Teratoma with Mediastinal Embryonic Carcinoma Concomiting Histiocytic Sarcoma in Bone Marrow

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Abstract

**Background:** Association of extragonadal germ cell tumors EGCT with haematological malignancies is rare with a very limited prognosis.

**Methods and findings:** A case is presented of a man, 21 years old, with progressive dyspnea, chest pain, night sweats, generalized edema, hemoptysis, pancytopenia and increased serum levels of alpha-fetoprotein (AFP), beta-fraction of the hormone chorionic gonadotrophin (beta-HCG) and lactic dehydrogenase. Chest computed tomography showed a mediastinum mass measuring 11.3 x 7.3 cm. A biopsy revealed malignant germ cell neoplasia positive for cytokeratin, CD30 and AFP, indicating an embryonal carcinoma with teratoma. A bone marrow biopsy revealed interstitial infiltration by malignant neoplastic cells positive for CD68, CD163 and lysozyme, resulting in the diagnosis of histiocytic sarcoma. The patient had poor evolution resulting in death, sixteen days after admission.

**Conclusion:** Histiocytic proliferations are very rare progress rapidly and are usually fatal. Etiopathogenic theories for the simultaneity of these malignancies have been described based on processes of transformation from a same cellular precursor.

**Keywords**
Neoplasms; Germ Cell and Embryonal; Carcinoma, Embryonal; Histiocytic Sarcoma; Mediastinal Neoplasms.

Introduccion

Germ cell tumors (GCT) are responsible for 2% of human malignancies, being the most common malignant tumor in the age group of 15 to 35 year old of males [1]. Gonads represent the most frequent site of involvement, however these tumors also originate from other structures of the body medial line [2, 3]. Extragonadal germ cell tu-
mors (EGCT) correspond to 2-5% of all germ cell tumors, with the mediastinum being the main focus of occurrence (54%), followed by the retroperitoneum (45%) [1, 3].

The association of GCT, especially EGCT, with malignant hematological malignancies was first reported in the 1980s [4-8]. The presentation of haematological neoplasia occurs within a period of up to six months after diagnosis of the germ tumor [1]. The hematological pathologies most frequently involved in this association are acute megakaryoblastic leukemia, myelodysplasia with abnormal megakaryocytes, or essential/idiopathic thrombocytosis, acute myeloid leukemia and, rarely, malignant histiocytosis/systemic mastocytosis [9, 10]. Histiocytic proliferations, such as hemophagocytic syndrome, malignant histiocytosis and histiocytic sarcoma, stand out for their rarity and highly aggressive biological behavior [10, 11]. In this article, a case is presented of EGCT concomitant to histiocytic hematological malignancy diagnosed in bone marrow.

**Methods and Findings**

Man, 21 years old, white, driver, previously healthy. On admission to the hospital, the patient had progressive dyspnea, chest pain, dry cough, nocturnal sweating, generalized edema and hemoptysis. These symptoms had begun two months before. There were no reports of fever or weight loss in this period. The physical examination indicated abolition of the vesicular murmur in the pulmonary bases bilaterally, and hepatomegaly.

Chest radiographic revealed bilateral pleural effusion and increased cardiac area. Computed tomography of the chest revealed pleural effusion, pericardial effusion, and hypodense mass with lobulated and septate contours, measuring 11.3 x 7.3 cm, located in the pre-vascular mediastinum. The echocardiogram confirmed cardiac tamponade caused by the mass.

Laboratory tests indicated pancytopenia, increased alpha-fetoprotein levels (549.02 ng/mL, normal to 10 ng/mL), increased beta-fraction of the hormone chorionic gonadotrophin (beta-HCG levels, 21.87 mUL/mL, normal to 5mUL / mL) and increased lactic dehydrogenase (DHL values always above 5000 U/L, normal up to 300 U/L). The patient underwent mediastinal mass biopsy and bone marrow evaluation.

