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CASE REPORT

Development of angiosarcoma in a mediastinal non-seminomatous germ cell tumor that exhibited growing teratoma syndrome during chemotherapy

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Abstract

Herein, we report a case of an angiosarcoma in a mediastinal non-seminomatous germ cell tumor that exhibited growing teratoma syndrome during chemotherapy. A 26-year-old man presented with a giant anterior mediastinal mass, which was diagnosed as a non-seminomatous germ cell tumor. The patient was administered three cycles of chemotherapy (bleomycin, etoposide, and cisplatin), but the mass grew despite normalization of tumor markers. Massive bleeding during thoracic surgery resulted in incomplete resection, and the mass was clinically and pathologically diagnosed as growing teratoma syndrome (only mature teratoma). The residual mass continued to grow, and complete resection was subsequently achieved after a detailed analysis of its vascular anatomy using angiography. The final pathological findings revealed angiosarcoma, which indicated a rare somatic type of mediastinal non-seminomatous germ cell tumor.

Introduction

Mediastinal germ cell tumors account for 1–4% of mediastinal tumors[1] and are subdivided into seminoma and non-seminomatous germ cell tumors (NSGCTs). The most successful treatment for mediastinal germ cell tumors involves cisplatin-based chemotherapy followed by surgical resection.[2] However, patients with NSGCTs have variable clinical and/or pathological features. Growing teratoma syndrome (GTS) describes tumor growth during or after chemotherapy, despite normalization of tumor markers, with histological evidence of mature teratoma. Non-germinal tumors, such as sarcoma or adenocarcinoma, are rare but well described in NSGCTs that involve a "somatic-type" malignancy or transformation. Residual teratoma from GTS carries a risk of malignant transformation.[3] Furthermore, giant mediastinal tumors are challenging to resect based on the limited operative field and rich local blood supply.[4] Herein, we report a rare case of GTS developing during chemotherapy and NSGCT (angiosarcoma) that emerged after standard chemotherapy and thoracic surgery.

Case report

A 26-year-old man presented with a one-month history of dyspnea on exertion, orthopnea, and fever. Contrast-enhanced computed tomography (CT) revealed a large mass in the anterior mediastinum with heterogeneous enhancement (Fig 1a), which prompted the transfer of the patient to our hospital for further examination and treatment. Laboratory test results revealed elevated levels of serum α-fetoprotein (711.8 ng/mL, normal < 10 ng/mL) and β-human chorionic gonadotropin (2.0 ng/mL, normal < 0.1 ng/mL). Combined NSGCT was suspected based on seminomatous, teratomatous, and yolk sac components detected using CT-guided core needle biopsy. The patient completed three cycles of chemotherapy (bleomycin, etoposide, and cisplatin), resulting in the normalization of serum tumor marker levels. Nonetheless, chest CT revealed that the mass had grown and was highly vascular (Fig 1b). T2-weighted magnetic resonance imaging revealed heterogeneous high signal intensity (Fig 1c), and the maximum standardized uptake of the mass on positron emission

