Journal of Hematopathology (2019) 12:37–40
https://doi.org/10.1007/s12308-019-00341-3

CASE REPORT

Mediastinal germ cell tumor with associated myeloid sarcoma: An exceptional co-occurrence

Renu Sukumaran[1] · Rekha A. Nair[1] · Anil Prahladan[2] · Anitha Mathews[1]

Received: 26 September 2018 / Accepted: 14 January 2019 / Published online: 28 January 2019

Abstract

The association of mediastinal germ cell tumor (GCT) and hematological malignancy is a well-documented but extremely rare phenomenon. This syndrome is characterized by the occurrence of nonseminomatous mediastinal germ cell tumor and an associated hematological neoplasm that usually involve the megakaryocytic lineage. The hematopoietic malignancies can involve the mediastinum or present as infiltration of bone marrow or lymphoid organs. In majority of cases, the hematological malignancy was detected in the bone marrow simultaneously or within 6 months after the detection of mediastinal germ cell tumor. There are very few limited case reports on the presence of hematopoietic or leukemic cells within the germ cell tumor itself and mass formation due to myeloid sarcoma is exceptionally rare. Herein we report the case of a 36-year-old male patient with a large mediastinal mass, excision biopsy of which showed areas of yolk sac tumor, immature teratoma and a separate round cell component. On immunohistochemical examination, the round cell component showed positivity for CD45 (dim), CD43, MPO, CD11c, and CD68 and were negative for CD117, CD20, CD5, CD34, Tdt, CD30, CD123, and CD61. A diagnosis of mediastinal germ cell tumor with yolk sac tumor and immature teratoma components and associated myeloid sarcoma was given. Peripheral smear and bone marrow examination showed no evidence of leukemic involvement.

Keywords Mediastinal germ cell tumor · Myeloid sarcoma · Yolk sac tumor

Introduction

Mediastinal germ cell tumors represent 3–4% of all GCTs. Clinicopathological characteristics of mediastinal GCTs are different from testicular and retroperitoneal germ cell tumors. Mediastinal NSGCTs exhibit a worse prognosis than their gonadal counterparts. Nongerm cell or somatic-type malignant transformation is more common in mediastinal GCT. Most frequent is the sarcomatous transformation. The hematopoietic malignancy associated with GCT represents a variant of somatic-type malignancy that is unique to mediastinal GCTs [1, 2].

✉ Rekha A. Nair
drrekhanair@gmail.com

[1] Division of Pathology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India

[2] Division of Imageology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India

Hematologic malignancies associated with mediastinal GCTs denote an intriguing and biologically distinctive aspect of germ cell tumors [1–3]. A nonseminomatous mediastinal germ cell tumor and associated hematological malignancy involving the megakaryocytic lineage is the common characteristic of this syndrome. Rare cases of mediastinal germ cell tumor associated with myelomonocytic leukemia and malignant histiocytosis have been documented [2]. The pathogenesis of this association is still obscure and various theories have proposed to the origin of the hematopoietic malignancy. It is suggested that the hematopoietic cells originate from totipotent or pluripotent primordial germ cell. Extramedullary hematopoiesis occurring in the yolk sac tumor component of some GCT lead to the theory that some hematopoietic malignancies can arise from more committed hematopoietic cells by malignant transformation. The hematological neoplasms associated with mediastinal germ cell tumors have a very aggressive clinical course. Usually, the patients die before initiating therapy, do not respond to therapy or achieve only short remissions [2, 3].

Case report

A 36-year-old male patient had history of fullness and a vague mass in the neck region for 1-month duration. Investigations revealed a mediastinal mass measuring 15 × 11 × 6.5 cm (Fig. 1). Fine needle aspiration cytology was taken from the mediastinal lesion which showed diffusely arranged large atypical cells. Excision of the mass was done in an outside center. We reviewed the specimen and histopathology slides. Gross examination showed extensive areas of necrosis with focal grey white and yellowish solid areas (Fig. 2). Microscopy showed a neoplasm composed of yolk sac tumor, immature teratoma, and a separate round cell tumor component which showed diffusely arranged large atypical cells with round nuclei, some showing nuclear indentations and small eosinophilic nucleoli (Figs. 3 and 4). We proceeded with immunohistochemistry to ascertain the nature of the round cell component. The cells were CD45 positive (dim), CD43 positive, MPO positive, CD68 positive, CD11c positive, CD117 negative, CD20 negative, CD5 negative, CD34 negative, Tdt negative, CD30 negative, CD123 negative, and CD61 negative (Fig. 5). Correlating the morphology and IHC findings, a diagnosis of nonseminomatous mediastinal germ cell tumor showing yolk sac tumor and immature teratoma components with associated myeloid sarcoma was given.

