



Case Report

Two Different Somatic-type Malignancies Arising from a Mediastinal Germ Cell Tumor: A Case Report

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Abstract

Background: Mediastinal germ cell tumors (GCTs) are rare malignant neoplasms that occasionally develop somatic-type malignancies (SMs), such as sarcomas, carcinomas, and hematologic malignancies. **Case presentation:** We report a unique case of a 16-year-old male patient with a mediastinal GCT that simultaneously developed two different SMs: well-differentiated angiosarcoma and acute megakaryoblastic leukemia (AML). The patient initially presented with left shoulder pain and intermittent shortness of breath. The imaging study demonstrated a 12.5 × 9.0 × 8.5 cm heterogeneous mass in the left anterior mediastinum. The mediastinal mass was resected and showed a cystic mature teratoma with somatic transformation into well-differentiated angiosarcoma and AML. A subsequent bone marrow biopsy confirmed the diagnosis of AML, and next-generation sequencing demonstrated the presence of *PTEN* and *TP53* gene mutations in the AML. Despite aggressive chemotherapy and allogeneic stem cell transplantation, the patient died 10 months after diagnosis. **Conclusions:** Our report demonstrates the unique capability of mediastinal GCTs to simultaneously develop two different SMs. The presence of two different SMs in mediastinal GCTs is associated with extremely aggressive behavior and a poor prognosis.

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Introduction

Most germ cell tumors (GCTs) arise from the gonads, i.e., the testicles and ovaries, but a small subset occurs at other locations.^{1,2} Extragenital GCTs typically develop in midline structures, such as the mediastinum, retroperitoneum, pineal region, and suprasellar areas. The mediastinum is the most common location of extragenital GCTs and accounts for 15% of all tumors located in that area.^{3–5} Mediastinal

GCTs share similar histological and immunohistochemical features with their gonadal counterparts, including the presence of isochromosome 12p.^{6,7} Furthermore, like gonadal GCTs, a subset of mediastinal GCTs develops secondary somatic-type malignancies (SMs), such as sarcomas, carcinomas, and hematologic malignancies.^{8,9} The development of SMs in GCTs is usually associated with a poor response to chemotherapy and a dismal prognosis.^{8–10} Herein, we report a unique case of mediastinal GCT that developed two different types of SM: well-differentiated angiosarcoma and acute megakaryoblastic leukemia.

Case presentation

A 16-year-old Caucasian male patient presented with left shoulder pain and intermittent shortness of breath. Chest X-ray and computed tomography scan demonstrated a 12.5 × 9.0 × 8.5 cm heterogeneous mass in the left anterior mediastinum. His serum alpha-fetoprotein (73.9 ng/mL; normal <4) and lactate dehydrogenase (2,408 U/L; normal 135–225) levels were elevated, and his Beta-human chorionic gonadotropin level was normal (<2 IU/L). He also had anemia, with a hemoglobin of 12.1 g/dL (normal 14–18) and hematocrit of 35.5% (normal 40–54), and thrombocytopenia with a platelet count of 97,000/μL (normal 150,000–450,000). He underwent a core needle biopsy of the mediastinal mass, which showed immature cartilage elements with focal necrosis, consistent with teratoma. In the stroma, there were areas of atypical spindle cell proliferation associated with vascular channel formation and hemorrhagic changes, raising the possibility of somatic transformation to angiosarcoma. Seven days after the biopsy, he developed postoperative hemorrhage associated with hemorrhagic shock, requiring resuscitation with blood transfusion. He subsequently underwent thoracotomy with evacuation of the hematoma. The resection of the mediastinal mass showed a multicystic lesion lined by bland glandular epithelium, admixed with immature cartilage, consistent with cystic mature teratoma (Fig. 1a). There were focal areas of atypical spindle cell proliferation forming irregular vascular spaces with intraluminal budding and papillary-like projections. In some areas, the vascular spaces were poorly formed with subtle cleft-like spaces (Fig. 1b and c). Immunohistochemical stains showed that the atypical cells were positive for endothelial markers CD31, CD34, and ERG (Fig. 1d–f), while negative for cytokeratin, SALL4, and OCT3/4. The overall features were consistent with well-differentiated angiosarcoma. In addition, there were small

