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Immature mediastinal teratoma with unusual histopathology

A case report of multi-lineage, somatic-type malignant transformation and a review of the literature

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Abstract

Germ cell tumors (GCTs) represent a well-recognized group of heterogeneous neoplasms with diverse clinical, histopathological, diagnostic, and prognostic characteristics. We present a rare case of a locally aggressive, chemotherapy-resistant immature mediastinal teratoma with a peculiar histological finding of a multilineage somatic-type malignant degeneration. A 21-year-old male patient presented with a 3-week history of persistent, blood-tinged productive cough and shortness of breath. A contrast-enhanced computed tomography (CT) scan of the chest showed a heterogeneous mass occupying the right hemithorax and abutting on adjacent structures. CT-guided biopsy was consistent with immature teratoma. Combination chemotherapy with bleomycin, etoposide, and cisplatin was initiated, albeit without success; the mass showed interval progression in size, and surgical resection through clamshell incision was performed. Histological assessment of the resected mass confirmed the diagnosis of immature teratoma and revealed an extensive multilineage malignant differentiation into sarcomatous, carcinomatous, and melanomatous components. The patient underwent an uneventful recovery but presented 2 months later with extensive liver and bone melanomatous metastases. In this report, relevant findings from the literature are also highlighted. Despite being exceptionally rare, such tumors carry poor prognosis. Understanding the clinicopathological characteristics and biological behavior of such tumors may provide an insight into interventions tailored to improve the otherwise dismal disease outlook.

Abbreviations: AFP = α-fetoprotein, CT = computed tomography, FDG = 18F-fluorodeoxyglucose, GCT = germ cell tumor, LDH = lactate dehydrogenase, PE = pulmonary embolism.

Keywords: carcinoma, extragonadal, germ cell tumors, immature teratoma, malignant teratoma with nongerminal malignant tumor, melanoma, sarcoma, somatic-type, teratoma with malignant transformation, teratoma with non-germ cell malignancy

1. Introduction

Germ cell tumors (GCTs) represent a well-recognized group of heterogeneous neoplasms with diverse clinical, histopathological, diagnostic, and prognostic characteristics. Being the most common

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solid tumor in the 3rd and 4th decades, GCTs assume a particular significance among young adult males.[1] Gonads are the most common primary site of GCTs, although a very small proportion is extragonadal in origin.[2–4] The most common site of the scarcer extragonadal GCTs is the mediastinum, with retroperitoneum being the close runner-up.[5] Immature teratomas, a subtype of GCTs, are particularly rare in the mediastinum.[6] In a review of 322 primary mediastinal GCTs, only 6 immature teratoma cases were identified, which represented 1.8% of all mediastinal GCTs and 4% of mediastinal teratomas.[7] Even rarer is a GCT with somatic malignant transformation, occurring in around 2% of all male GCTs and in 10% to 20% of mediastinal teratomas.[8–10] We report herein a case of an aggressive, chemotherapy-resistant immature teratoma harboring foci of sarcoma, melanoma, adenocarcinoma, and squamous cell carcinoma.

2. Case report

2.1. Clinical history and findings

A 21-year-old man was referred to our service from a local hospital for further management of a right hemithoracic extra-pleural mass with a provisional diagnosis of immature teratoma. The patient—previously healthy—presented to the referring hospital with a 3-week history of productive cough with blood-tinged sputum, right-sided intermittent pleuritic chest pain, and mild shortness of breath. He also experienced intermittent fever
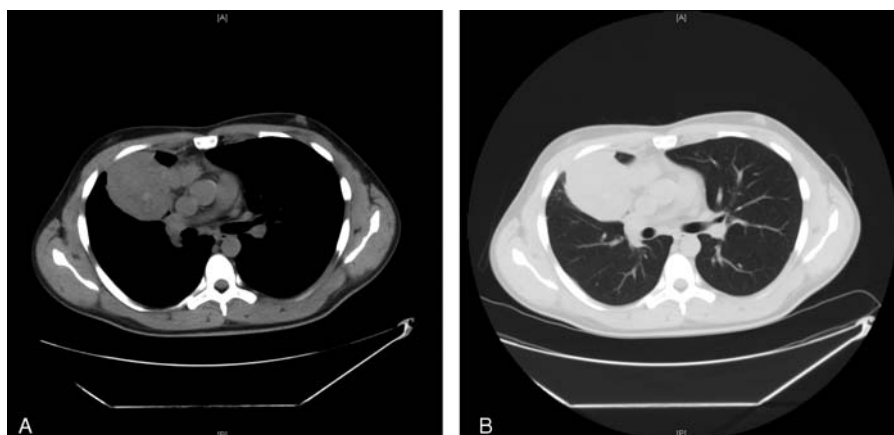
Figure 1. (A, B) A contrast-enhanced computed tomography scan, using the mediastinal (A) and lung (B) windows, showing a mediastinal mass that is extending into the adjacent lung.

