid tumour and 14 to lymphoma. Regarding the solid cancers, the cases of TMA were more often secondary to an adenocarcinoma producing mucin of gastric, mammary, prostatic, pulmonary, or undetermined origin. In general, the solid cancer was metastatic at the time of diagnosis and tumour medullary infiltration shown at biopsy [3,5]. The majority of the cases occurred late in the disease history, especially during a relapse or in the presence of a metastatic dissemination [4], as was the case with our patient.

The path physiology of TMAs secondary to cancer has not been clearly elucidated. One of the causes would be medullary infiltration by the metastatic tumour, leading to fragmentation of the red blood cells and platelet destruction into the vessels or the tumour tissue, particularly into the marrow or the lung. This could also cause the release of vWF, whose destruction is limited by the reduced activity of ADAMTS13 [5]. This theory of tumour infiltration is controversial because the majority of patients with metastatic tumour do not develop TMA. Cytokines produced by the tumour or activation of the endothelium may also be responsible for the TMA, but these phenomena have not been proven yet [2-4]. As described previously, the role of the decrease in ADAMTS13 in TTP is clearly established, but it is less clear in cases of TMA secondary to cancer, especially as the activity of ADAMTS13 is generally decreased in metastatic cancers, but also certain hepatic pathologies, chronic inflammatory stimulations, pregnancy (HELLP syndrome), anti-cancer treatment, and Disseminated Intravascular Coagulation (DIC). This effect would not be secondary to autoimmunity and does not straightaway involve TMA.

The treatment of TMA secondary to cancer is different from that of classic TMA (TTP and HUS), which is treated with plasma therapy, plasmapheresis, corticosteroid therapy, possibly rituximab, eculizumab for SHU, and splenectomy. In the cases of TMA secondary to cancer, the recommended treatment is for tumour progression [2]. We did not find any recommendation regarding the treatment proposed in this rare situation.

In the literature, we found that patients generally undergo chemotherapy with anthracyclines, cyclophosphamide, and 5-fluorouracil at variable doses and using a fractionated schedule to limit the haematological toxicity [2]. The choice of targeted therapy combined with hormone therapy is influenced by several parameters, especially tumour characteristics and the patient's general condition,

which did not make it possible in this case for her to receive classic chemotherapy.

If we concentrate on the cases of MAT associated with progressive breast cancer, we found two interesting reviews in the literature. The first included 168 cases of TMA of tumour origin, with 36 cases secondary to breast cancer [3], and the second discussed 15 more cases [15]. In first 36 cases, 17 patients received any cancer therapy (surgery, chemotherapy, or hormonal therapy), 12 were not treated, and they had no data on 7 cases. In the evaluated cases, 12 of 14 treated patients had a response. In 26 analysable cases, the median survival was approximately 4 months after treatment and 0.5 months without curative treatment. In the 15 new patients in the second review, 7 were treated with chemotherapy (1 with chemotherapy and plasma therapy), 2 with plasma therapy alone, and 6 received any treatment. Survival varied between a few hours without plasma exchange to more than 1 year with chemotherapy. Everolimus is an mTor metabolic pathway inhibitor proven to be effective in combination with exemestane in relapsing or progressing hormone-sensitive breast cancer after hormone treatment [6]. The choice of this treatment for our patient was based on it having fewer side effects than other systemic treatments, especially chemotherapy. To the best of our knowledge, no clinical case has been reported regarding the efficacy of this treatment in cases of TMA secondary to cancer. The complete correction of the platelet level in our patient shows that this combination may be effective in this type of paraneoplastic syndrome.

Conclusion

Haemolytic anaemia in a cancer patient may suggest TMA as potential marker of tumour progression. This must be looked for and adequate anti-tumour treatment started immediately. No recommendation regarding the choice of anti-tumour treatment is currently validated. The efficacy of everolimus and exemestane was demonstrated for our patient.

Author's Contributions

SB analysed and interpreted the patient data, performed the literature review, and provided major contributions to writing the manuscript. LF, LD, and TV participated in the treatment. All authors reviewed the manuscript. LF gave final approval of the version to be published.

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