ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 11, pp.14605-14607, November, 2020

DOI: https://doi.org/10.24941/ijcr.39821.11.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

MICROANGIOPATHIC HAEMOLYTIC ANAEMIA AS A BAD PROGNOSTIC PARANEOPLASTIC SYNDROME: A CASE REPORT

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ARTICLE INFO

Article History:
Received 10th August, 2020
Received in revised form
17th September, 2020
Accepted 30th October, 2020
Published online 30th November, 2020

Key Words:
Planned Teaching Programme (PTP), Sibling Rivalry, Mothers of Under Five Children.

ABSTRACT

Introduction: Microangiopathic haemolytic anaemia is defined by evidence of haemolysis, schistocytes in the peripheral blood smear and a negative direct antiglobulin test and is usually associated with thrombocytopenia. It may be primary, like thrombotic thrombocytopenic purpura, or secondary, including systemic malignancy, which is very rare. It usually occurs at a terminal stage of cancer and it is associated with metastasis. Pathogenesis remains unknown. **Case presentation:** An 83 year- old- woman with diffuse metastatic right breast carcinoma, including bone marrow metastases suspicion, already submitted to mastectomy and palliative radiotherapy, presented with a two-week history of asthenia and dyspnoea. Routine analysis revealed acute normocytic normochromic, haemolytic anaemia, schistocytes in the peripheral blood smear, negative Coombs test and thrombocytopenia. Space-occupying lesions of the brain observed in CT scan were confirmed by RM to be brain metastasis. Because the initial diagnosis of cancer was already known, no further investigation was made, and cancer associated microangiopathic haemolytic anaemia was diagnosed. She was no candidate to antineoplastic treatment, so she received prednisolone for 4 days followed by a pulse regimen of 1g methylprednisolone daily for 3 consecutive days. Several transfusions were given, but there was little improvement of anaemia. The patient's health condition continued to worsen resulting in her passing. **Conclusion:** It is very important to correctly diagnose cancer associated microangiopathic haemolytic anaemia in order to start the right treatment as soon as possible. Even today there exists no definitive treatment schedule for these patients. Systemic antineoplastic therapy is the best option to achieve clinical response. Despite this, the prognosis is extremely poor, most patients die within a few weeks after diagnosis

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Citation: ***Bárbara Pereira Machado and Gonçalo Sarmento.*** **2020.** "Microangiopathic haemolytic anaemia as a bad prognostic paraneoplastic syndrome: a case report.", *International Journal of Current Research*, 12, (11), 14605-14607.

INTRODUCTION

Microangiopathic haemolytic anaemia was first described in 1962 (Lin, 1995; Arkenau, 2005; Oliveira, 1998) and is defined by evidence of haemolysis (increased serum indirect bilirubin, elevated serum lactate dehydrogenase and decreased haptoglobin), schistocytes in the peripheral blood smear and a negative direct antiglobulin test and is usually associated with thrombocytopenia (Lin, 1995; Arkenau, 2005; Oliveira, 1998; Morton, 2016). It may be primary, like thrombotic thrombocytopenic purpura (TTP) or secondary, as for example, systemic malignancy (Oliveira, 1998; Bayer, 2019; George, 2014), which is very rare (Lin, 1995; Kaidar-Person, 2011). Cancer induced microangiopathic haemolytic anaemia is associated with metastatic disease (Elliott, 2010) and it usually occurs at the terminal stage of cancer, but can be the initial presentation of malignancy, which is extremely rare (Lin, 1995; Oliveira, 1998).

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Gastric cancer is the most common (Kaidar-Person, 2011) followed by breast cancer (Lin, 1995; Arkenau, 2005; Oliveira, 1998). Two main aetiologies are known: cancer induced or chemotherapy induced microangiopathic haemolytic anaemia (Morton, 2016), but in this article we will only focus on the first. Pathogenesis of cancer induced microangiopathic haemolytic anaemia remains unknown, but some hypotheses have been discussed over the past few years (Lin, 1995; Arkenau, 2005; Kaidar-Person, 2011; Werner, 2007). Some authors postulate that there are tumour cell aggregation in the microcirculation creating tumour cell emboli as well as immune complexes that cause endothelial damage and vascular obstruction leading to fragmentation of red blood cells (Lin, 1995; Arkenau, 2005; Oliveira, 1998; Morton, 2016; Bayer, 2019) and platelet consumption (Arkenau, 2005; Morton, 2016). Another common finding that most patients have is bone marrow involvement or necrosis (Lin, 1995; Morton, 2016; Elliott, 2010; Werner, 2007), which indicates that bone marrow microangiopathy may play an important role in the physiopathology (Lin,