(38.5 °C), nausea, vomiting, anorexia, and significant weight loss. He is nonsmoker. His past medical, family, travel, contact, and occupational histories are unremarkable. Physical examination revealed a thin-built man with normal vital signs. Respiratory examination suggested a reduction of air entry on the right side with no rhonchi, wheezing, or crepitation. General, cardiac, abdominal, testicular, and lymph-node examinations were unremarkable.

Laboratory investigations showed anemia (hemoglobin [Hb] = 107 g/L, normal = 135–180; mean corpuscular volume = 71 fL, normal = 75–95; mean corpuscular hemoglobin = 23.3 pg, normal = 24–30), mild leukocytosis (total leukocyte count = 12.49 × 10^9/L, normal = 3.9–11.0), thrombocytosis (platelets = 1061 × 10^9/L, normal = 155–435), and an elevated lactate dehydrogenase (LDH) level (LDH = 567 U/L increased to 727 U/L in few weeks, normal = 135–225). Renal, bone, hepatic, and coagulation profiles were within acceptable limits. Notably, α-fetoprotein (AFP) and cancer antigen 19–9 were elevated (AFP = 9.13 µg/L increased to 19.3 µg/L in few weeks, normal <7; cancer antigen 19–9 = 38.5 U/mL, normal <27), while carcinoembryonic antigen and β-human chorionic gonadotropin levels were within normal limits.

2.2. Radiology findings

A chest radiograph showed a large, well-defined substernal mass obscuring the right cardiac border. Contrast-enhanced computed tomography (CT) at presentation revealed a large (approximately $4 \times 4 \times 5$ cm^3) noncalcified, heterogeneous mediastinal mass extending to the right upper lobe and pleura (Fig. 1A and B). Several mediastinal and cardiophrenic lymph nodes were noted, with the largest measuring 1.2 cm in its widest diameter. No focal lesions in the liver, spleen, pancreas, adrenals, or kidneys were identified. A CT-guided core needle biopsy was suggestive of immature teratoma (Fig. 2A and B). Whole-body combined 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed an FDG-avid mediastinal mass with a single FDG-avid superior mediastinal lymph node (Fig. 3). No disease activity was seen elsewhere.

2.3. Clinical course

Combination chemotherapy with bleomycin (30 units IV on days 1, 8, and 15), etoposide (100 mg/m^2 IV on days 1–5), and cisplatin (20 mg/m^2 IV on days 1–5) was subsequently initiated. However, notwithstanding the mild improvement initially, the patient showed steady symptomatic deterioration; after completing two 3-week chemotherapy cycles, he presented to the emergency room with chest pain, cough, and hemoptysis. CT pulmonary angiogram was performed. Although no evidence of pulmonary embolism (PE) was found, the study showed an interval progression of the tumor size, reaching around $12 \times 13 \times 12$ cm^3. The ill-bordered mass appeared to have invaded the lung
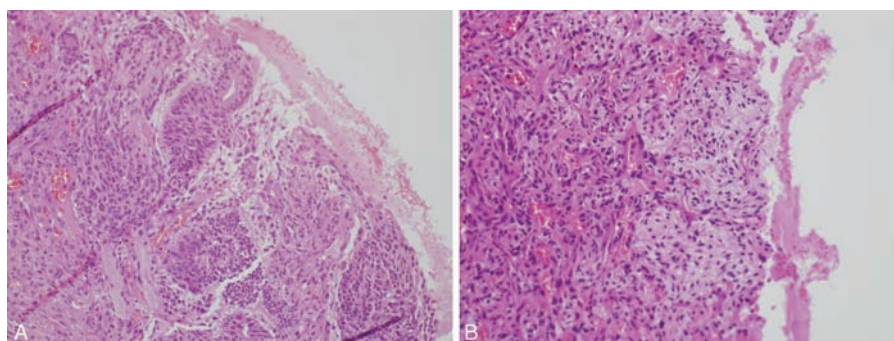

