En bloc resection of an extremely giant mediastinal immature teratoma with somatic-type malignancy: A case report with a brief review of the literature

qinghua zhou[1], kaili huang[2], pengfei li[1], hanyu deng[1], and xiaojun tang[1]

[1]West China Hospital of Sichuan University
[2]Sichuan University West China Hospital Lung Cancer Center

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En bloc resection of an extremely giant mediastinal immature teratoma with somatic-type malignancy: A case report with a brief review of the literature

Kai-li Huang, MD[1#], Pengfei Li, MD[1#], Han-Yu Deng, MD[1], Xiaojun Tang[1], Qinghua Zhou, MD[1*]

[1]Lung cancer center, West China Hospital, Sichuan University, Chengdu 610041, China

*Correspondence to: Qinghua Zhou. Lung Cancer Center, West China Hospital of Sichuan University, No.37 Guoxue Alley, Chengdu 610041, China. Email: prof_qh_zhou@126.com

#These authors contributed equally to the study and were co-first authors.

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Abstract: Primary mediastinum immature teratoma with somatic-type malignant transformation (SM) is extremely rare, and the clinical prognosis is poor. Immature teratoma with SM is hardly to be eradicated by chemotherapy for the poor sensitivity, therefore surgical resection is recommended whenever possible for it may offer a better survival. We herein report a case of a chemotherapy-resistant and extremely giant immature teratoma who received en bloc resection with pathologic findings of foci of sarcoma and poorly differentiated squamous cell carcinoma, and the literature is reviewed. To our best knowledge, this is the largest primary mediastinum immature teratoma with somatic-type malignant transformation treated with an en bloc resection so far.

Key words: Primary mediastinum immature teratoma, somatic-type malignant transformation, en bloc, surgery

1. Introduction

Germ cell tumors (GCTs) are a family of neoplasms with diverse histopathological, clinical features and prognosis, which are widely considered to arise from almighty primordial germ cells(1). Gonads are the most common organ that GCTs predominantly occurs, while a small proportion of GCTs primarily develops in extra-gonad regions such as pineal gland, coccyx, mediastinum, retroperitoneum(2) and the anterior mediastinum is the prior anatomical position in which approximately 10–20% of primary extra-gonad GCTs occur(3). Pathologically, GCTs are divided into two categories: pure seminomas and non-seminomatous germ

cell tumors (NSGCT)[4]. Teratoma, a subtype of NSGCT, accounts for about 40% - 60% of all mediastinal GCTs with the majority of its histology being mature[5]. While the immature teratoma, a particularly rare subtype of teratomas with poor clinical prognosis, accounts for only approximately 1.8% of mediastinal GCTs and about 4% of mediastinal teratomas[3]. Moreover, the immature teratoma with somatic-type malignant transformation (SM) is extremely rare[6], and there are only a few cases described about this topic[7-12]. We herein report a case of a chemotherapy-resistant and extremely giant immature teratoma who received en bloc resection with pathologic findings of foci of sarcoma and poorly differentiated squamous cell carcinoma. To our best knowledge, this is the largest primary mediastinum immature teratoma with somatic-type malignant transformation treated with an en bloc resection so far.

2. Case presentation

An 18-year-old adolescent came to our medical center from a local hospital for further management of a giant anterior mediastinum mass. Four months before this admission, he made a routine health examination at local health institution and found a huge mass in the mediastinum without any clinical symptoms such as chest pain, dyspnea, or cough. For further treatment, he was referred to a comprehensive oncology hospital and malignant GCT was diagnosed by mediastinal biopsy. Therefore, combined chemotherapy with etoposide (100 mg/m2IV on days 1–5), bleomycin (30 units IV on days1, 8, and 15), and cisplatin (20 mg/m2IV on days 1–5) was subsequently initiated. However, when four cycles of chemotherapy were finished, he underwent a chest CT again which indicated that there was no obvious improvement. Hence, he received radiotherapy (specific dose was not known) at another oncology hospital and the mediastinum mass failed again to respond to radiotherapy and the tumor volume even grew since then. In our hospital, physical examination revealed a thin-built man with normal vital signs and weight loss. Superior vena cava syndrome (SVCs) such as facial edema and jugular vein distention was not observed. Respiratory, cardiac, abdominal, testicular and lymph node examination were negative.

