



Primary mediastinal seminoma with leiomyosarcoma: a rare case report

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ABSTRACT

Germ cell tumor is the most common malignant tumor of the gonads, sometimes they are found in locations other than the gonads, called Extra-gonadal Germ cell tumours (EGCTs). Primary mediastinal germ cell tumors (PMGCTs) are a kind of rare neoplasm in the anterior mediastinum, including seminoma and non-seminomatous, or appear as a mixture. Primary mediastinal seminoma mixed with sarcoma is an extremely rare clinicopathologic entity. Previous studies have revealed that primary pure mediastinal seminomas are commonly sensitive to chemoradiotherapy and possibly to palliative excision. The treatment options for mixed germ cell tumor composed of seminoma and sarcoma remain unknown. Only one case of primary mediastinal seminoma with rhabdomyosarcoma has been reported in the literature up to date and the patient benefited from chemotherapy as the neoadjuvant therapy. However, cases of primary mediastinal seminoma with leiomyosarcoma have not been documented. Herein, we report a case of an 18-year-old patient, who presented with dyspnea, orthopnea, and chest pain, the CECT scan of the chest showed a large mass in the anterior mediastinum, which turned out to be seminoma mixed with leiomyosarcoma after partial excision. We investigate the treatment strategy and potential molecular mechanism of this disease. Finally, our study demonstrated that the patient benefited from the treatment of chemotherapy alone, or combined with target therapy after the operation. Meanwhile, the *BRAF* p.G466V, TP53 mutations, MTOR p.T1977I and exons 2-5 deletion of *FLCN* may be potential molecular mechanisms and oncogenic drivers of this disease.

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Introduction

Extragenital germ cell tumors (EGCTs) are extragenital in origin and are rare that account for approximately 5-7% of germ cell tumors (1, 2). EGCTs frequently occur in young males in the midline, predominantly in the mediastinum or the retroperitoneum (1). Patients with EGCTs normally have no suspicious testicular lesions (3, 4). Primary mediastinal GCTs comprise three distinct histologic types including teratoma, seminoma, and non-seminomatous GCTs (5). Seminomas are less frequent than non-seminomatous tumors (6). Due to the slow growth of seminomas, most of them have been found large and bulky at diagnosis. Although a number of published papers have demonstrated the clinical prognosis of patients with primary mediastinal seminoma, the cases of primary mediastinal seminoma with mediastinal leiomyosarcoma have not been documented. In the present work, we report for

the first time to our knowledge a unique case of primary mediastinal seminoma with leiomyosarcoma and the potential molecular mechanisms of this disease.

Case description

An 18-year-old man was brought to the thoracic surgery department of our hospital with a chief complaint of dyspnea, orthopnea, and chest pain for the past 1 month in May 2020. Chest enhanced computed tomography (CECT) scans revealed a large mass measuring 6.3 × 10.3 cm lying in the anterior mediastinum with heterogeneous enhancement and a clear boundary, which was suspected to be a mediastinal thymoma or lymphoma. Abdominal enhanced CT, brain magnetic resonance imaging (MRI), and whole-body bone scan revealed that none of the organs showed any abnormality or any evidence of metastasis. Laboratory findings suggested the

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levels of α -fetoprotein (AFP) and β -human chorionic gonadotropin (β -hCG) in the serum were within the normal limits. The patient subsequently underwent an exploratory thoracotomy on May 20, 2020. However, partial but not gross total resection of tumor was achieved because the tumor with severe adhesion to the pericardium and great vessels was observed during the operation. The resected specimen measured 7.5×4.0 cm and weighed 580 g. Pathological examination of the resected specimen revealed the mixed features of seminoma (10%) and sarcoma (90%) (Figure 1).

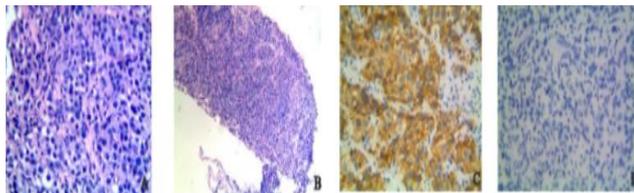


Figure 1. H & E and IHC staining in resected specimens. A: H & E and IHC staining of metastatic seminoma in the inguinal lymph node; B: H & E and IHC staining for CD117, PLAP and OCT3/4 of seminoma. C: H & E and IHC staining for VIM, Vimentin; D: H & E and IHC staining for CD117 KIT proto-oncogene, C-Kit, PLAP, ALPP; OCT3/4, POU.

