Vasoformative Lesions in Mediastinal Mixed Germ Cell Tumors: an Interesting Account of Two Cases Spanning the Benign to Malignant Spectrum

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Abstract

Extragonadal germ cell tumors are most commonly encountered in the anterior mediastinum. The presence of sarcomatous malignancies in these tumors is a rare phenomenon that adversely impacts patient prognosis because of poor response to conventional cisplatin-based chemotherapy. Even more unusual is the presence of florid benign somatic proliferations that overshadow the germ cell component, often resulting in misdiagnosis and inappropriate management. Two young male patients aged 17 and 28 years respectively presented with mass in the anterior mediastinum. Histopathology of both cases revealed mixed germ cell tumor admixed with prominent vascular component. Interestingly, one case showed malignant vasoformative neoplasm (angiosarcoma) while in the other the vascular proliferation was of benign nature (venous hemangioma).

Keywords Angiosarcoma · Mediastinal germ cell tumor · Somatic malignancy · Vasoformative lesion

Introduction

The anterior mediastinum is the commonest primary site for extragonadal germ cell tumors (EGCTs), accounting for 50–70% of all cases [1]. Like gonadal GCTs, mediastinal GCTs demonstrate a wide spectrum of histologic phenotypes and are classified using a similar classification scheme [2]. Teratomas (40–60%) are the commonest followed by mixed GCTs (13–25%) and seminomas (15–20%) [2]. Diagnosis is generally made using a preoperative biopsy. However, histologic predominance of one component in a mixed GCT or the presence of a non-germ cell/somatic component and non-diagnostic components such as totally necrotic tissue or fibrovascular

tissue can lead to an erroneous diagnosis and inappropriate treatment. We report herein, two such rare cases showing vasoformative lesions arising in mediastinal mixed GCT and spanning the benign to malignant spectrum.

Case History

Case 1

A 17 young male without any comorbidity presented with right sided chest pain for 4 months. He was evaluated with chest X-ray which was suggestive of a suspicious shadow in the mediastinum and right upper zone. CECT chest revealed a heterogeneously enhancing, circumscribed mass occupying the lower third of the right thoracic cavity. Trucut biopsy from the mass revealed a yolk sac tumor. Following 3 cycles of BEP (bleomycin, etoposide, cisplatin)-based chemotherapy, repeat CECT chest revealed a residual 15.6 × 13.2 × 10.8-cm mass. Subsequently, a clamshell thoracotomy with resection of the residual mediastinal mass alongwith wedge resection of lower and middle lobe of right lung with pericardial resection and mesh repair with diaphragm resection was done under general anesthesia. The excised mass was largely necrotic [Fig. 1a] and revealed extensive chemotherapy induced

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changes on microscopic examination. Only few small areas of viable mixed GCT comprising yolk sac tumor and mature teratoma components were identified [Fig. 1b, c]. Arising within the teratoma, a sarcomatous component (comprising 20–25% of the viable tumor) characterized by irregular, variably sized vascular spaces freely anastomosing in a sinusoidal fashion was present. The endothelial cells lining the vascular spaces were plump and epithelioid, mitotically active and displayed mild to moderate cellular atypia [Fig. 2a, b]. This sarcomatous component was positive for CD 31 and CD 34 with a high Ki67 proliferation index [Fig. 2c, d]. A final diagnosis of (residual) mixed GCT with angiosarcoma was rendered. Postoperative recovery was uneventful. The patient was discharged and received an additional 3 cycles of BEP based chemotherapy. Patient also received radiotherapy from another institute.

Case No 2

A 28 years old male presented with dry cough and right sided chest discomfort for 3 months. He consulted a chest physician who prescribed him symptomatic management. In view of persistence of symptoms, he was investigated with a X-ray chest which revealed mediastinal mass. The patient was then referred to the Department of Thoracic surgery of our institute. CT chest revealed a $11 \times 12 \times 11.7$ -cm mass in the anterior mediastinum having loss of fat planes with the pericardium, as well as upper and middle lobes of right lung [Fig. 3a]. Serum tumor markers for germ cell tumor were negative. Core biopsy from the mass revealed a network of multiple, irregularly dilated vascular channels of varying caliber and wall thickness. No other elements were seen and possibility of a venous malformation/hemangioma was suggested. Subsequently, clamshell thoracotomy with radical excision of the anterior mediastinal mass along with removal of anterior pericardium with wedge resection of upper and middle lobe of right lung and reconstruction of pericardial defect with vicryl mesh was performed under general anesthesia. The excised mass had a complex solid cystic gross appearance. The

cystic areas had a congested lining and were filled with hemorrhagic fluid. Intervening solid areas were firm to necrotic.