Discussion

Germ cell tumors can develop nongerm cell or somatic-type malignancy. The nongerm cell component can be epithelial, mesenchymal, hematopoietic, neurogenic malignancy, or a combination of them. The malignant transformation is rare in gonadal GCT, whereas its occurrence is disproportionately high in mediastinal GCTs. Mediastinal GCTs account for less than 5% of all GCTs but 50% somatic transformation occur in mediastinal GCTs. The most common malignant

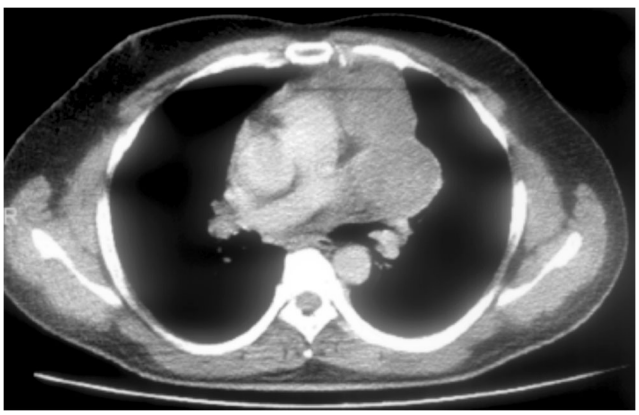

Fig. 1 CT scan—axial post contrast sections of the thorax (soft tissue window) showing a lobulated heterogeneous soft tissue density mass in the anterior mediastinum

Fig. 2 Macroscopic examination of the resected specimen showing extensive areas of necrosis with grey white and yellowish solid areas in between

transformation in mediastinal GCT is sarcomatous transformation. The hematopoietic malignancy associated with GCT represents a variant of somatic-type malignancy [2–4].

In 1983, Garnick and Griffin observed severe idiopathic thrombocytopenia unresponsive to therapy in three patients with mediastinal germ cell tumor [5]. In 1985, Nichols et al. described three cases of mediastinal germ cell tumor that developed hematologic malignancy within a short-time interval [1]. Two patients developed acute megakaryocytic leukemia and one patient developed myelodysplastic syndrome with a prominent megakaryocytic component. As primary mediastinal germ cell tumor and megakaryocytic leukemia are rare tumors, the authors believed that this is not a mere coincidence and postulated that the syndrome of mediastinal GCT and hematopoietic neoplasm may be due to an intrinsic biologic link between primordial germ cell and hematopoietic stem cell.

From then, isolated case reports and short case series began to appear in the literature. Researchers tried to find out the

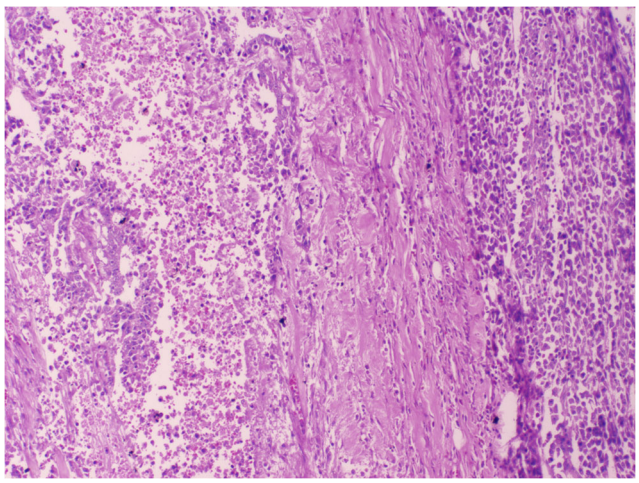

Fig. 3 Microscopy showing areas of yolk sac tumor and round cell component. (H&E, 100×)

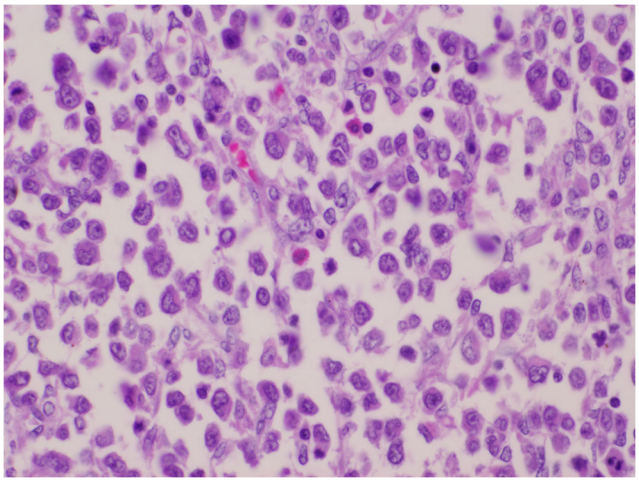

Fig. 4 Higher power of the round cell component. (H&E, 400×)

association between mediastinal GCT and hematologic malignancy and various theories have been put forward. In majority of cases, the germ cell tumor was nonseminomatous tumor and showed yolk sac tumor component [2].