Contrast-enhanced CT showed that a large (approximately $21.6\times12.3\times10.5cm^3$) solid mass with heterogeneous enhancement and noncalcified in the anterior mediastinum. Heart and great vessels including superior vena cava (SVC), ascending aorta, pulmonary artery and left principal bronchus were compressed and surrounded by the tumor with well-defined margin while mediastinal lymph nodes were not noted (Figure 1). Brain MRI, abdominal contrast-enhanced CT, bone scan and pulmonary function test were normal.

Laboratory investigations showed thrombocytopenia (platelets=21×10^9/L, normal=100 300x10^9/L), anemia (hemoglobin[Hb]= 92g/L, normal range=130-175g/L) and normal leukocyte count. Lactate dehydrogenase (LDH), alpha fetoprotein (AFP), β-human chorionic gonadotropin(β-HCG) and carcinoembryonic antigen (CEA) were elevated(AFP¿1210ng/ml, normal¡8ng/ml; β-HCG=270.48mIU/ml, normal¡3.81mIU/ml; CEA=3.71ng/ml, normal¡3.4ng/ml). After chemotherapy and radiotherapy, the level of AFP decreased to 69.56ng/ml and β-HCG decreased to normal (β-HCG=0.26mIU/ml). Other laboratory examinations including renal, hepatic, coagulation function were within acceptable limits. Therefore, the patient underwent surgical resection of the tumor after informed consent was obtained from the patient.

A giant solid mass with intact capsule was observed macroscopically. In the mass, most of the components were solid with local necrosis and multiple cysts. Two mediastinal lymph nodes were observed with a diameter of about 0.8 0.9cm. At the same time, a piece of pericardium attached to the tumor with a size of about 3.6cm×2.2cm was also observed. Microscopically, the tumor was consisted of epithelial tissue, cartilage tissue, skeletal muscle tissue and other mesenchymal tissue, part of which were presented as immature or malignant morphology (Figure 2). Immunohistochemical staining demonstrated that cytokeratin (CK), epithelial membrane antigen (EMA), smooth muscle actin (SMA), desmin (Des), MyoD 1 and Myogenin were positive while AFP and HCG were negative indicating that the large mass was an immature teratoma with poorly differentiated squamous cell carcinoma and sarcoma malignant transformation.

3. Discussion

GCTs are a group of neoplasms that stem from different anatomic sites and in different age group. They are mainly located along the middle line of the body with the gonads being the most frequent involving

organ and the mediastinum being the most common site of extragonadal GCTs[2, 13]. The majority of GCTs contain mixed components and about 15% of them have the potential to be malignant but rarely do these tumors actually undergo malignant degeneration[14]. Tumor malignant transformation (TMT) refers to that a non-germ cell tumor malignant component could be found within the bulk of a GCT or in its metastatic foci, which is called as GCT with somatic-type malignancy (SM)[15] accounting for about 6% of GCTs[16]. The SM of GCTs are most observed in retroperitoneum and recurrent cases and it is extremely rare in the mediastinum with immature teratoma[6, 17].