Figure 2. (A, B) Microscopic examination of needle core biopsy from the mediastinal mass showing predominant immature neuroectodermal elements forming glands and tubules lined by columnar embryonal cells with stratified hyperchromatic nuclei (A) and focal areas of a more mature neural tissue (B).
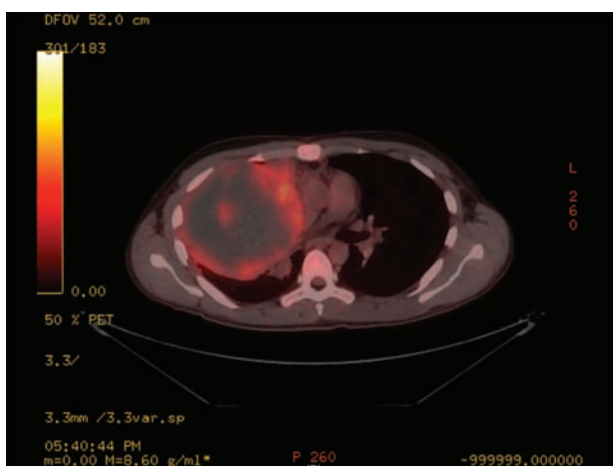
Figure 3. A whole-body combined 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scan showing an FDG-avid mediastinal mass with an intense peripheral hypermetabolic activity.

parenchyma, superior vena cava, and pericardium (Fig. 4A and B), while abutting on the carina, right main bronchus, right pulmonary artery, as well as the anterior, inferior, and superior pulmonary veins.

The case was thoroughly reviewed and discussed in a multidisciplinary team meeting, whose recommendation was to proceed with surgical resection. The patient underwent clamshell thoracotomy with an R0 resection of the mass along with the right middle and lower lung lobes. Local lymph nodes were also removed. The patient tolerated the procedure well. However, he presented 2 months later with extensive liver and bone metastasis, for which he received 1 cycle of palliative radiation. Liver biopsy confirmed melanoma metastases. Therefore, the decision was taken to treat him as a case of metastatic melanoma. One 5-day cycle temozolomide (150 mg/m^2 PO qDay for 5 days) was administered. Unfortunately, the patient passed away—5 and a half months after the initial diagnosis was made.

2.4. Pathology findings

Macroscopic examination of the resected mediastinal mass revealed solid and mucoid-filled cystic components with hemorrhagic cut surface measuring $18 \times 14 \times 13$ cm^3 in its maximum dimensions. Microscopically, the tumor consisted of a mixture of various ectodermal, endodermal, and mesodermal elements, of which immature neuroectodermal tissue areas were predominant. Anaplastic, pleomorphic glial tissues with marked nuclear atypia, and brisk mitosis were noted. These areas stained positive for glial fibrillary acidic protein and represented a glioblastoma component (Fig. 5A–C).

Other areas of the tumor contained pleomorphic spindle-to-round cells with large hyperchromatic nuclei, prominent nucleoli, and frequent atypical mitosis suggestive of malignant, undifferentiated spindle-cell sarcoma (Fig. 6A). Extensive immunohistochemical staining for relevant markers (smooth muscle actin, desmin, myogenic differentiation 1, cluster of differentiation [CD]34, CD31, and synaptophysin) were negative. Atypical, large pleomorphic cells with melanin pigment staining positive for S100, human melanoma black (HMB) 45, Melan A, and microphthalmia-associated transcription factor-1 were present in other areas—indicating a melanocytic differentiation consistent with transformation to malignant melanoma (Fig. 6B–E). Areas of endodermal differentiation with glandular structures, some of which showed malignant features consistent with adenocarcinoma, were also noted (Fig. 6F). Besides, mature and immature cartilaginous tissues were seen in areas of the tumor (Fig. 6G). Regional lymph nodes adjacent to the tumor were positive for metastatic squamous cell carcinoma (Fig. 6H).