The nearly constant association of the mediastinal location of GCT and the development of hematological malignancy indicates a fundamental link between the two processes. During embryogenesis, hematopoiesis initially occurs in the yolk sac and then shifted to the aorta-gonad-mesonephros region [6]. The mediastinum may contain rests of the primitive germ cells and hematopoietic stem cells. In cases of GCT with associated hematopoietic malignancy, either both the primitive germ cells and the hematopoietic stem cells may undergo malignant transformation or the transformed pluripotent germ cells may transdifferentiate into hematopoietic cells under the influence of environmental signals [2].

The hematological malignancies associated with mediastinal GCT are mainly of the megakaryocytic lineage which include acute megakaryoblastic leukemia, myelodysplasia with abnormal megakaryocytes, idiopathic thrombocytopenia, and essential thrombocythemia. Rare associations with acute myeloid leukemia, acute lymphoblastic leukemia, malignant histiocytosis, and systemic mastocytosis have also been reported [2, 3]. It is postulated that expression of hematopoietic growth and differentiation factors in some mediastinal GCTs could drive differentiation of primordial germ cells into hematopoietic progeny. The preferred commitment of transformed precursors into megakaryocytic or monocytic lineage depends on the profile of differentiation factors.

In most of the cases, the hematologic malignancy was detected in the bone marrow either simultaneously or within 6 months to 1 year of the detection of mediastinal germ cell tumors. The hematological malignancy associated with mediastinal GCT should be differentiated from therapy-related secondary leukemias [7]. The short-time interval between the occurrence of mediastinal GCT and hematological malignancy and no prior history of chemotherapy help to differentiate these cases from therapy-induced secondary leukemia.

Myeloid sarcoma is a tumor mass consisting of myeloid blasts with or without maturation occurring in an anatomic site other than the bone marrow. There were only very few reports on the presence of myeloid sarcoma or hematopoietic cells within the mediastinal germ cell tumor itself [2, 8, 9].

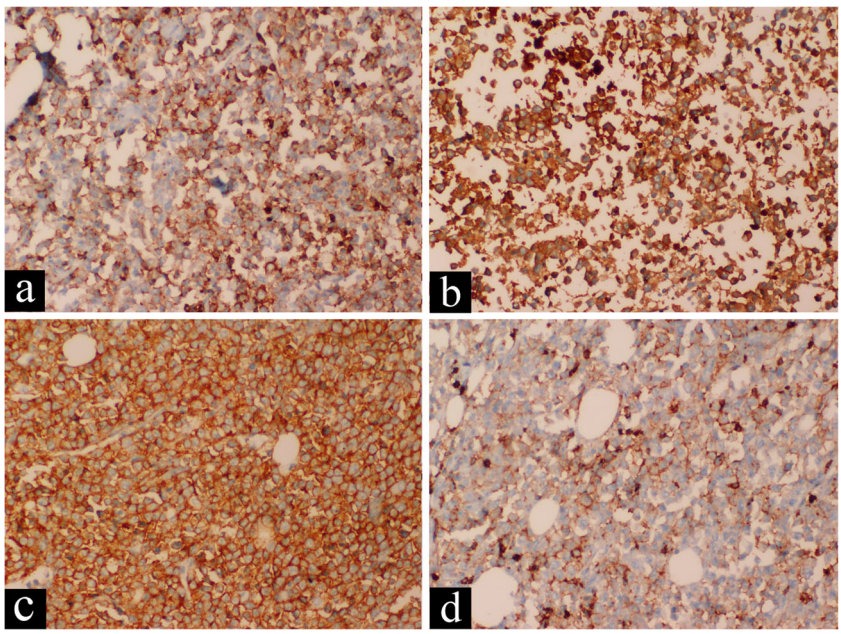

Fig. 5 The round cell component showing positivity for CD45, MPO, CD43, and CD68. (IHC, 200×)