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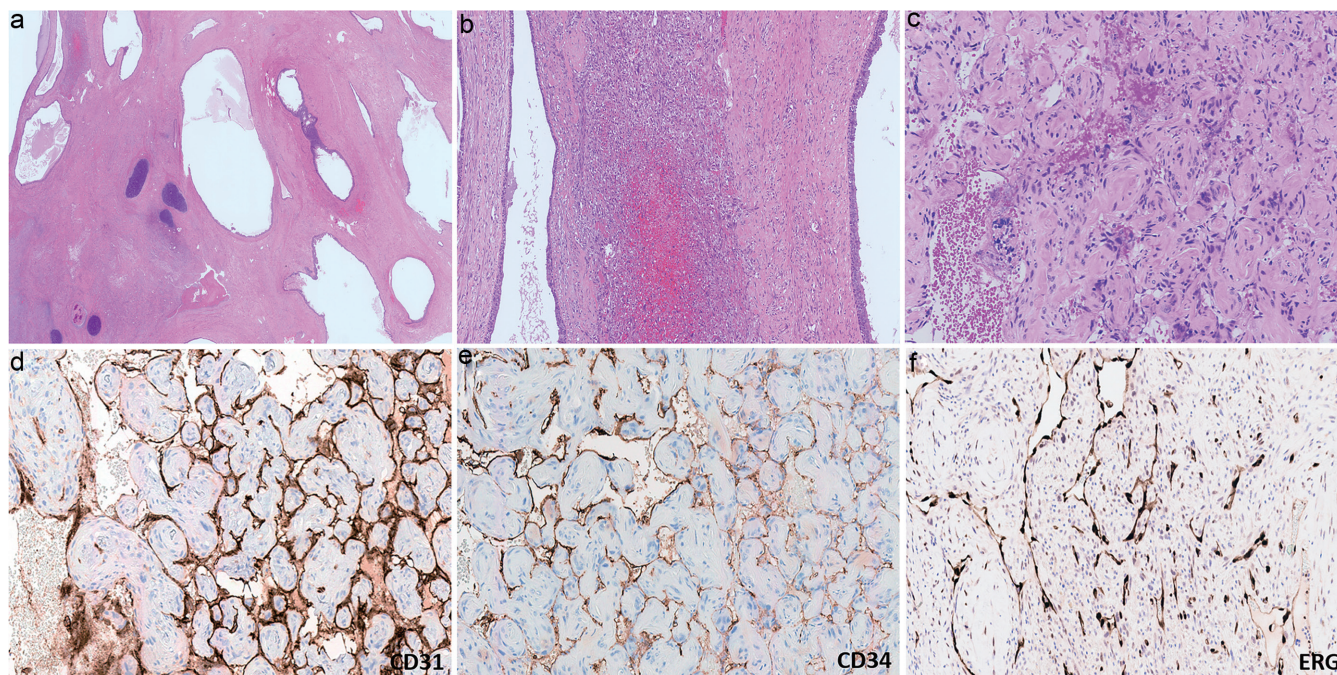


Fig. 1. Hematoxylin and eosin-stained section of mediastinal mass shows mature cystic teratoma (a). Spindle and epithelioid cells proliferate and form irregular vascular channels with intraluminal budding and papillary-like projections (b, c). The atypical cells are positive for CD31 (d), CD34 (e), and ERG (f), supporting the diagnosis of angiosarcoma. Original magnification: a 40 $\times$, b 100 $\times$, c-f 200 $\times$.

nests of atypical cells mixed with blood cells and fibrin in vascular spaces. The atypical cells were highly polymorphic, hyperchromatic, with irregular nuclei and a high nuclear/cytoplasmic ratio (Fig. 2a and b). Immunohistochemical stains showed that the atypical cells were negative for embryonal

carcinoma markers, such as OCT3/4 (Fig. 2c), CD30, SALL4, and cytokeratin, and did not express vascular markers such as CD31, CD34, and ERG. However, these atypical cells were positive for CD43, CD61, and factor VIII (Fig. 2d-f), supporting the diagnosis of acute megakaryoblastic leukemia (AML) with