3. Discussion

Malignant extragonadal GCTs are extremely rare. A 40-year, population-based review of Finland cancer registry suggested an incidence of 1.8 and 1.0 per 1,000,000 person-years among males and females, respectively.[11] Comparable rates were reported in the U.S. and Germany.[3,4] Despite the increasing incidence of gonadal GCTs, no temporal change was observed in the incidence of its extragonadal counterpart—a finding that is consistent across the studied populations.[2–4,11] Several reports suggested the mediastinum to be the most common site of origin of extragonadal GCTs in males,[3–5] while others found the central nervous system to be more common.[2] Teratomas account for 40% to 60% of all mediastinal GCTs, with the overwhelming majority being histologically mature.[7,12] Mediastinal teratomas are more common in males than females,[3,4,11] except during the first few years of life.[2]
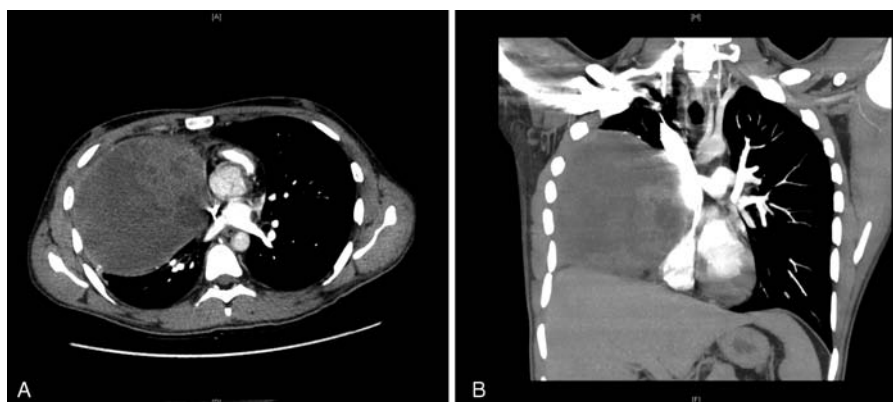

Figure 4. (A, B) Axial (A) and coronal (B) contrast-enhanced computed tomography scans—obtained after receiving 2 chemotherapeutic cycles—showing interval progression of size, reaching around $12 \times 13 \times 12$ cm^3 in its maximum dimensions.
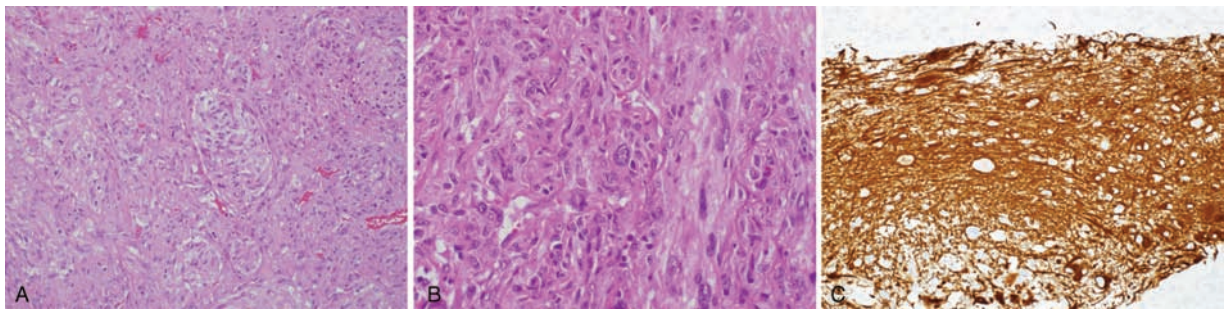
Figure 5. (A–C) Neural tissue with pleomorphic atypical cells and high nuclear-to-cytoplasmic ratio consistent with glioblastoma (A, B). Immunohistochemical staining of the tissue with glial fibrillary acidic protein (GFAP) showing positive reaction (C).