Microscopically, a vasoformative lesion comprising vascular channels of varying caliber and wall thickness formed the predominant component (comprising about 80% of the tumor). The vessels were lined by bland endothelial cells and some of them revealed luminal fibrin thrombi [Fig. 3b]. In few areas, this vascular component was intimately admixed with a malignant mixed GCT having mature teratoma and seminoma elements, each comprising about 10% of the total tumor [Fig. 3c, d]. The final diagnosis of a malignant mixed GCT with a venous hemangioma arising within the lesion was rendered. Postoperatively, the patient recovered well and was discharged in a stable condition. Subsequently, he received 6 cycles of BEP based chemotherapy.

Both patients were doing well at their 6-month postop follow-up exam.

Discussion

Development of somatic malignancies in GCTs is a rare but well-known phenomenon that can occur in neoplasms of gonadal, mediastinal, and intracranial origin [3]. Though rarely observed in gonadal GCTs, the frequency of this phenomenon is disproportionately high in mediastinal GCTs, with mediastinal GCTs accounting for upto 50% of GCTs with somatic components [3]. The somatic component can be an epithelial, mesenchymal, hematopoietic, neurogenic malignancy or a combination of these [3, 4]. Sarcomatous malignancies are the most common comprising 50% of cases, followed by carcinomas and primitive neuroectodermal tumors (PNET) which account for about 20 and 10% of cases respectively [5]. The most frequently reported sarcoma is embryonal rhabdomyosarcoma, followed by angiosarcoma. Leiomyosarcoma, undifferentiated sarcoma, myxoid liposarcoma, malignant peripheral nerve sheath tumor, osteosarcoma and chondrosarcoma have all been reported [3–5]. Adenocarcinoma is the commonest carcinoma encountered [3–5]. The GCT component so far encountered in majority of such cases is mature or

Fig. 1 a–c A panel of photographs depicting **a** gross image of the post chemotherapy resection specimen showing extensively necrotic tumor with few viable solid cystic areas at the periphery, **b** yolk sac tumor

component revealing large, pleomorphic tumor cells in loose sheets with a prominent Schiller Duval body (HE 10 $\times$), **c** teratoma component revealing mature elements derived from different germ layers (HE 10 $\times$)

Fig. 2 a–d A panel of photomicrographs revealing an angiosarcoma component composed of irregular, variably sized vascular spaces anastomosing in a sinusoidal fashion (HE 4×), **b** Atypical endothelial cells lining the vascular spaces showing moderate nuclear pleomorphism and mitotic activity (arrow) [HE 20×], **c** CD34 immunoreactivity in the atypical endothelial cells, **d** high Ki67 proliferation index in the angiosarcoma component

immature teratoma, pure or combined. Rarely pure yolk sac tumor, seminoma and intratubular germ cell neoplasia have been reported without any teratomatous components [3, 4].

The pathogenesis of the development of somatic malignancy including angiosarcoma remains unclear. The traditional theory by Mostofi and Sobin proposed malignant transformation of certain mesenchymal elements within teratomas as the origin [6]. The fact that most somatic malignancies are located in direct vicinity of teratoma supports this theory. Later, origin from primitive germ cells and transformation of the blastematous stroma in yolk sac tumor were suggested [3].

Finally, the rather frequent finding of somatic malignancy in tumors surgically resected after chemotherapy suggests a selection process of chemotherapy-resistant cell populations to be another pathogenetic factor [3]. However, a combination of factors may play a role, as was seen in our case where angiosarcoma was observed arising in the teratoma component in the post chemotherapy resection specimen.