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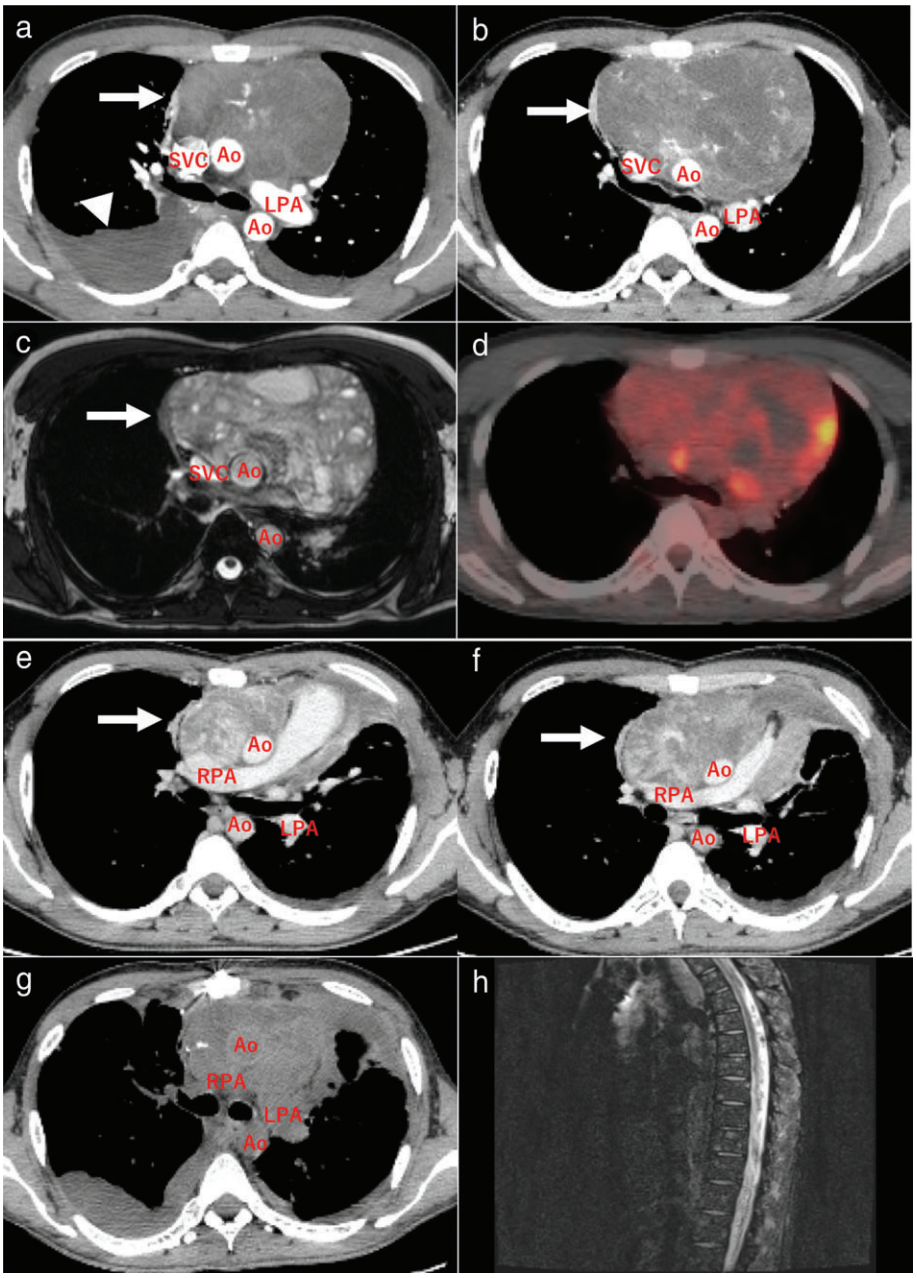

Figure 1 (**a**) Contrast-enhanced computed tomography (CT) before chemotherapy reveals a large anterior mediastinal mass (arrow) and right pleural effusion (arrowhead). (**b**) Contrast-enhanced CT after three cycles of chemotherapy revealed that the mass had grown to approximately 14 × 10 cm, with high vascularity in the anterior mediastinum (arrow). (**c**) T2-weighted magnetic resonance imaging (MRI) reveals a heterogeneous high signal intensity area and high signal intensity nodules in the tumor (arrow). (**d**) Positron emission tomography-CT revealing mixed spots of mild, moderate, and severe accumulation of fluorine-18 fluorodeoxyglucose in the tumor. The maximum standardized uptake value was 5.3. (**e**) Contrast-enhanced CT three months after the initial surgery shows the residual mass in the anterior mediastinum (arrow). (**f**) Contrast-enhanced CT six months after the initial surgery reveals regrowth of the residual mass in the anterior mediastinum (arrow). (**g**) Right pleural effusion on CT and resected residual mass. (**h**) Multiple high signal intensity areas in the spine on sagittal T2-weighted MRI. Ao, Aorta; LPA, left pulmonary artery; RPA, right pulmonary artery; SVC, superior vena cava.

tomography-CT was 5.3 (Fig 1d). Thoracic surgery via median sternotomy was performed based on a clinical diagnosis of GTS. However, only macroscopic incomplete resection was achieved because of massive bleeding and severe adhesions to the pericardium and great vessels. The resected specimen measured 7.5 × 4.0 cm and weighed 580 g. Pathological examination results revealed mature teratoma with massive necrosis and bleeding but no malignant components (Fig 2). Contrast-enhanced CT scans taken three and six months after the surgery revealed regrowth of the residual mass (Fig 1e,f). CT-guided core needle biopsy revealed only a very small teratomatous component. During subsequent follow-up, the patient developed progressive anemia, thrombocytopenia, and massive pleural effusion, without any elevation in serum tumor marker levels, which was attributed to the residual mass. Angiography was performed, which revealed that blood was supplied to the mass via the left internal thoracic artery and a collateral artery from the right coronary artery. One of the branches of the left internal thoracic artery also appeared to supply the right ventricle (Fig 3). A second life-saving surgery was attempted one year after