An uncommon but well-recognized phenomenon that may accompany GCTs is the somatic-type malignant transformation, in which a non-GCT malignant component is found within the bulk of a CGT or in its metastatic foci.[8–10] Somatic-type malignancy arising specifically in a teratoma setting remains an exceptionally rare event.[8] It may be more frequently observed in postchemotherapy and late recurrence cases.[10] Given the remarkable chemo-sensitivity of GCTs, chemotherapy is thought to eliminate the bulk of GCTs—exposing the non-GCT, chemo-resistant malignant components when present.[13]

Possibly due to the pluripotency of GCT components, several histological malignant transformations may occur. The most common histological subtype of malignant transformation is sarcoma (predominantly rahbdomyosarcoma), followed by adenocarcinoma and primitive neuroectodermal tumors.[9,14,15] Squamous cell transformation is rare[9,16] but may be relatively
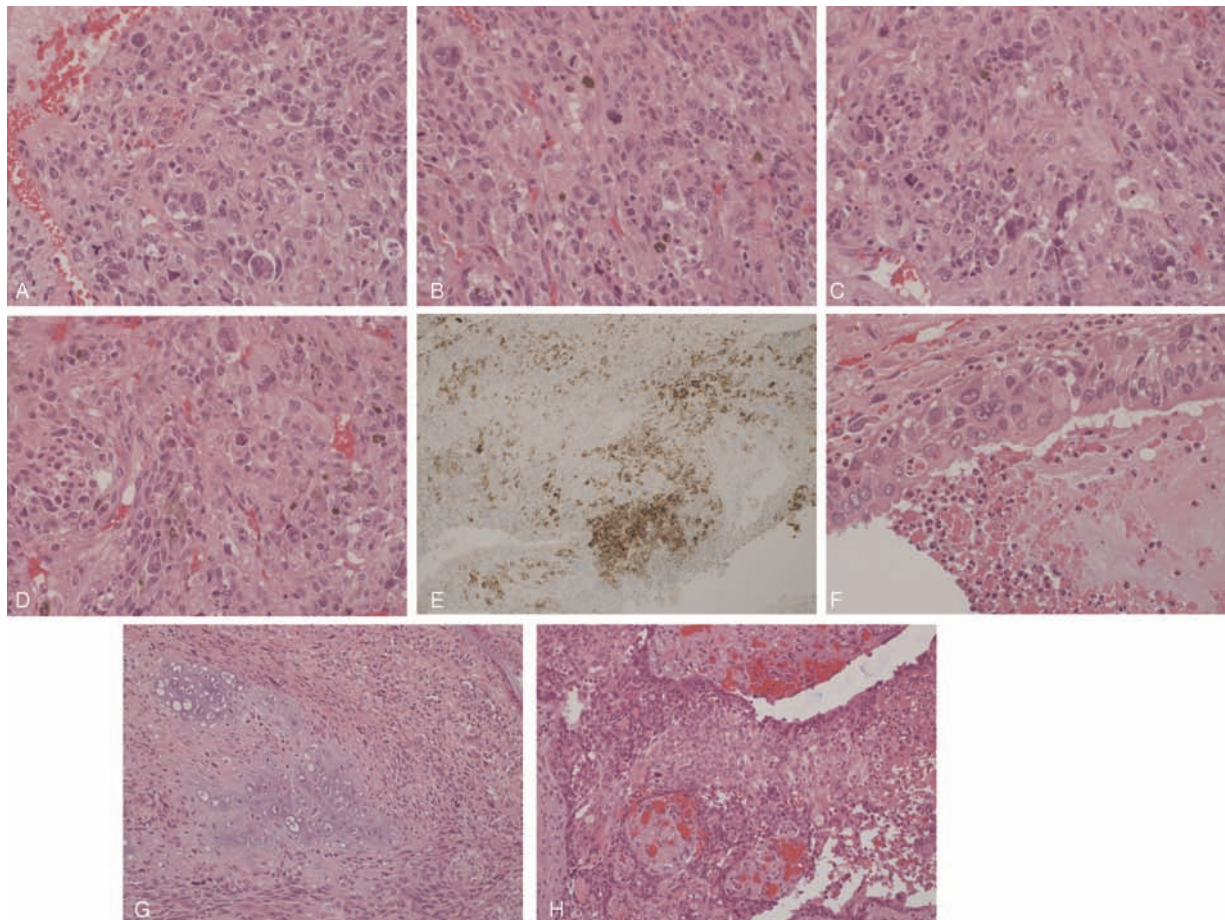
Figure 6. (A–H) Somatic-type malignancies: pleomorphic spindle to round cells and frequent atypical mitosis suggestive of sarcomatous differentiation (A). Malignant spindle cells with melanin pigment (B–D) which were positive for Melan-A (E). Malignant glandular epithelium depicting adenocarcinoma component (F). Cartilage with numerous lacunae containing small chondrocytes, surrounded by immature mesenchymal cells (G). Metastatic squamous cell carcinoma in a regional lymph node (H).