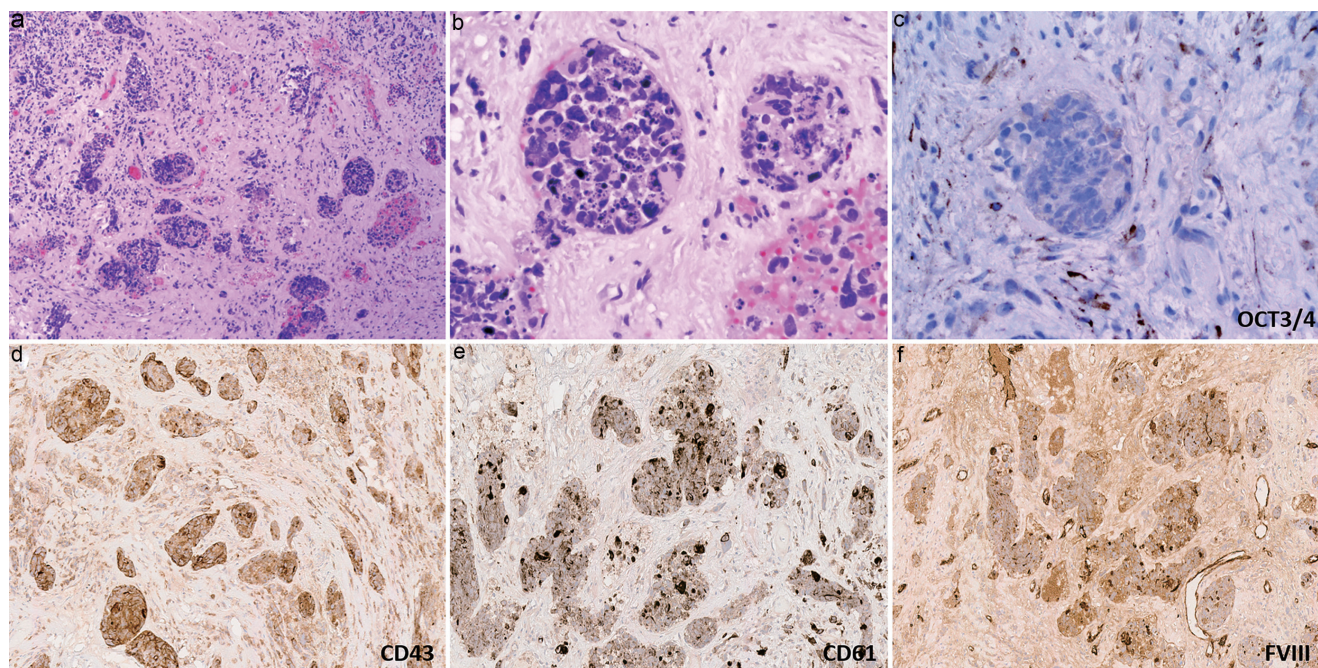


Fig. 2. Hematoxylin and eosin-stained section of mediastinal mass shows small nests of highly atypical tumor cells with large, polymorphic, hyperchromatic nuclei, mixed with blood cells and fibrin (a, b). The atypical cells are negative for OCT3/4 (c) and positive for CD43 (d), CD61 (e), and Factor VIII (f), consistent with acute megakaryoblastic leukemia. Original magnification: a 100 $\times$, b-c 200 $\times$, d-f 100 $\times$.