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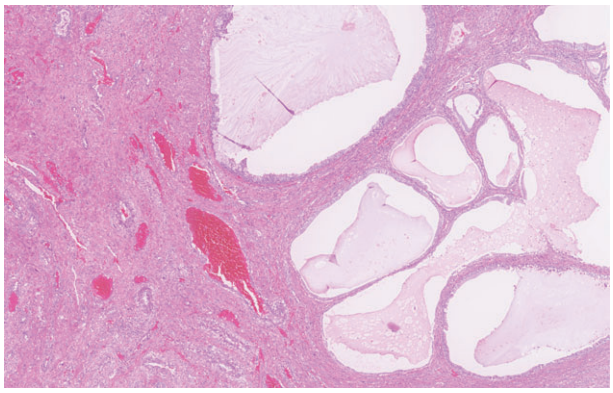

Figure 2 Hematoxylin and eosin staining showing cystic lesions lined with mature epithelial cells, which consisted of bronchial mucosa and glands, as well as gastrointestinal mucosa with hemorrhagic and necrotic tissues but no malignancy.

the first surgery, with ligation of the feeding arteries to control bleeding. This resulted in macroscopic complete resection of the tumor. The final pathological examination revealed angiosarcoma (Fig 4). Despite the second surgery, the patient continued to present with anemia, thrombocytopenia, and pleural effusion and developed back pain. Sagittal T2-weighted magnetic resonance imaging revealed multiple spine metastases (Fig 1h). The patient could not tolerate chemotherapy because of his poor general condition and died as a result of respiratory failure three months after the second surgery.

Discussion

This case involved GTS during chemotherapy and the development of angiosarcoma, which are rare clinical manifestations of NSGCT. Although GTS was first reported by Logothetis *et al.* in 1982,[5] only a few case reports have described GTS in primary mediastinal NSGCTs,[6–8] which generally developed during chemotherapy and required emergency surgical resection or transbronchial stent implantation to preserve airway patency. Surgical resection is the acceptable treatment for GTS because of its resistance to chemotherapy and radiotherapy.[9,10] The etiology of this condition is unclear, although consistent with our findings, previous pathological findings have revealed a small amount of residual mature teratoma surrounded by massive hemorrhage and necrotic tissues[11]

Malignant transformation of NSGCT reflects a germ cell tumor with somatic-type malignancy that is accompanied by a non-germ cell malignant sarcoma or carcinoma component.[12] The cause of the malignant transformation remains unclear, although it is associated with teratomatous components[13] or residual teratoma of GTS.[3,10] Glass *et al.* described two cases in which residual intracranial teratomas of GTS developed malignant transformation three to four years after the initial surgery.[3] In our case, the angiosarcoma component may have been present before chemotherapy, despite elevated serum tumor marker levels and CT-guided core needle biopsy indicating combined NSGCT. Although the initial surgery resulted in incomplete resection, most of the mass was removed (Fig 1b,e), and it was pathologically reported as mature teratoma without malignant components. This clinical course, including the normalization of serum tumor marker levels and the regrowth of the mass as evident on imaging during chemotherapy, was consistent with GTS. The residual teratoma of GTS then developed malignant transformation. Ours is the first report to describe primary mediastinal GTS with subsequent malignant transformation, although one reported case involved postoperative recurrence transformed malignancy of mediastinal GTS.[8]

