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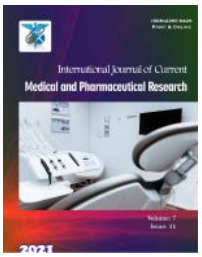

DIAGNOSIS OF MYELOID SARCOMA WITH INV (16) CBFB-MYH11 FUSION IN PLEURAL FLUID: A CASE REPORT

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ABSTRACT

Objective: This report aimed to present a rare clinical case of a male patient diagnosed with myeloid sarcoma with CBFB-MYH11 fusion of chromosome 16 inversion (inv(16)) in pleural fluid. **Case presentation:** Immunohistochemical analysis of the appendix, epiplon biopsy and immunophenotypic analysis of the patient's pleural fluid showed the presence of neoplastic cells with a phenotype suggestive of acute myeloid leukemia/myeloid sarcoma, and RT-PCR of the pleural fluid showed the presence of the CBFB-MYH11 fusion gene from inv(16). **Discussion:** Granulocytic myeloid sarcoma is a rare neoplastic disease that most commonly develops in soft tissue, bones, peritoneum, lymph nodes and gastrointestinal system. In these anatomical sites there is a proliferation of immature cells of the myeloid lineage. Diagnosis is performed by immunocytochemical, immunohistochemical and/or immunophenotypic analyses. The immunophenotype observed by the immunohistochemistry of appendix, epiplon biopsy and pleural fluid immunophenotyping were important for the diagnosis of myeloid sarcoma and are in agreement with what has been reported in the literature for the diagnosis of this disease. **Conclusion:** The joint analysis of biological samples by immunohistochemistry and immunophenotyping was essential for the correct diagnosis of the patient and, therefore, for the most appropriate therapeutic decision for this disease.

INTRODUCTION

Myeloid sarcoma (MS) or granulocytic sarcoma (GS) is a rare condition of neoplasia, defined as an extramedullary proliferation of immature cells of the myeloid lineage, with or without maturation (ALMOND *et al*., 2017). This disease can manifest itself in an isolated form in 8-20% of patients undergoing allogeneic stem cell transplantation (SWERDLOW *et al*., 2017), or affect patients with a history of relapse of acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and other myeloproliferative neoplasms (MPN) (SHAHIN; RAVANDI, 2020).

MS can occur at any age and in any part of the body, being more common in soft tissue, bones, peritoneum, lymph nodes and the gastrointestinal system. In less than 10% of cases, it can be present in multiple anatomical sites (SWERDLOW *et al*., 2017; CAMPIDELLI *et al*., 2009). Among adults, the incidence is only 2/1,000,000, and there is a slight predominance of males over females (1:2) (SWERDLOW *et al*., 2017; ALMOND *et al*., 2017; YILMAZ *et al*., 2013).

MS can be associated with several genetic abnormalities, among which the most common is t(8;21)(q2;q22). Although less common, it can also be associated with inv(16)(p13;q22), which is present mainly in cases where the gastrointestinal tract (GIT) is involved. Cases of MS reported in the literature show the association between the presence of CBFB-MYH11 fusion and the involvement of abdominal sites (DALLAND *et al*., 2020). In 2011, a clinical case report showed the association of CBFB-MYH11 fusion with inv(16)(p13;q22) in a patient with MS in the small intestine, greater omentum and peritoneum (ÁLVAREZ *et al*., 2011).

Malignant pleural effusion in MS is uncommon, only isolated cases have been described in the literature. In 2004, a clinical case report of MS was published in which there was an involvement of the pleural fluid and this can be analyzed by flow cytometry, which showed a population of approximately 90% of blasts (DETTRICK; ROBERTSON; MORRIS, 2004).

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Due to the rarity of this condition, the aim of this report is to present a case of a patient diagnosed with MS with the presence of the CBFB-MYH11 fusion gene of inv 16 in the pleural fluid.