In the case series of six patients with mediastinal germ cell tumor with associated hematological malignancy, Orazi et al. detected morphologically identifiable hematologic cells within the yolk sac tumor component of four patients [9]. In all the six cases, bone marrow was involved by the hematologic malignancy-AML M7 in two cases, AML M6 in one case, AML M4 in one case, mixed lineage leukemia in one case, and malignant histiocytosis in one case. The leukemic cells within the mediastinal GCT and in the bone marrow had similar morphology. The leukemic cells in the GCT occurred predominantly within the vascular structures of the mesenchyme-like component of the yolk sac tumor. According to the multistep hematologic transformation theory, pluripotent hematopoietic stem cells are formed in the mesenchyme-like component of yolk sac tumor, and they can differentiate in the permissive areas of the tumor and the germ cells act as promoters through the secretion of hematopoietic growth factors. Through the blood vessels, the leukemic cells will spread to the bone marrow. Concomitant mediastinal and extra mediastinal leukemias show comparable immunophenotype suggesting spread of hematopoietic tumor cells from GCT to blood, bone marrow, and extramedullary sites.

Clonal relationship between mediastinal GCT and hematopoietic neoplasms was demonstrated by cytogenetic examination and recognition of isochromosome(12p) in both the tumors [2, 10]. Isochromosome(12p) is the consistent and specific cytogenetic abnormality in testicular germ cell tumor and is present in some cases of mediastinal GCTs. This is consistently absent in routine leukemia cases. But, the demonstration of i(12p) in leukemic cells associated with mediastinal GCTs points to the clonal relationship between these two malignancies. In 2014, Oshrine et al. demonstrated shared mutations in TP53 and PTEN in a patient with concurrent mediastinal nonseminomatous GCT and megakaryoblastic leukemia [11]. They also demonstrated the presence of i(12p) in both the tumors [2, 11].

In our case, the GCT consisted of yolk sac tumor, immature teratoma, and a large area showing features of myeloid sarcoma. Bone marrow examination was normal. There was no evidence of leukemic involvement. The hematopoietic malignancy was confined to the mediastinal mass and formed major bulk of the tumor. This case points to the pluripotent nature of the germ cells and highlights the need of detailed and thorough histopathological examination along with immunohistochemistry in cases of mediastinal GCTs as the treatment and prognosis vary considerably if there is an associated hematological malignancy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Nichols CR, Hoffman R, Einhorn LH, Williams SD, Wheeler LA, Garnick MB (1985) Hematological malignancies associated with primary mediastinal germ cell tumors. Ann Intern Med 102:603–609
2. Orazi A, Wick MR, Hartmann JT, Marx A (2004) Germ cell tumours with associated hematologic malignancies. In: Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 219–220
3. Hartmann JT, Nichols CR, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Fizazi K, Einhorn L, Kanz L, Bokemeyer C (2000) Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumours. J Natl Cancer Inst 92:54–61
4. Takeda S, Miyoshi S, Ohta M, Minami M, Masaoka A, Matsuda H (2003) Primary germ cell tumors in mediastinum: a 50-year experience at a single Japanese institution. Cancer 97:367–376
5. Garnick MB, Griffin JD (1983) Idiopathic thrombocytopenia in association with extragonadal germ cell cancer. Ann Intern Med 98:926–927
6. Baron MH, Isern J, Fraser ST (2012) The embryonic origins of erythropoiesis in mammals. Blood 119:4828–4837
7. Vardiman JW, Arber DA, Brunning RD, Larson RA, Matutes E, Baumann I, Thiele J (2008) Therapy-related myeloid neoplasms. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues., 4th edn. IARC Press, Lyon, pp 127–129
8. Saito A, Watanabe K, Kusakabe T, Abe M, Suzuki T (1998) Mediastinal mature teratoma with coexistence of angiosarcoma, granulocytic sarcoma and a hematopoietic region in the tumor: a rare case of association between hematological malignancy and mediastinal germ cell tumor. Pathol Int 48:749–753
9. Orazi A, Neiman RS, Ulbright TM, Heerema NA, John K, Nichols CR (1993) Hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with mediastinal germ cell tumors. Cancer 71:3873–3881
10. Ikdahl T, Josefsen D, Jakobsen E, Delabie J, Fosså SD (2008) Concurrent mediastinal germ-cell tumor and hematological malignancy: case report and short review of literature. Acta Oncol 47:466–469
11. Oshrine BR, Olsen MN, Heneghan M, Wertheim G, Daber R, Wilmoth DM, Biegel JA, Pawel B, Aplenc R, King RL (2014) Acquired isochromosome 12p, somatic TP53 and PTEN mutations, and a germline ATM variant in an adolescent male with concurrent acute megakaryoblastic leukemia and mediastinal germ cell tumor. Cancer Genet 207:153–159