Case Report

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Simultaneous occurrence of primary mediastinal germ cell tumor and myelodysplastic syndrome: A case study and a concise review

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Abstract

Background: Primary mediastinal germ cell tumors are potentially aggressive neoplasms that are rarely associated with hematological malignancies in young men. The association between primary mediastinal germ cell tumors and hematological malignancies involves complex oncogenesis that has yet to be established, and these uncertainties are reflected in the unresponsiveness to the current therapeutic interventions, hence, leading to an unfavorable prognosis.

Case presentation: A case of simultaneous occurrence of primary mediastinal germ cell tumors and myelodysplastic syndrome is presented, along with a review on the association between primary mediastinal germ cell tumors and hematological malignancies.

Conclusion: A diagnosis of associated primary mediastinal germ cell tumors and hematological malignancies must be suspected when cytopenia occurs in patients with primary mediastinal germ cell tumors or when mediastinal enlargement is detected in patients with malignant myeloid disorders. Specific recommendations regarding treatment for synchronous primary mediastinal germ cell tumors and hematological malignancies are needed.

Keywords: Neoplasms; Germ Cell and Embryonal; Mediastinal Neoplasms; Hematologic Neoplasms; Myelodysplastic Syndromes; Carcinogenesis.

Introduction

Primary mediastinal germ cell tumors (PMGCT) are potentially aggressive neoplasms that are rarely associated with hematological malignancies (HM) in young men.1 Among HM, an association between PMGCT and myelodysplastic syndrome (MDS) is extremely uncommon. The association between PMGCT and HM involves complex oncogenesis that has yet to be established, and these uncertainties are reflected in the unresponsiveness to the current therapeutic interventions, hence, leading to an unfavorable prognosis. The present study reports a case of simultaneous occurrence of PMGCT and MDS, along with a brief review on the association between PMGCT and HM.

Case Report

A 20-year-old male patient presented with a 2-week history of asthenia and syncope following exertion and was hospitalized. There was no history of fever, weight loss, adenopathy, dyspnea, chest pain, or symptoms of bleeding. On physical examination, pallor and splenomegaly (spleen palpated 2 cm below the left costal margin) were observed. There was no family history of cancer or personal history of hematologic abnormalities.

Initial laboratory evaluation showed pancytopenia with severe anemia (serum hemoglobin level: 3.8 g/dL; mean corpuscular volume: 84.6 fL; mean corpuscular hemoglobin concentration: 30.6 g/dL), reticulocytopenia (10 × 109/L), leukopenia

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with lymphopenia (2.67 × 109/L – 71% neutrophils, 23% lymphocytes, 6% monocytes), severe thrombocytopenia (29 × 109/L), and severe hyperferritinemia (10,733 ng/mL [normal: 23.8–274.6 ng/mL]). The following parameters were within the normal range: serum lactic dehydrogenase (186 U/L [normal: 125–220 U/L]), serum vitamin B12 (555 pg/mL [normal: 187–882 pg/mL]), serum folate (16.4 ng/mL [normal: 4.6–18.7 ng/mL]), total bilirubin (0.9 mg/dL [normal: <1.1 mg/dL]), serum triglyceride level (145 mg/dL [normal: <150 mg/dL]), and serum fibrinogen (197 mg/dL [normal: 150–450 mg/dL]). The direct antiglobulin test was negative. Serology for human immunodeficiency virus, viral hepatitis (B and C), and acute parvovirus were non-reactive. Bone marrow (BM) aspiration revealed preserved global cellularity, erythroid hypoplasia with severe dysplasia (Figure 1A, B) without ring sideroblasts, granulocytic dysplasia, myeloid to erythroid ratio of 5.1:1, and 2% blasts. BM biopsy showed increased cellularity (Figure 1C) with megakaryocytic hyperplasia with dysplasia (presence of hypolobated megakaryocytes) (Figure 1D), and excessive hemosiderin, without increased blasts (0.5% CD34+ cells). BM cytological and histological analysis showed no signs of infiltration by non-hematological cancer or hemophagocytosis. The karyotype analysis from the BM aspirate was 46,XY [20]. The combination of the peripheral blood and bone marrow findings led to a diagnosis of MDS with multilineage dysplasia.