The mediastinal mass biopsy revealed a neoplastic lesion characterized by irregular distribution of cellularity with large and oval cell clusters with squamous-like nuclei, atypia, mitotic figures and stromal proliferative fibroblasts (**Figure 1**). Foci of cartilaginous and neural tissue were found in this material (**Figure 2**). Morphological aspects defined
a malignant germ cell neoplasm that was confirmed and classified as a mediastinal teratoma with embryonal carcinoma, which was shown by immunohistochemical reactions. The tumor showed immunopositivity for cytokeratins (AE1/AE3) (Figure 3), CD30 (Figure 4) AFP, S-100 and vimentin. Markers such as 35BH11, beta-HCG, PLAP, desmin, myogenin, myo-D1 and CD117 were negative.

A bone marrow biopsy confirmed a morphological pattern of intense hypercellularity for the patient’s age characterized by interstitial infiltration of neoplastic cells, containing large nuclei, ovals, evident nucleoli and some binucleation (Figure 5). Similar cells were also found in the patient’s myelogram. Immunohistochemical study revealed these cells were immunonegative for cytokines (AE1/AE3), EMA, AFP, CD45, CD15, CD20, CD3 and beta-HCG. They were positive for CD68, CD163 (Figure 6) and lysozyme. Thus, the immunohistochemical profile concluded with the diagnosis of histiocytic sarcoma in the bone marrow of the patient.

Therefore, the patient had the concomitance of two malignant neoplasms: a teratoma with embryonal carcinoma in the mediastinum associated with histiocytic sarcoma in bone marrow. The clinical sta-

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**Figure 3:** (H&E, 400x) Mediastinal mass: atypical cells with squamous-like nuclei.

**Figure 4:** (Immunohistochemistry, 400x) Cytokeratins (AE1/AE3) were positive, indicating the epithelial histogenesis.

**Figure 5:** (H&E, 400x) Bone marrow biopsy: interstitial infiltration of neoplastic cells.

**Figure 6:** (Immunohistochemistry, 400x) The atypical bone marrow cells were positive for CD163. This finding and the staining for other histiocytic markers confirmed the diagnosis of histiocytic sarcoma in the bone marrow.
tus deteriorated with thrombocytopenia, which associated with the mass, caused the cardiac tamponade. The respiratory and neurological depression result in cardiorespiratory arrest resulting in death, sixteen days after hospitalization.

Discussion
The EGCTs’ etiopathogenesis is not yet known and some theories have been maintained that could explain the genesis of these tumors. One of them, called Burned-Out phenomenon, defines the EGCT as a metastasis of a gonadal tumor that spontaneously involuted. However, the possibility of concomitance can also occur. Another theory defines EGCT as derivatives of germ cell groups located in the liver, bone marrow and brain that, due to embryogenesis failures, did not migrate completely from the urogenital crest to the gonads, remaining in midline structures of the body, developing this tumor [1].

Moran et al. [2] subdivided mediastinal germ cell tumors into three groups: teratomatous tumors (mature and immature teratomas), teratomatous tumors composed of other malignant neoplastic elements (combinations of teratomas with other germinal tumors or epithelial or mesenchymal tumors), and non-teratomatous tumors (seminomas, yolk sac tumors, embryonal carcinomas, choriocarcinoma, and combinations of these tumors) [2]. The case presented here is a mediastinal tumor defined as a teratoma with embryonal carcinoma component.

Embryonal carcinoma presents as large and invasive, pure or mixed masses. Epidemiologically, they are 12% of mediastinal GCTs and 30-65% of non-seminomatous mediastinal GCTs [3]. The embryonic carcinoma presents with elevation of serum AFP levels and, eventually, of beta-HCG [1, 3, 4]. In the case of the patient presented here, there was an increase in the levels of AFP and beta-HCG. As for morphology, the tumor composition is of primitive cells, with a polygonal aspect and abundant cytoplasm, clear or granular. The nuclei are large and oval, and there may be atypical mitoses and areas of necrosis and hemorrhage. The immunohistochemical evaluation of these tumors were positive for CD30, low molecular weight cytokeratins, PLAP and AFP [1]. In the case of the patient presented here, tests were positive for cytokeratins, CD 30 and AFP.