The testes were subsequently examined clinically to ensure their normal anatomical position bilaterally, and a scrotal ultrasound was also done to rule out any occult primary tumor in the testes. These findings were consistent with the diagnosis of primary mediastinal seminoma with sarcoma. After one month of the surgery, re-examined CECT scans revealed a residual tumor measuring 4.1×2.4 cm in the anterior mediastinal (Figure 2). He was subsequently administered bleomycin combined with etoposide and cisplatin (BEP regimen) on June 16, 2020. After two cycles of the treatment, the patient achieved stable disease (SD) with a slight tumor shrinkage (3.9×2.0 cm) on August 6, 2020 (Figure 2). The patient was free from BEP-related adverse effects. Pathological consultation from pathologists of Ruijin Hospital Affiliated to Shanghai Jiao Tong University revealed that the tumor was the mixed germ cell tumor of seminoma (10%) and leiomyosarcoma (90%). The treatment against seminoma and sarcoma was then given with two alternating regimens, VDC (vincristine sulfate, doxorubicin hydrochloride liposome injection, cyclophosphamide) and IE (ifosfamide and etoposide) on August 11, 2020. After 2 cycles of VDC/IE treatment, CECT showed progressive disease (PD)

with an increased diameter of the tumor measuring 9.3×5.0 cm on November 19, 2020 (Figure 2).

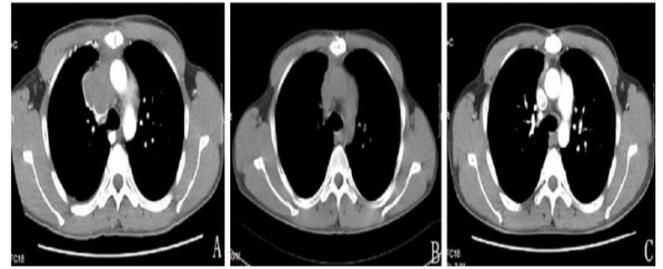


Figure 2. CECT scans tomography reveal the summary of the patient's treatment history. A: CECT scans after 2 cycles of treatment B: CECT scans after both 3& 4 cycles C: CECT scans after 5 cycles of treatment

He had grade I gastrointestinal disorders and grade II myelosuppression during VDC/IE treatment. BEP combined with anlotinib was subsequently given based on the fact that seminomas are sensitive to BEP as previously reported and anlotinib has been recommended for second-line treatment of sarcomas. After 2 cycles of the treatment, CECT scans revealed a significantly enlarged tumor measuring 13.0×7.8 cm and the tumor response assessment was PD. The AFP level was within the normal limits but increased to 8.38 ng/ml (Figure 3).

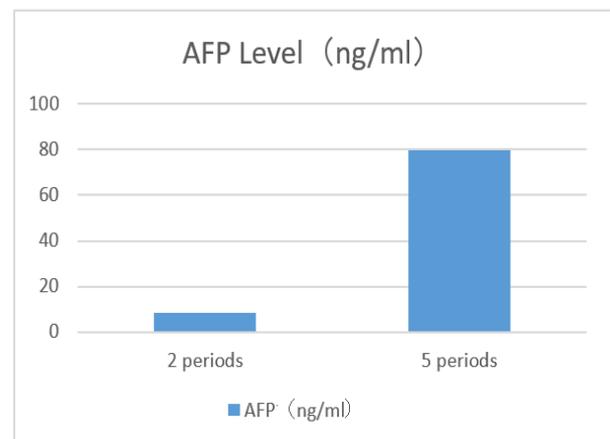


Figure 3. Change of the level of AFP. AFP: α -fetoprotein.

Based on these findings, we hypothesized that the progressive disease might be a result of the presence of histological transformation of the tumor. Next, ultrasound-guided percutaneous biopsy on mediastinal mass was performed for pathological examination, however, the result of which indicated the necrotic tissue and no tumor cells. Due to the challenging