Mediastinal enlargement was found on a contrast-enhanced chest computed tomography scan (CT), which showed a mass in the anterior mediastinum, measuring 8.7 x 6.7 cm (Figure 2A, B). An abdominal CT scan showed moderate splenomegaly (splenic index: 3240 cm3 [normal: <480 cm3]). Ultrasonography of the scrotal sac showed no evidence of tumor. Transthoracic biopsy of the mediastinal mass was performed, and the sample underwent histological and immunohistochemistry analysis. A diagnosis of nonseminomatous germ cell tumor (GCT) was made as yolk sac tumor histology (Figure 2C) and characteristic immunohistochemistry (α-fetoprotein [AFP] positive; and CD57, cytokeratin 7, cytokeratin 20, p63, PAX8, placental alkaline phosphatase, and terminal deoxynucleotidyl transferase negative) findings were found (Figure 2D). Evaluation of tumor markers showed high levels of serum AFP (231 ng/mL [normal: 0.9–8.8 ng/mL]) and normal levels of human chorionic gonadotropin β subunit levels (2.31 mIU/mL [normal: <5 mIU/mL]).

The management consisted of frequent transfusion support with packed red blood cells (36 units) and prophylactic or therapeutic platelets transfusions (126 random donor units and 2 apheresis donor units) during the 7 weeks of assistance. The diagnosis of PMGCT (stage I – tumor restricted to the mediastinum without evidence of macroscopic and/or microscopic infiltration of adjacent structures) associated with MDS was made after considering the cytological and histological BM findings and the transfusion dependence, and excluding bone marrow infiltration by non-hematological cancer and hemophagocytic lymphohistiocytosis. Neoadjuvant chemotherapy was initiated with idarubicin (8 mg/m² D1 and D3), cytarabine (100 mg/m² in continuous infusion D1-D5), etoposide (100 mg/m² D1-D5), and cisplatin (20 mg/m² D1-D5). However, the patient died due to sepsis 9 days after initiation of chemotherapy.

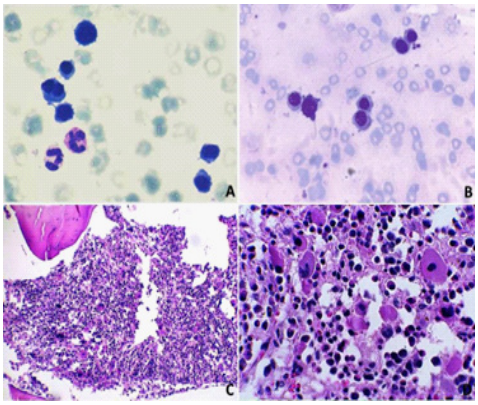

Figure 1: *Bone marrow cellularity from aspiration and biopsy. A, B: Bone marrow aspirate showing erythroid precursor and granulocytic dysplasia, Leishman stain, ×1000 magnification. C: Bone marrow biopsy showing increased cellularity and no signs of germ cell tumor infiltration, Hematoxylin & eosin stain, ×200 magnification. D: Bone marrow biopsy showing megakaryocyte hyperplasia presenting hypolobated megakaryocytes, Hematoxylin & eosin stain, ×400 magnification.*

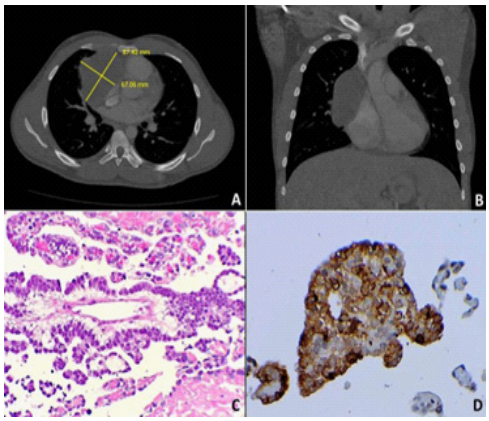

Figure 2: *Computed tomography, histology, and immunohistochemistry of mediastinal mass. A, B: Contrast-enhanced chest tomography showing large mediastinal mass. C: Mediastinal mass biopsy showing epithelial cells in papillary and microcystic arrangement, Schiller-Duval corpuscles (in the center of the image), and areas of necrosis, Hematoxylin & eosin stain, ×200 magnification. D: Positive α-fetoprotein reaction in immunohistochemical study, ×270 magnification.*