CASE REPORT

A 36-year-old male patient required medical care in Itajaí (Santa Catarina, Brazil) with complaints of diarrhea, post-voiding pelvic pain, abdominal pain and pressure. For investigation, a magnetic resonance imaging (MRI) of the abdomen was realized and appendectomy were performed. Epiplon and appendectomy product biopsies suggested a small cell malignant neoplasm infiltrating the adipose tissue. Since the surgery, the patient's clinic evolved with abdominal distension, ascites and loss of 11 kg. Due to these symptoms, the patient sought assistance in the emergency department of the University Hospital of the Federal University of Santa Catarina/EBSERH (HU-UFSC/EBSERH). At the HU-UFSC/EBSERH, the patient underwent a cavity inspection, in which omentum and peritoneum thickening involving mesenteric arteries was evidenced, suggesting peritoneal neoplasia/carcinomatosis. In that surgery, appendectomy and biopsy of the omentum were performed, and the results showed diffuse infiltration by immature monocytic/histiocytic cells, suggesting MS with myelomonocytic differentiation or non-Langerhans histiocytosis. A tomography performed showed mesenteric thickening with mesenteric lymph nodes, pleural effusion and ascites. For clinical investigation, an immunophenotyping of bone marrow, peripheral blood and cerebrospinal fluid (CSF) aspirates were requested. However, no neoplastic cells were detected in these biological samples. In the morphological and immunohistochemical analysis of the bone marrow biopsy, no neoplastic myeloid cells were observed. Nevertheless, in the appendix and epiplon biopsy, neoplastic cells with a phenotype suggestive of AML/MS (CD117+, CD123+, CD33+, CD34+, CD68+ and MPO+) were detected. In the morphological analysis of the ascitic fluid, cells with neoplastic characteristics were observed, whose phenotype (CD33 and CD34 positive) and the presence of mesothelial cells (calretinin+), analyzed by immunohistochemistry, suggested mesothelial hyperplasia and leukemic pleural effusion. Biochemical tests performed in peripheral blood presented lactate dehydrogenase (LDH) 243 U/L, C-reactive protein 8.80 mg/L, creatinine 0.82 mg/dL and uric acid 4.0 mg/dL.

Subsequently, paracentesis of the pleural fluid was performed, in which cytology showed 11,030 cells/mm³ and in the morphological analysis, 37% of cells presented an increased size, high nucleus/cytoplasm ratio, nucleus with irregular contour and some with nucleolus, cytoplasm with moderate to intense basophilia and sometimes vacuolized and frequent presence of cytoplasmic projections. Pleural fluid immunophenotyping showed the presence of 55.1% of blasts (CD45+, CD34-/+) committed to the myeloid lineage (CD38+, MPO+, CD117+, HLA-DR+, CD33+, CD13+, CD15+) and 25% of cells from the monocytic series, 40% of these cells were immature and had the following phenotype: CD300e-, CD14-/+ and CD117-/+. The search for genetic alterations in the pleural fluid by nested RT-PCR showed the presence of a band compatible with the CBFB-MYH11 fusion of inv(16). The biochemical analysis of the pleural fluid presented LDH levels of 797 U/L.

Based on clinical and laboratory diagnosis, the therapeutic decision was made using the same protocol used for AML, which starts with induction therapy (7" + 3" protocol) with three days of daunorubicin and seven days of cytarabine. Over the next three months, consolidation therapy was performed, which included the administration of cytarabine chemotherapy at higher doses.

DISCUSSION

MS, despite technological advances, has been an incorrectly diagnosed disease in 25-45% of cases. Despite being listed as a distinct entity in the World Health Organization (WHO) classification, MS without evidence of spinal cord involvement must be extensively investigated to be classified into an AML subtype (ARBER *et al*., 2016). MS with a monocytic component is an even more difficult case to make the differential diagnosis. For this, there are techniques such as immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH), cytogenetics and molecular studies that are essential for the correct diagnosis (SHAHIN; RAVANDI, 2020).