complications, a rebiopsy was not performed. In order to explore alterations associated with this disease and determine whether the patient could benefit from targeted therapies, next-generation sequencing (NGS) using a panel consisting of 520 cancer-related genes (OncoScreen Plus, Burning Rock Biotech, Guangzhou, China) for molecular analysis was performed on the resected specimen on February 2, 2021. NGS results showed that the patient carried 14 somatic mutations, five of which had definitive or potential clinical significance, including *BRAF* p.G466V, *MTOR* p.T1977I, *TP53* p.R280T, *TP53* p.E286K, and exons 2-5 deletion of *FLCN*. In addition, NGS indicated microsatellite stability and a low level of tumor mutation burden (3.99 mutations per megabase) in the resected specimen (Figure 2). These data suggested that the patient did not harbor genetic alterations serving as targets in approved targeted therapies. In addition, thoracic surgeons of our hospital did not recommend palliative surgery. In the context of the lack of effective treatment strategy for this disease, the continuation of BEP beyond progression combined with anlotinib was given by compromise. CECT scans revealed disease stabilization after both 3 (March 5, 2021) and 4 cycles (April 6, 2021) of treatment compared with CECT scans after 2 cycles of treatment on January 25, 2021 (Figure 2), but he developed an significantly enlarged tumor (16.8 × 10.7 cm), chest tightness, shortness of breath, and an increased AFP level of 79.8 ng/ml after five cycles of treatment on May 6, 2021 (Figure 2, Figure 3). The patient experienced grade I dermatitis during the treatment of BEP plus anlotinib. He visited Affiliated Chest Hospital of Shanghai Jiao Tong University in May 2021 for further medical treatment, while he was considered as unsuitable for palliative surgery according to a full medical workup. He subsequently developed increasing chest tightness and shortness of breath. Unfortunately, he succumbed to his disease on June 15, 2021.

To the best of our knowledge, this is the first study to report a case of primary mediastinal seminoma with leiomyosarcoma. Our work revealed that platinum-based chemotherapy might be the management option for patients with primary mediastinal seminoma with leiomyosarcoma.

Due to the rarity of primary mediastinal seminoma, standard-of-care in patients with primary mediastinal seminoma has not been established. Traditional treatments of mediastinal seminoma consist of surgery, chemotherapy, and radiotherapy. Patients with seminomas have a favorable prognosis after preoperative adjuvant cisplatin-based chemotherapy followed by surgical resection of residual disease or surgical (partial/complete) resection followed by postoperative adjuvant chemotherapy and or radiotherapy (6-9). Patients with mixed mediastinal seminoma with sarcoma also respond to platinum-based chemotherapy. Raad et al. (10) have reported a case of primary mediastinal seminoma with rhabdomyosarcoma and right supraclavicular lymph node metastasis who benefited from BEP as preoperative adjuvant therapy and then underwent surgical resection and received postoperative radiotherapy due to the microscopical sarcoma component. He had a disease-free survival of more than 5 months. Consistent with previous studies, the patient responded to platinum-based chemotherapy after partial resection. However, he did not benefit from BEP plus anlotinib after the failure of VDC/IE treatment. These findings suggested that the lack of durable benefit from surgical resection and chemotherapy might be attributed to several factors. First, only partial resection could be achieved. Second, seminoma cells might be killed by BEP after partial resection, but residual leiomyosarcoma cells were not sensitive to platinum-based chemotherapy. The origin of sarcoma components in germ cell tumors is unclear. Some studies have documented that sarcomas are tumors of mesenchymal origin and linked by the transformation of teratoma (11). In this context, sarcoma components should respond to BEP treatment. In addition, sarcoma components might also be associated with the presence of somatic mutations, which suggests that sarcoma components could respond to VDC/IE regimens or anlotinib. However, a lack of durable response to VDC/IE regimen or BEP plus anlotinib was observed in this patient. These findings suggested that the mixed feature of seminoma with leiomyosarcoma might result in a relatively high malignancy.

The hCG, AFP, and lactate dehydrogenase (LDH) are well-established serum tumor marks for guiding the management of patients with GCTs (12, 13).

Rising concentrations usually indicate progressive disease and the need for salvage therapy. Patients with mixed GCTs may have an elevated AFP at relapse after chemotherapy for advanced disease. In the present work, the patient had a dramatically increased AFP level after the progression on BEP plus anlotinb, which suggested that histological transformation of seminoma might occur. It is necessary to perform rebiopsy for a primary tumor that guide treatment options. However, we failed to obtain specimens of tumors based on the biopsy method.