Hematologic malignancies occur in 2-6% of patients with non-seminomatous mediastinal GCT that present clinical signs such as pancytopenia, hepatosplenomegaly and/or thrombocytopenia [1]. Hematologic malignancies associated with non-seminomatous mediastinal EGCTs must be distinguished from secondary leukemias, which occur after therapies with alkylating agents or topoisomerase II inhibitors. Secondary leukemias should be diagnosed two to seven years after treatment [5-8]. Hartman et al. [7] have explained that in the cases of this type of neoplastic association the mean interval between the diagnosis of mediastinal tumor and the diagnosis of haematological neoplasia was six months. In one third of the cases reviewed, the manifestation was concomitant, as was seen in the case presented here [5, 6]. The clinical course of hematological malignancies in these patients with germ cell tumors (gonadal or extragonadal), tends to be aggressive, resulting in death, often before the therapeutic intervention [7-10].

In the retrospective and multicenter study conducted by Hartman et al. [7], in 2000, in partnership with cancer centers in the United States of America and Europe, of the 635 patients selected because of diagnosis of EGCT, in 341 cases the mediastinum was the main topography. Among all the patients studied, 17 had hematological malignancies diagnosed up to six months after the diagnosis of a non-seminomatous mediastinal EGCT, and the diagnosis was simultaneous. The study also demonstrated an increased risk of hematologic malignancy among patients with this type of tumor, of the mediastinum that was statistically
significant in relation to the general population. Confirming the unfavorable prognosis of the association, none of the 17 patients studied survived beyond two years of diagnosis [7].

Regarding the cytogenetic aspects, GCTs, gonadal and extragonadal, 90% of cases have the presence of one or several isochromosomes 12p and deletion of the long arm of chromosome 12. In cases with association between mediastinum GCT and haematological malignancies, such as leukemias, the same cytogenetic changes seen in the cells of mediastinal tumors are found in leukemic blasts in up to 38% of the patients, suggesting the same precursor for germ and hematological malignancies [1]. Karyotype studies have already found, in the blasts of the leukemias of these patients, evidence of numerical chromosomal abnormalities such as XXY and trisomy 21, which is compatible with reports of association of mediastinal GCT with Down’s Syndrome and Klinefelter’s Syndrome [3, 11]. Nichols et al., in 2008 [6], studied non-seminomatous EGCT cells and showed they could exhibit differentiation morphological patterns, from embryonic carcinoma to extraembryonic or somatic tissue elements, and that they could be indistinguishable from malignancies such as sarcomas and adenocarcinomas. Thus, hematological malignancies could originate from a process of malignant transformation of hematopoietic components present in the GCT [6].

The histiocytic proliferations associated with mediastinal GCT are rare, progress rapidly and are fatal and include hemophagocytic syndrome, malignant histiocytosis and histiocytic sarcoma [11]. Histiocytic sarcoma is a malignant neoplasm that may present with solitary or systemic masses, with hepatosplenomegaly. The association with GCTs can be explained by a common origin, which is represented by pluripotent germ cells [3]. The morphology of this hematological neoplasm exhibits cells with nuclear atypia in varying degrees, with dissemination to multiple organs [11]. Diagnostic determination is made from tests positive for immunohistochemical markers such as CD68, CD163 and lysozyme, with at least two of these markers being sufficient [3,11]. Cytogenetic abnormalities are also described for this type of hematologic malignancy. In addition to abnormalities related to chromosome 12, other alterations such as chromosome 8 trisomy, deletion of the long arm of chromosome 5 (5q) and trisomy of chromosome 9 have been reported [11-14].

**Conclusion**

The association between GCT of the mediastinum and hematologic malignancies is an uncommon condition whose etiopathogenesis is poorly understood and attributed to the same group of progenitor cells. The case presented in this article describes the clinical-pathological evolution of a young patient with teratoma and embryonal carcinoma of the mediastinum concomitant with histiocytic sarcoma in bone marrow. The patient died, confirming the reserved prognosis of this type of neoplastic association.

**Support funding**

This project did not receive any grant.

**References**