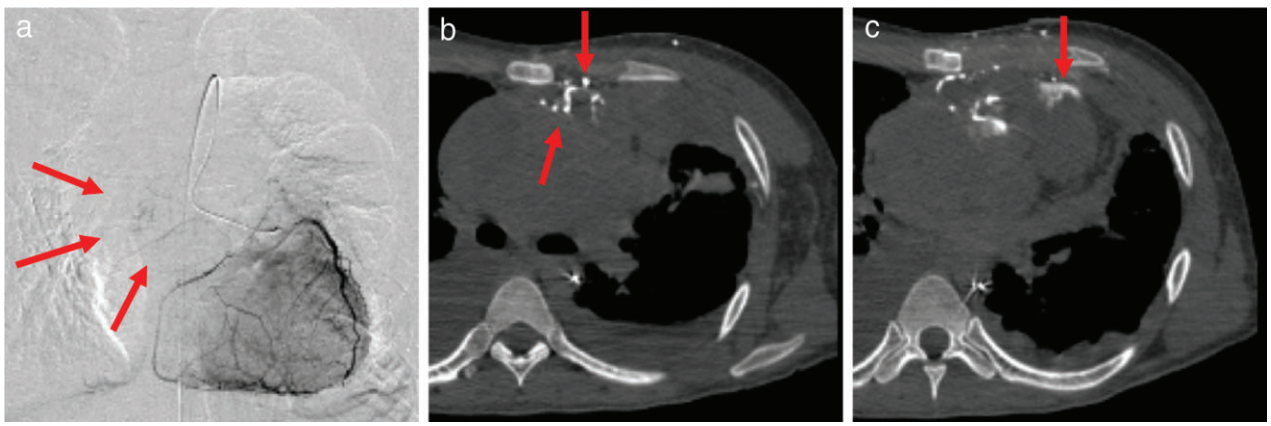

Figure 3 (**a**) Coronary angiography showing collateral artery supply to the residual mass (arrow). (**b**) Computed tomography (CT) angiography showing that the left internal thoracic artery and arterial branches were supplying the residual mass (arrow). (**c**) CT angiography showing an arterial branch of the left internal thoracic artery, which appeared to supply the right ventricle (arrow).

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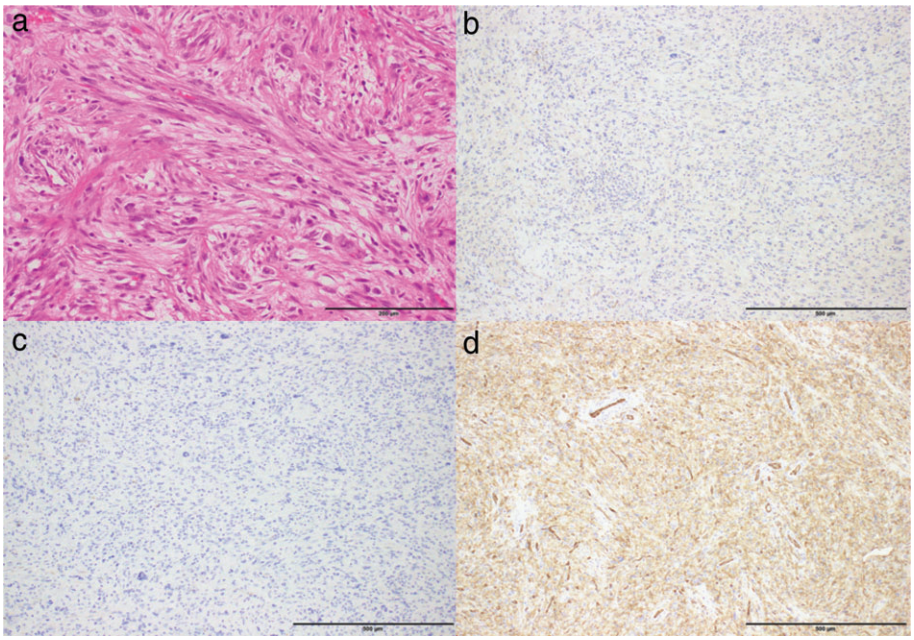

Figure 4 (**a**) Hematoxylin and eosin staining showing that the tumor consisted of atypical spindle and pleomorphic cells. (**b–d**) Immunohistochemical examination shows that tumor cells were (**b**) negative for AE1/AE3 and (**c**) epithelial membrane antigen, (**d**) but expressed CD31.

Mediastinal germ cell tumors with sarcomatous components are associated with a poor prognosis.[13] Angiosarcoma in mediastinal germ cell tumors also has an aggressive behavior and poor clinical course,[14,15] unlike pure mediastinal angiosarcoma.[16] Therefore, resection of residual teratoma of GTS is required to prevent malignant transformation. Our initial surgery resulted in incomplete resection because of massive bleeding. Similarly, Khairy *et al.* described the use of preoperative embolization of the feeding artery to decrease the size of highly vascular mediastinal giant tumors by 20–30% and to induce perilesional ischemia, which facilitated dissection of the mass.[17] We performed angiography before the second surgery but could not perform preoperative embolization because of the risk of myocardial infarction. Thus, the main feeding arteries supplying the mass were only ligated during the second surgery. Moreover, Contreras *et al.* reported that patients with angiosarcomatous components in mediastinal GCTs who received doxorubicin, a sarcoma-oriented drug, achieved long-term survival. Patients with angiosarcomatous transformation in mediastinal GTS may also benefit from doxorubicin treatment.[15]

We encountered a rare somatic-type mediastinal NSGCT (angiosarcoma) that developed in a patient with GTS during chemotherapy. Clinicians should be aware of the variable clinical features and/or complications in patients with mediastinal non-seminomatous germ cell tumors. Detailed preoperative evaluations and extensive planning are likely needed to completely resect giant mediastinal tumors.

Disclosure

No authors report any conflict of interest.

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