An array of published studies have documented the clinical prognosis and biological features of primary mediastinal seminoma, but molecular mechanisms of this disease have not been reported in the literature. In this study, capture-based targeted sequencing was performed for investigating its potential molecular mechanisms and therapeutical targets. Several somatic mutations were identified including *BRAF* G466V. Besides *BRAF* V600E, *BRAF* G466X is another hotspot mutation in the non-small cell lung cancer dataset from The Cancer Genome Atlas (TCGA) (14). *BRAF* G466X was also identified in melanoma and colorectal cancer datasets from TCGA, but it was not observed in the sarcoma dataset from TCGA (<https://www.cbioportal.org/>). A previous study indicated that *BRAF* G466V activated MEK and ERK and non-small cell lung cancers with *BRAF* G466V exhibited the sensitivity to dasatinib (15). These findings suggested that *BRAF* G466V might play a vital role in tumorigenesis of primary mediastinal seminoma.

There are some limitations to this work. First, although several somatic alterations occurring in primary mediastinal seminoma were observed in this study, we cannot conclude that these alterations play oncogenic roles in primary mediastinal seminoma. Further studies are needed to investigate the associations between somatic mutations identified in this study and tumorigenesis of primary mediastinal seminoma. Second, whether patients with the mixed feature of primary mediastinal seminoma could benefit from first-line chemotherapy needs to be explored in a large cohort.

In conclusion, we first report a case of primary mediastinal seminoma with leiomyosarcoma who benefited from platinum-based chemotherapy. Our work provides clinical evidence on the efficacy of

platinum-based chemotherapy in the treatment of patients with primary mediastinal seminoma and leiomyosarcoma.

Author contributions

Study conception: Feixue Song. Data collection: Yali Qi, Chi Dong, and Wenjun Cui. Patient management: Yali Qi, Lijun Da, Enxi Li, and Yating Liu. Data analyses: Yali Qi and Chi Dong. Manuscript writing: Yali Qi and Feixue Song. Final manuscript approval: all authors.

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Ethical approval: This study was approved by the Ethics Committee of the Lanzhou University Second Hospital.

Informed consent: Informed consent was obtained from the participant.

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Interest conflict

The authors declare no conflict of interest.

References

1. Busch J, Seidel C, Zengerling F. Male Extragenadal Germ Cell Tumors of the Adult. *Oncol Res Treat* 2016; 39(3): 140-144.
2. Malde S. Primary retroperitoneal seminoma: an unusual cause of testicular pain. *JRSM Short Rep* 2010; 1(7): 63.
3. Bokemeyer C, Nichols CR, Droz JP et al. Extragenadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol* 2002; 20(7): 1864-1873.

4. Schmoll HJ. Extragonadal germ cell tumors. *Ann Oncol J Eur Soc Med Oncol* 2002; 13 Suppl 4: 265-272.
5. Stram AR, Kesler KA. Mediastinal Germ Cell Tumors: Updates in Diagnosis and Management. *Surg Oncol Clin North Am* 2020; 29(4): 571-579.
6. Koizumi T, Kanda S, Nihonmatu R et al. Primary mediastinal germ cell tumors - A retrospective analysis of >30 years of experience in a single institution. *Thor Cancer* 2021; 12(6): 807-813.
7. Takeda S, Miyoshi S, Ohta M, Minami M, Masaoka A, Matsuda H. Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. *Cancer* 2003; 97(2): 367-376.
8. Napieralska A, Majewski W, Osewski W, Miszczyk L. Primary mediastinal seminoma. *J Thor Dis* 2018; 10(7): 4335-4341.
9. Bilal I, Xie S, Elburki MS, Azizaram Z, Ahmed SM, Jalal Balaky ST. Cytotoxic effect of diferuloylmethane, a derivative of turmeric on different human glioblastoma cell lines. *Cell Mol Biomed Rep* 2021; 1(1): 14-22.
10. Raad RA. Imaging of Non-thymic Anterior Mediastinal Tumors. *Diag Imag Thor Surg* 2018: 235-252.
11. Hoefkens F, Dehandschutter C, Somville J, Meijnders P, Van Gestel D. Soft tissue sarcoma of the extremities: pending questions on surgery and radiotherapy. *Radiat Oncol* 2016; 11(1): 136.
12. Gilligan TD, Hayes DF, Seidenfeld J, Temin S. ASCO Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors. *J Oncol Pract* 2010; 6(4): 199-202.
13. Ercisli MF, Kahrizi D, Azizaram Z. Environmental factors affecting the risk of breast cancer and the modulating role of vitamin D on this malignancy. 2020.
14. Cerami E, Gao J, Dogrusoz U et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2012; 2(5): 401-404.
15. Sen B, Peng S, Tang X et al. Kinase-impaired BRAF mutations in lung cancer confer sensitivity to dasatinib. *Sci Transl Med* 2012; 4(136): 136ra170.