Discussion

PMGCT are rare neoplasms that occur due to malignant transformation of germinal elements in the mediastinum without a primary gonadal focus [1]. They represent up to 10%– 20% of all primary mediastinal tumors and possibly originate due to a failure in the migration process of primordial germ cells along the urogenital crest during early embryogenesis [1]. They can be classified as seminomas or nonseminomatous tumors, including in this last group, teratomas, yolk sac tumors, choriocarcinomas, embryonic carcinomas, and mixed GCTs [2]. Some studies have shown an association between HM and GCT in male patients with nonseminomatous extragonadal GCT in the mediastinum (usually anterior mediastinum) [3, 4]. The HM associated with PMGCTs are mainly represented by myeloid neoplasms with megakaryocytic lineage disorders,

such as acute megakaryoblastic leukemia, MDS with abnormal megakaryocytes, and essential thrombocythemia [3-5]. Rarely, other hematological conditions have been reported, including other subtypes of acute myeloid leukemia (AML), acute lymphoblastic leukemia, malignant histiocytosis, systemic mastocytosis, myeloid sarcoma, acute mixed lineage leukemia, and nonimmune-mediated thrombocytopenia [3-5]. The estimated HM incidence in patients with nonseminomatous PMGCT is approximately 2% per year, and is highest in the first year after PMGCT diagnosis [3]. The risk of acute leukemia in PMGCT patients is estimated to be 250-fold higher than that in the general population of the same age [4].

No specific recurrent cytogenetic abnormality has been found in patients with both PMGCT and HM [3, 5]. However, the detection of an isochromosome i(12p) (a testicular GCT chromosome marker not found in hematological cancers) in leukemic blasts in 38% of patients supports the relationship between PMGCT and HM [3]. Other genetic abnormalities that have been reported include chromosome 8 trisomy (16%) and XXY karyotype (14%) [3]. A normal karyotype was found in 46% of patients [3].

Increasing evidence has been found that support the clonal relationship between PMGCT and HM, which are as follows: (1) isochromosome i(12p) detection in leukemic blasts and PMGCT cells, (2) cytokeratin expression and p53 hyperexpression in leukemic blasts, (3) identical cytogenetic findings from PMGCT cells and bone marrow aspirate cells in MDS- PMGCT patients, and (4) detection of leukemic blasts, bone marrow precursors, and organized hematopoiesis in the GCT microenvironment [3,4,6-8].

According to this, hematological neoplasms associated with PMGCT would not be classified as de novo, as they have resulted from the malignant transformation of hematopoietic tissue that is related to extragonadal GCT or have directly originated from totipotent or pluripotent germ cells [4,5,9]. A differential diagnosis of myeloid disorders due to therapeutic use of alkylating agents or topoisomerase II inhibitors must be considered when myeloid disorders (AML or MDS) are diagnosed after PMGCT treatment. However, treatmentrelated myeloid disorders usually appear much later after PMGCT diagnosis (2–7 years) and present cytogenetic abnormalities that are normally found in secondary myeloid disorders [3].

The mean age of patients affected by the association of PMGCT and HM is 23 years (17–35 years) [3]. The mean duration between PMGCT diagnosis and HM detection is 6 months (range, 0–122 months), and both conditions are simultaneously diagnosed in up to one third of cases [3]. The main laboratory finding associated with hematological cancer in PMGCT patients is pancytopenia, which is present in 35.2% of patients [3]. Bone marrow findings in five patients with PMGCT and MDS included megakaryocytic dysplasia, excessive blasts, marrow cellularity abnormalities, and severe dyserythropoiesis [3].

The clinical course of HM tends to be very aggressive in patients with PMGCT [3-5]. The mean survival from PMGCT diagnosis was significantly lower in patients who developed HM than in patients without HM (14 vs. 51 months) [3]. The possible explanations for such unfavorable outcomes are related to the biological characteristics of HM-PMGCT association, the prominent ones including: (1) the fulminant clinical course of hematological neoplasia due to unfavorable response to chemotherapy and infrequent and short-lasting complete remission, (2) the possible synchronous presentation of cancers with accumulated toxicity and absence of a specific protocol to treat the association, and (3) the unresectable nature of the residual PMGCT after chemotherapy. A review of eight AML patients treated with anthracycline and cytarabine induction chemotherapy showed remission in only one patient (short-lasting) [3]. In this case report, the simultaneous presentation of the cancers with severe bone marrow dysfunction that was aggravated by the toxicity of the chemotherapeutic agents may have contributed to the patient's early death.

The complex association between PMGCT and HM has not been well established and represents a wide scope for study and research. Its rarity contributes to the difficulty in conducting prospective studies. A diagnosis of associated PMGCT and HM must be suspected when cytopenia occurs in patients with PMGCT or when mediastinal enlargement is detected in patients with malignant myeloid disorders; hence, targeted investigation and intervention must be performed despite the possible disappointing results. Specific recommendations regarding chemotherapeutic regimens for synchronous PMGCT and HM are needed.

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