more common in ovarian teratomas,[17] especially in the mature cystic variants.[18] Other rare histological subtypes include carcinoid tumors, hemangioendothelioma, and nephroblastoma.[15] Melanocytic neuroectodermal transformation is among the rarest. An international, multicentric review of 635 patients with extragonadal GCTs identified secondary melanoma in 2 cases, which occurred few years later after the primary diagnosis.[5] Few other cases of melanoma either occurring as secondary tumors or in conjugation with the primary mediastinal GCT have been reported (Table 1).[19–24] To our knowledge, this is the first report of combined sarcomatous, carcinomatous, and melanomatous malignant transformation arising in the setting of immature mediastinal teratoma.

Clinically, GCTs with somatic-type malignancy tend to be more symptomatic than pure GCTs, although symptoms are clinically indistinguishable when present.[10] Symptoms may arise from compression, invasion, or rupture and include chest pain, dyspnea, and cough.[25] Patients may also experience weight loss, fever, malaise, night sweats, nausea, hemoptysis, postobstructive pneumonia, dysphagia, hoarseness, and superior vena cava syndrome. Radiologically, attenuation heterogeneity is a common characteristic of the mass, due to the presence of somatic malignancy (i.e., a solid mass) along with areas of teratomatous, necrotic, or hemorrhagic zones.[26] Invasion to adjacent structures, such as the great vessels, lung, and heart can also be seen. Metastasis to regional lymph nodes, lung, brain, liver, and spleen may be evident at the time of diagnosis or as a recurrence. Most of the clinical and radiological features were present in the herein mentioned case. Since no evidence of testicular involvement was found on physical examination or ultrasonography, testicular biopsy was deemed unnecessary in this case.[27]

The patient's clinical presentation featured postchemotherapy disease progression–that is, tumor growth and symptomatic deterioration. This observation has been associated with "growing teratoma" syndrome and teratoma rupture, respectively, which are infrequently but characteristically seen in mature mediastinal teratomas.[28,29] However, the rapid tumor progression in this case is likely due to the aggressive nature of the underlying non-GCT malignant transformation, especially sarcoma.[30] In fact, it is likely that the tumor's poor response to cisplatin-based therapy was due to the presence of sarcomatous component.[31]

Elevation of AFP or β-human chorionic gonadotropin is not uncommon in GCTs with malignant transformation.[10] Taniyama et al[30] presented a case of immature teratoma with AFP elevation. Busmanis and Tay[32] suggested the lack of immunohistochemical correlation with the AFP serum levels in a pure immature ovarian teratoma with extra-ovarian implants. The possibility of yolk sac component being present in our case (given the elevation of AFP) could not be ruled out. Although chemotherapy might have accounted for the eradication of yolk-sac components,[13] the absence of histological evidence led to the designation of this case as an immature teratoma.

A combined approach of surgery and chemotherapy has been recommended for immature mediastinal teratomas.[6,33] Standard chemotherapeutic regimens commonly fail to eradicate immature teratomas with somatic-type malignancy.[34] Given the significant resistance to cisplatin-based chemotherapy, Motzer et al[9] suggested using chemotherapeutic agents based on the transformed histology as the strategy of choice for regimen selection. Others advocated initiating GCT-standard cisplatin-based regiment and reserving chemotherapeutics of the specific

Table 1

Clinicopathological characteristics of primary mediastinal GCTs cases reported in the literature with an associated melanomatous degeneration.