The diagnosis of MS is performed by immunocytochemical, immunohistochemical and/or immunophenotypic analyses. Such techniques allow the cell sample of biological material to be differentiated from other blast proliferations that can occur in AML, or in conjunction with the acute transformations of the myelodysplastic syndrome (MDS) and myeloproliferative neoplasms, as well as in cases of extramedullary hematopoiesis after administration of growth factors. In MS, immunophenotypic analysis by flow cytometry shows the expression of the following markers: CD33, CD13, KIT (CD117) and MPO, which are characteristic antigens of myeloid cells. In immunohistochemistry the myeloid phenotype is not different, immature myeloid cells express CD33, CD34, CD68 (KP1, but not PGM1) and KIT. The monoblastic variant expresses CD68/PGM1 and CD163, whereas CD34 and MPO are often negative. In addition, markers such as CD14 and KLF4 are also present (SWERDLOW *et al*., 2017; DALLAND *et al*., 2020).

In the case reported in this study, the immunophenotype observed by the immunohistochemistry of appendix and epiplon biopsy and pleural fluid immunophenotyping were important for the diagnosis of MS and are in accordance with what has been reported in the literature (SWERDLOW *et al*., 2017). In the evaluation of genetic alterations in the pleural fluid of this patient, the presence of the CBFB-MYH11 fusion gene of inv(16) was detected by nested RT-PCR. This inversion of chromosome 16 involving the fusion of the CBFB gene, present in the 16q22 region, with the MYH11 gene, in the 16p13 region, results in the formation of a chimeric protein that inhibits the differentiation of hematopoietic cells (KUNDU; LIU, 2001). According to Swerdlow *et al*. (2017), adult patients with KIT mutations have a higher risk of recurrence and worse survival; even so, the prognostic implications of the KIT mutation in AML with inv(16) or t(16;16) did not prove to be as significant as in AML with t (8;21). A study by Schwind *et al*. (2013) suggested that only the occurrence of mutations in KIT affects the clinical outcome, but not the type of transcript of the fusion.

In a retrospective study of 345 patients with myeloid sarcoma without associated AML, a three-year survival rate was observed. However, it was observed that this rate varies

according to the anatomical site of the disease and the context in which it develops (associated MDS and myeloproliferative neoplasm----). Due to the rarity of this disease, there is little information about prognosis in the literature. Thus, it is important to carry out more studies to obtain more knowledge about this subject (SHAHIN; RAVANDI, 2020).

The recommended treatment for isolated MS is the same as for AML. Some studies show that standard chemotherapy followed by hematopoietic stem cell transplantation has results similar to those of AML therapy (MINISTÉRIO DA SAÚDE, 2014). Treatment with consolidation therapy (eg, high-dose cytarabine) is associated with a high remission rate and favorable overall survival in AML patients with inv(16) (SWERDLOW *et al*., 2017).

According to Swerdlow *et al*., (2017), patients who receive allogeneic or autologous bone marrow transplants are more likely to survive or have longer survival time. In 2008, a study by Chevallier *et al*. (2008) showed a 47% 5-year overall survival rate among 51 patients with MS treated with allogeneic bone marrow transplantation. So far, the patient reported in this case report is undergoing chemotherapy, with a good response to treatment and is not yet scheduled for a bone marrow transplant.

CONCLUSION

In this report, a rare case of MS with CBFB-MYH11 fusion of inv (16) diagnosed in pleural fluid was described. Due to the existence of other proliferations of immature cells of myeloid origin, it is essential to jointly analyze the immunocytochemical, immunohistochemical and immunophenotypic methodologies for the differential diagnosis among these neoplasms. The absence of neoplastic cells in the bone marrow and the presence of immature cells committed to the myeloid lineage in the appendix and epiplon biopsy and in the pleural fluid defined the diagnosis of MS. The presence of the genetic alteration of inv(16) with CBFB-MYH11 fusion generally shows that there is monocytic differentiation, and therefore the importance of investigating this genetic alteration.

Interest conflicts

The authors declared no conflicts of interest.

Ethics Committee Approval

This study was conducted in accordance with the 1964 Helsinki declaration and Brazilian National Health Council Resolution No. 196/1996, approved by the Human Research Ethics Committee of the Federal University of Santa Catarina, Brazil (CASE: 61598816.7.0000.0121).

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