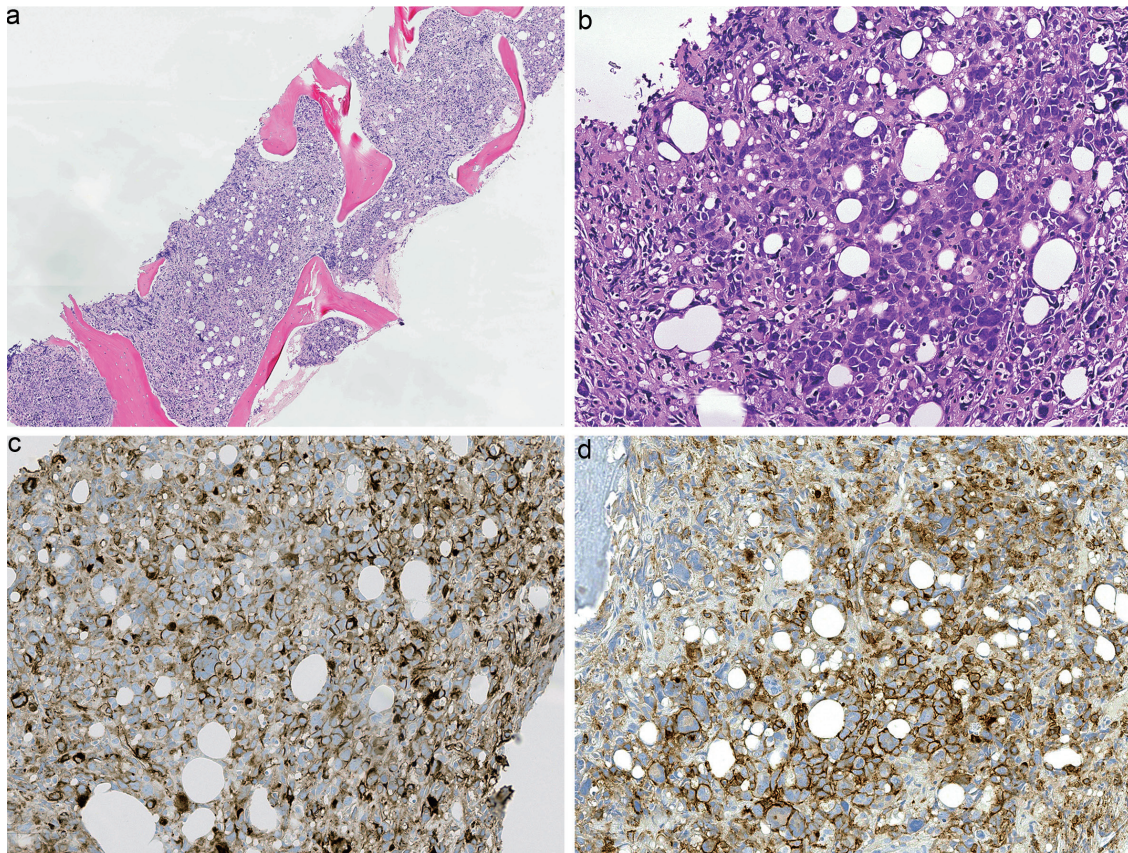


Fig. 3. Hematoxylin and eosin-stained section of bone marrow shows extensive infiltration of large and anaplastic cells (a, b). The atypical cells are positive for CD43 (c) and CD31 (d), consistent with acute megakaryoblastic leukemia. Original magnification: a 40 $\times$, b–d 200 $\times$.

megakaryoblastic differentiation. A bone marrow biopsy showed hypercellular marrow with a cellularity of 80%–90% and extensive infiltration by sheets of large/anaplastic cells (Fig. 3a and b). The anaplastic cells were positive for CD34, CD43, CD45, CD31, CD61, CD117, and CD56 (Fig. 3c and d), confirming the diagnosis of AML with megakaryoblastic differentiation. Next-generation sequencing (NGS) testing performed on the bone marrow biopsy using the MD Anderson Mutation Analysis Precision Panel—a custom high-throughput NGS assay that uses targeted hybridization-based capture technology for detection of sequence variants/mutations in 610 genes, copy number variants in 583 genes, and select gene rearrangements in 34 genes—revealed the presence of *PTEN* and *TP53* gene mutations in AML cells.

The patient was initially treated with vincristine and doxorubicin, but the mediastinal mass continued to increase in size. The mediastinal tumor was resected and showed cystic teratoma without SM. He received additional chemotherapy with cladribine, daunorubicin, cytarabine, and venetoclax, and then underwent haploidentical hematopoietic stem cell transplantation. Unfortunately, his leukemia relapsed three months after transplantation, and his condition was complicated by multiple bacterial and fungal infections. He developed acute hypoxic respiratory failure despite mechanical ventilation and died 10 months after the initial diagnosis of mediastinal GCT with SM.

Discussion

Mediastinal GCT is a rare disease, constituting only 1–3% of

all GCTs.^{3–5} Patients with mediastinal GCTs are young, with a median age of 31 years, and show a male predominance with a male-to-female ratio of 9:1.³ Mediastinal GCTs may be associated with Klinefelter syndrome in some patients.³ By histological classification, teratoma represents the most common type of mediastinal GCT, followed by seminoma and other GCT components.¹¹ Mediastinal GCTs carry a worse prognosis than GCTs at other sites, and seminoma appears to have a better clinical outcome than other types of mediastinal GCTs.^{9,12} The etiology of extragonadal GCTs is largely unclear. It has been hypothesized that extragonadal GCTs may arise from abnormal migration of germ cells from the yolk sac to the genital ridge along the midline during embryogenesis.¹² Retention and reprogramming of these germ cells in ectopic sites lead to the development of extragonadal GCTs.¹² An alternative theory is that extragonadal GCTs result from the reverse migration of transformed germ cells in the gonads.^{1,2}

A small subset of mediastinal GCTs may develop distinct SMs characterized by malignant components resembling non-germ cell cancers in other organs.^{8,10} Most SMs are associated with teratoma, and a small subset coexist with yolk sac tumor.⁹ The histologic subtypes of SM are diverse and include carcinomas, sarcomas, and hematologic malignancies.⁸ Rhabdomyosarcoma is the most common sarcomatous SM, while adenocarcinoma is the most common carcinomatous SM.¹⁰ The pathogenesis of SM is not well established. It has been postulated that SM may result from transformation of a teratomatous component, as most SMs are associated

with teratoma.¹⁰ Some studies propose a “dedifferentiation” theory, suggesting SM may arise from transformation of the blastematos stroma in GCT.¹³ Another hypothesis is the “stem-like cell theory”, proposing that both GCT and SM originate from common pluripotent progenitor cells, supported by the detection of isochromosome 12p in both GCT and SM.^{6,7} Furthermore, most SMs share identical patterns of loss of heterozygosity with their matched GCTs, also supporting their common origin along the GCT lineage.¹⁰