1995). It is speculated that bone marrow endothelial cells of vessels may be injured by direct invasion of aggressive tumour growth, abnormal angiogenesis and secondary myelofibrosis (Werner, 2007). In addition, according to the relevant number of patients with mucin producing adenocarcinomas (Elliott, 2010), a mechanism of injury of endothelium caused by mucin has been proposed (Werner, 2007). The reason may be related to mucinous tumours being able to secret enzymes capable of activating coagulation factor X (Morton, 2016) or can affect Von Willebrand factor (Bayer, 2019).

Case Report:

We present a 83 year old Caucasian woman with stage IV invasive micro papillary carcinoma, HER + of the right breast with lymph node, abdominal and bone metastasis and suspicion of bone marrow involvement. She had already been submitted to right mastectomy and palliative radiotherapy, refusing palliative chemotherapy, without significant symptoms improvement. The patient was admitted to the hospital presenting a two week history of asthenia, dyspnoea and constant pain in the right lower limb. On admission, the medical examination showed pallor and leg edema, but no other pathological findings. First routine analysis revealed acute normocytic normochromic anaemia (hemoglobin: 6.2 g/dL), thrombocytopenia (platelet count 42000/uL) and elevated d-dimer (4162ng/ml). Chest CT angiography excluded pulmonary emboli, but space-occupying lesions were observed in CT brain scan. She received two blood transfusions and was hospitalized. The etiological investigation proceeded and analysis showed haemolytic anaemia (hemoglobin 6.8 g/dl; reticulocytes: 28.52%; haptoglobin < 8 mg/l ; total bilirubin: 5.10 mg/dL; indirect bilirubin: 4.03mg/dl; lactic dehydrogenase: 469 U/L), schistocytes in the peripheral blood smear, negative Combs test and thrombocytopenia (platelet count 42000/uL). Others analysis were performed, highlighting fibrinogen: 246 mg/dL with normal INR and protrombine time. Brain RM confirmed brain metastasis with vasogenic edema. Because the initial diagnosis of disseminated cancer was already known, continuing the investigations was unnecessary. No further investigation was made, and cancer associated microangiopathic haemolytic anaemia was diagnosed. She was no candidate to antineoplastic treatment, so she received prednisolone for 4 days followed by a pulse regimen of 1g methylprednisolone daily for 3 consecutive days. Several transfusions (total: eight) were also made, but despite all treatment, there was little improvement of anaemia and platelet count continued to drop. The patient's health condition continued to worsen, resulting in her passing twelve days after the diagnosis.

DISCUSSION

When a patient without known cancer presents with microangiopathic haemolytic anaemia and thrombocytopenia it becomes necessary to search for malignancy (Lin, 1995; Arkenau, 2005). Also in patients with cancer or previous history of cancer, diagnostic evaluation for cancer induced microangiopathic haemolytic anaemia should be pursued (4) because it may be the first sign of recurrence or can reveal the first sign of metastatic disease (Arkenau, 2005; Oliveira, 1998). That includes imaging and/or bone marrow biopsy (Arkenau, 2005; Morton, 2016), especially if there is bone pain (Elliott, 2010). Documentation of malignant cells in the marrow provides the diagnosis (Morton, 2014). However, in most patients with advance malignancy it is not carried out considering no clinical benefit of performing clinical studies since these patients have a poor prognosis regardless treatment (Kaidar-Person et al., 2011). Because of this, it is believed that cancer associated microangiopathic haemolytic anaemiamay be underdiagnosed (Kaidar-Person et al., 2011). As you can see in our case report the patient already had metastatic disease with suspicion of bone marrow involvement, so after analysis results, diagnosis was perceptive. As so, performing bone marrow biopsy would not change therapeutic approach, would only cause pain. However it is interesting that brain metastasis were discovered at the same time as cancer induced microangiopathic haemolytic anaemia, emphasizing the role of cancer induced microangiopathic haemolytic anaemia as sign of metastatic disease.