It is important to note that scattered atypical cells in the stroma of otherwise conventional GCTs should not be misinterpreted as sarcoma [3, 4]. Contreras et al. opined that only when the atypical stromal cells form a pure nodule of

Fig. 3 a–d A panel of photographs showing **a** CT chest revealing a 11 × 12 × 11.7-cm mass in the right anterior mediastinum having loss of fat planes with the pericardium, as well as upper and middle lobes of right lung, **b** vasoformative lesion comprising vascular channels of varying caliber and wall thickness lined by bland endothelial cells forming the predominant component. (HE 4×), **c** malignant mixed germ cell tumor—seminoma component comprising nests of tumor cells interspersed in between the vascular component (HE 10×), **d** malignant mixed germ cell tumor—teratoma component revealing mature elements derived from different germ layers (HE 10×)

substantial size (larger than a half field viewed with a $\times 4$ objective), should they be considered to represent a sarcomatoid transformation [4]. This finding is particularly important as the mere presence of stromal atypia is not correlated with patient prognosis whereas the emergence of a sarcomatous component such as angiosarcoma portends a dismal prognosis due to poor response to conventional cisplatin-based chemotherapeutic regimens. Mortality rates for GCT with sarcomatous malignancy are far worse than for age and stage matched GCT without sarcomatous components (80 vs 32%; $p < 0.001$) [3]. Further, Malagon et al. showed that mediastinal GCT with sarcomatous components tended to behave even more aggressively than their testicular counterparts [3]. Contreras et al. noted that despite surgery and chemotherapy, all 10 mediastinal GCT cases with angiosarcoma either developed metastasis or local recurrence, and 7 died of disease [4]. Interestingly, the same dismal outcome is observed in mediastinal GCTs with an angiosarcomatous component as small as 5% of the tumor [4]. This finding highlights the importance of awareness among pathologists for accurate diagnosis of even small tumor foci. Further, recent reports suggest that GCT patients with a single histologic type of somatic malignancy respond well to specific chemotherapy tailored to that malignancy [7, 8]. Workers have shown that GCTs with rhabdomyosarcoma or angiosarcoma respond well to a doxorubicin-based regimen, while those with adenocarcinoma benefit from a 5-fluorouracil-based regimen [7, 8]. Therefore, in today's era, identification and accurate classification of the malignant somatic component has also assumed important therapeutic implications.

Our experience was unique because in addition to vascular malignancy (angiosarcoma) arising in a mediastinal GCT, we encountered another challenging case of mediastinal GCT with florid vascular proliferation albeit of a benign nature. An extensive literature search revealed only few reported cases of florid/hemangiomatous vascular proliferation in a GCT, with most reports confined to ovarian teratomas [9]. Only a handful of mediastinal GCTs with this finding have been reported thus far [10]. Consequently, mediastinal lesions where the benign vasoformative component forms the bulk of a tumor pose a diagnostic challenge, especially in small biopsy samples. It can both be overlooked as a non-diagnostic element, or misdiagnosed as a pure vascular neoplasm. In our case (case no 2) also, the initial preoperative biopsy was misdiagnosed as a hemangioma leading to excision of the mass rather than preoperative chemotherapy which is the standard treatment protocol for GCT.

Pathogenesis of this rare finding remains poorly understood. With respect to ovarian GCTs, it has been suggested that the expression of growth factors such as vascular endothelial growth factor by the neural component of the teratoma induces vascular proliferation [9]. However, Cha et al. could not reproduce the same pathogenesis in mediastinal GCT, since none of their five cases showed any neural components [10]. They

therefore postulated that the benign vasculoconnective component is an intrinsic part of mediastinal mixed GCT [10]. Regardless of pathogenesis, differentiation of this florid benign vascular proliferation from an angiosarcoma is vital given the poor prognostic implications of the latter. Benign vascular proliferation is intermingled with the GCT, rather than forming a mass-like lesion that infiltrates into the surrounding tissue [3, 10]. Furthermore, though a variable degree of cellular atypia may be encountered in benign vascular proliferations (possibly due to chemotherapy-induced changes), angiosarcoma cells show distinct anaplasia in the form of prominent cytologic atypia, brisk mitotic activity and an architecturally complex growth pattern.

In conclusion, to add to the myriad of patterns and histologic combinations possible within a germ cell tumor, a non-germ cell or somatic malignant component may be encountered. Our experience highlights that pathologists must be aware of the possible benign or malignant nature of these components. Therefore, presence of what seems to be a hemangiomatous lesion in a mediastinal mass biopsy, should serve as a warning for the possibility of a lurking GCT, especially in a young male and further work up including examination of serum AFP and beta HCG levels should be performed. Similarly, a thorough sampling of GCTs is vital for accurate identification of any somatic malignancy. This finding is especially critical in light of recent evidence that patients of GCT with a single histologic type of somatic malignancy may achieve long-term survival when treated with a chemotherapeutic regimen tailored to that malignancy.

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