Mediastinal GCTs demonstrate a high tendency to develop hematologic SM.^{8,9} Hematologic SM occurs in 2–6% of mediastinal GCTs but is rarely seen in GCTs at other sites.¹⁴ The most common hematologic SMs are acute leukemia with megakaryocytic and monocytic/histiocytic differentiation, although several other types have also been reported.^{15–19} Hematologic SMs derived from mediastinal GCTs share similar morphologic and immunohistochemical features with *de novo* hematologic malignancies. Several studies have reported that hematologic SMs and mediastinal GCTs may arise from common progenitor cells, as there are similar molecular alterations in both tumors, including the presence of isochromosome 12p, which is usually absent in hematologic malignancies not associated with mediastinal GCTs.^{15,16,19} Taylor *et al.*¹⁹ investigated the clonal relationship between matched mediastinal GCTs and hematologic SMs using whole-exome sequencing and found allelically imbalanced p53 and/or RAS pathway mutations in both tumors, supporting a common origin. Furthermore, hematologic SMs carried multiple distinct gene mutations not detected in mediastinal GCTs, suggesting that additional genetic alterations might contribute to the development of hematologic SMs in mediastinal GCTs.¹⁹ Interestingly, our current case also demonstrates p53 and PTEN gene mutations in the bone marrow specimen with AML. p53 and PTEN are two of the most frequently mutated tumor suppressor genes in human cancers. Simultaneous inactivation of both PTEN and p53, often termed a “double-hit,” promotes cancer progression and transformation.²⁰ As NGS was not performed on the mediastinal tumor with teratoma and angiosarcoma components, the role of p53 and PTEN genes in somatic transformation of GCT remains to be studied.

The development of two different histologic types of SMs in mediastinal GCTs is an extremely rare phenomenon. Saito *et al.*²¹ reported a case of coexistence of angiosarcoma and myeloid sarcoma in mediastinal teratoma. Dominguez Malagon *et al.*²² reported a case of mediastinal teratoma with well-differentiated angiosarcoma and atypical hematopoietic cells within the vascular spaces, and the patient subsequently developed AML involving the spleen. Motzer *et al.*²³ described four patients with mediastinal GCTs containing sarcomatous SMs who also had hematologic malignancies, including non-Hodgkin’s lymphoma and non-lymphocytic leukemia. The development of different SMs in mediastinal GCTs is associated with an extremely aggressive clinical course, with a median survival time of six months,^{8,17,18,24,25} as SMs are refractory to chemotherapy and allogeneic bone marrow transplantation.^{26,27}

Limitations

There are several limitations in our report. First, our report is based on a single case, and it is difficult to establish the causal relationship between mediastinal GCT and SM components because of the limited sample size. Second, our study is retrospective in nature and relies on the existing medical records, which is subject to recall and selection biases. Furthermore, NGS test was performed only on the bone mar-

row specimen with AML but not on the mediastinal tumor with GCT and angiosarcoma components. Therefore, we do not have molecular evidence that the SM components indeed result from transformation of GCT in this patient. However, both SM components, AML and angiosarcoma, are admixed with the GCT component in the mediastinal tumor, indicating a close relationship in oncogenesis. Nonetheless, our findings need to be verified by further independent studies.

Conclusions

In the current report, we present a rare case of a 16-year-old male patient with mediastinal GCT that developed two different SMs: well-differentiated angiosarcoma and AML. The simultaneous development of angiosarcoma and AML in the same tumor suggests that they likely originate from the same pluripotent progenitor cells. The tumor showed a poor response to chemotherapy and allogeneic bone marrow transplantation, and the patient died approximately 10 months after diagnosis. Our study indicates that the presence of two different SMs in mediastinal GCT is associated with a dismal clinical outcome. Advanced molecular techniques can detect genetic alterations that underlie somatic transformation in mediastinal GCT and facilitate the exploration of targeted therapy.

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Conflict of interest

Charles C. Guo has been an associate editor of the *Journal of Clinical and Translational Pathology* since January 2021. The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Author contributions

Data collection, drafting of the manuscript (LZ, SH, CCG), editing of the manuscript (SH, BC, CCG), and finalizing the manuscript (CCG). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study was performed in accordance with the Declaration of Helsinki (as revised in 2024). This case report does not include any identifiable patient information. According to institutional policy, this case report is exempt from Institutional Review Board approval and informed consent.

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