Most cases of microangiopathic haemolytic anaemia have an abrupt onset (Arkenau, 2005). It is very important to correctly diagnose cancer associated microangiopathic haemolytic anaemia in order to start the right treatment as soon as possible (Morton, 2014; Kaidar-Person et al., 2011; Elliott, 2010; Werner, 2007). In patients without obvious malignancy, TTP, that requires life save therapy, is the main differential diagnosis. At initial evaluation it can be clinical indistinguishable from cancer associated microangiopathic haemolytic anaemia (Arkenau, 2005; Elliott, 2010).Also, laboratory features are very similar between both syndromes. (Morton, 2014). Regarding symptoms, both patients may present with weakness(Morton, 2014), fatigue, or dizziness related with severe anaemia and/or with bruises or bleeding related with severe thrombocytopenia(Arkenau, 2005). However, pulmonary symptoms, such as dyspnoea, and back/ or bone pain, usually related with bone marrow involvement, are common in cancer induced microangiopathic haemolytic anaemia, but rarely occur in TTP (Morton, 2016; Elliott, 2010). Data available suggest that the major site of cancer induced microangiopathic haemolytic anaemia is the pulmonary vessel, which can explain the respiratory symptoms (Lin, 1995). Renal failure is rare but may appear in advanced stages of the malignancy (Arkenau, 2005) or in cases of chemotherapy related toxicity (Lin, 1995; Morton, 2016). Both TTP and cancer induced microangiopathic haemolytic anaemia can cause severe microangiopathic hemolytic anemia and thrombocytopenia (Morton, 2016). Higher levels of lactic dehydrogenase (Morton, 2016; Elliott, 2010), alkaline phosphatase and C- reactive protein are also found in malignancy and may help identify patients with bone metastasis (Arkenau, 2005). Coagulation abnormalities and abnormal liver function both suggest cancer-associated microangiopathic haemolytic anaemia rather than TTP (Bayer, 2019). Search for TTP in this particular case was avoidable; however, it is mandatory in a patient without unknown malignancy. Symptoms described above were also found in our patient with bone metastasis and they can give clues to suspect of underlying cancer with bone metastasis. On the other hand, disseminated intravascular coagulation needs to be among the diagnostic consideration in patients with cancer presenting with thrombotic microangiopathy with thrombocytopenia (Morton, 2016; Elliott, 2010). Despite elevated d-dimers levels, level of fibrinogen and coagulation tests were normal, so disseminated intravascular coagulation was excluded. Even today there exists no

definitive treatment schedule for these patients (Arkenau, 2005), and plasma exchange and immunosuppression, which are thrombotic thrombocytopenic purpura therapies of choice, have poor response and may cause toxicity (Elliott, 2010; Werner, 2007). Systemic antineoplastic therapy is the best option to achieve clinical response (Lin, 1995; Arkenau, 2005; Kaidar-Person, 2011; Werner, 2007). Due to acute onset, blood and platelets transfusions are required in almost all patients (Arkenau, 2005; Oliveira, 1998). Despite this, the prognosis is extremely poor (Morton, 2016; Kaidar-Person, 2011; Werner, 2007) and seems directly related with the underlying cancer and response to effective treatment rather than the presence of microangiopathic haemolytic anaemia (Lin, 1995; Oliveira, 1998). Most patients die within a few days to weeks after diagnosis (Lin, 1995; Werner, 2007). Unfortunately, that is what happened with our patient in a very short time despite all treatment, which was a foreseeable developing, attending to diffuse metastatic disease.

Conclusion

Cancer induced microangiopathic haemolytic anaemia usually occurs at terminal stage of cancer suggesting metastatic disease. It is important to make the right diagnosis as soon as possible in order to start the right treatment. Malignancy must be suspected, especially if previous history of cancer is known or the patient also presents with respiratory symptoms, such as dyspnoea and/or bone pain. However, despite treatment, prognosis is poor and related with disease progression, so microangiopathic haemolytic anaemia is a bad prognostic paraneoplastic syndrome.

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