Publication	Age (y)	Gender	Presenting symptoms	Duration of symptoms	GCT type	Associated histological malignancies	GCT-to-melanoma interval (site)	Radiation	Surgery	Chemotherapy	Survival (last to follow-up)
Chua and Mortimer[19]	25	Male	Dry cough, dyspnea, l ethargy	3 months	Immature teratoma	None in the dissected specimen	13 months (skin)	No	No	Yes (PEB)	NS
Ganjoo et al[20]	NS	NS	NS	NS	Teratoma	None in the dissected specimen	24 months (spine)	No	Yes	Yes	24 months[a]
Orduz et al[21]	17	Male	Fever, other symptoms.	NS	Teratocarcinoma	None in the dissected specimen	2 weeks (bone marrow)	No	No	Yes	4 months[b]
McNab et al[22]	32	Male	Chest pain	NS	Mixed GCT	Melanoma	0 (mediastinal mass)	Yes	Yes	Yes (PEB/TIP)	13 months[a]
Hannan et al[23]	31	Male	Dyspnea	2 weeks	Teratoma	None in the dissected specimen	16 months (bone and liver)	No	Yes	Yes (PEB)	16 months[a,b]
Hartmann et al[24]	35	NS	NS	NS	Nonseminoma	None in the dissected specimen	13 months	No	NS	Yes (PEB/VIP)	29 months

GCT=germ cell tumor, NS=not specified, PEB=cisplatin, etoposide, and bleomycin, TIP=paclitaxel, ifosfamide and cisplatin, VIP=vinblastine, ifosfamide and cisplatin.
* To metastasis.
† Dead at the time of publication.

somatic-type transformed malignancy for relapses.[35] Although the rarity of GCTs with malignant transformation have not permitted the generation of a strong body of evidence, it is agreed that an aggressive surgical approach with complete resection may be beneficial whenever deemed feasible, since it appears to afford the best survival.[14,16,36,37] As demonstrated by the case presented herein, the radiologic evidence of postchemotherapeutic interval growth in the context of a known immature teratoma may serve as a useful clue as to the presence of somatic-type transformation, favoring urgent surgical intervention over other treatment modalities (e.g., salvage chemotherapy).

Mediastinal GCTs' predisposition to nontreatment-related blood malignancies has been well-established.[38,39] In fact, it was shown that such a tumor may harbor hematopoietic stem cells within its bulk,[40] providing a possible explanation for the source of the hematologic derangements. With the exception of thrombocytosis, there were no overly aberrant blood indices in our case that would warrant further investigation. It is worth mentioning that GCTs may predispose to thrombotic events especially during chemotherapy treatment,[41] and a sudden occurrence of hemoptysis raises the suspicion of PE. CT pulmonary angiogram may be deemed optimal in an emergency setting, it aids in PE diagnosis and, if PE is ruled out, delineation of any structural alterations of the underlying pathology.

Mediastinal nonseminomatous GCTs are notorious for their poor prognosis.[42] Favorable factors include younger age,[42] limited disease extent at diagnosis,[16,43] feasibility of complete resection,[6] the absence of somatic-type malignancy (especially metastatic sarcoma-type histological transformation),[16,44] and the response to standard chemotherapeutic regimens.[37] Teratomas with malignant transformation have an aggressive course, high recurrence rate, and poor survival when present in the mediastinum.[14] Nonetheless, when confined to primary site, such tumors tend to carry mortality risk that is comparable to its teratomatous counterpart with no malignant transformation.[16,45]

For GCTs with somatic-type malignancy, the survival-determining factor may be the histopathological component that is most aggressive. The patient had an overall survival of around 6 and 2 months from the initial diagnosis and metastasis, respectively. This seems to mirror the survival of melanoma with metastasis to the liver, brain, or bone, whose median survival was found to be 4.4 months.[46] The patient also had several of the poor prognostic indicators, including an elevated LDH[47] and leukocytosis.[48] However, what determines the metastatic potential in GCT-associated melanomas remains largely unknown. Although our patient presented with metastatic disease 4 months after the diagnosis, 13 months elapsed before metastatic disease occurred in a previously reported GCT-associated melanoma.[22]

4. Conclusion

Somatic-type malignant degeneration is a rare but well-recognized phenomenon that occurs in the settings of GCTs. Due to its rarity, distinct nature, and remarkable heterogeneity, this disease warrants comprehensive reporting of the clinical, radiological, and pathological features. In case of more-than-single transformation, the clinical outcomes and overall survival may well correlate with that of the most aggressive and poorest prognosis tissue type. The presence of melanomatous transformation, as illustrated by this case, likely confers aggressive biological behavior. As the literature is enriched with additional studies,

understanding the clinical implications of the distinct malignant transformations will expectedly aid in clarifying the optimal, possibly tailored, management lines.

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