Probably because the components of GCTs have pluripotency, varies types of histological malignant transformation may occur simultaneously within a GCT, of which sarcoma (predominantly rahbdomyosarcoma) is the most frequent histological type of SM followed by adenocarcinoma and primitive neuroectodermal tumors while the melanocytic neuroectodermal transformation is the rarest [17, 18]. Other histology types include squamous cell transformation, carcinoid tumors, hemangioendothelioma, and nephroblastoma[18]. In our case, the immature tumor was proved to have a SM, and the histological types were squamous cell tumor and sarcoma(rhabdomyosarcoma, chondrosarcoma and fibrosarcoma) while the lymph node metastasis was found to be squamous cell tumor malignant transformation, which meant a higher recurrence rate and aggressiveness than teratomas without malignant transformation[17]. GCTs that developed SM naturally had been reported rarely, and they were seen more frequently in older patients with the peak age at 50 to 60 years old[15, 19, 20], most of them occurred subsequently to chemotherapy or irradiation in young patients with a malignant GCT initially[15]. Therefore, it could explain that our case with initially a malignant GCT developed SM at last after chemotherapy and irradiation. However, the specific mechanisms of GCTs with SM are poorly understood and two pathogenesis were assumed. Firstly, chromosomal abnormalities have been detected such as isochromosome 12p or rearrangement of 2q[21] and it has been proved by Honecker F et al[22]that mature teratoma cells could undergo de-differentiate in vitro into malignant tissues, Secondly, a totipotential embryonal carcinoma cell transformed to a neoplasm of the somatic type through malignant de-differentiation could also be related with this phenomenon[23]. Few other cases of immature teratoma with somatic-type malignancy have been reported previously (Table 1)[24-28]. To our best knowledge, this is the largest primary mediastinum immature teratoma with somatic-type malignant transformation which received an en bloc resection so far.

Clinically, due to the mediastinal structures can accommodate large teratomas and their insidious growth, the manifestation of symptoms are not obvious even though GCTs with SM tend to be more symptomatic than those without SM, but the symptoms are rarely indistinguishable when they were present[29]. However, several syndromes have been identified in association with nonseminomatous mediastinal GCTs that may aid diagnosis, such as Klinefelter's syndrome and Hematologic neoplasms[30]. As our case, the patient did not find the pretty large solid mass in the anterior mediastinum until he conducted a physical examination without presentation any anomalous symptoms. Symptoms such as cough, chest pain, dyspnea, heart failure, dysphagia, hemoptysis, hoarseness, postobstructive pneumonia and et al could arise when the tumor invaded or compressed the surrounding organs in the mediastinum[31], but these symptoms are not specific. Even though teratomas could grow extremely large, patients with superior vena cava syndrome (SVC) were rarely observed, accounting for no more than 10% of the cases[32]. Radiologically, due to coexistence of tumor cells with different proliferation rates, attenuation heterogeneity is a common characteristic of the mass and GCTs with SM could present as solid mass along with areas of teratomatous, necrotic, or hemorrhagic zones in the contrast-enhanced CT scan[33]. However, it did not suggest a particular subtype of malignant transformation which was mainly diagnosed based on the histological analysis via a biopsy or surgical specimen[34]. But contrast-enhanced CT scanning is useful to determine whether the adjacent structures such as great vessels, heart and lung are invaded by the tumor or whether tumors metastasize to regional lymph nodes or other organs such as lung, brain, liver and spleen as well as tumors recurrence[27]. In the case we reported herein, multiple characteristics were demonstrated in the contrast-enhanced CT scanning. Laboratory examination could find that serum tumor markers such as AFP and LDH are frequently elevated in 80% of patients with primary non-seminoma mediastinal GCTs, however, there are only about 30% to 35% of the patients with elevated β-HCG[35]. Mediastinal nonseminomatous GCTs with elevated AFP and β-HCG have been

previously reported in GCTs with SM, suggesting the presence of malignance and poor prognosis[5, 36]. In the herein mentioned case, a high level of AFP(¿1210ng/ml) and β-HCG(270.48mIU/ml) was observed before treatment. After chemotherapy and radiotherapy, the level of AFP as well as β-HCG decreased and neither AFP or HCG producing cells were confirmed in the resected specimens indicating that necrosis or de-production in the AFP and HCG-producing cells were induced by pre-operative chemotherapy and radiotherapy[37]. However, the patient clinical presentation was getting deterioration with tumor growing rapidly and larger than before, which was not deemed as teratoma syndrome characteristically seen in mature mediastinal teratomas[38]. In this case, the rapid tumor aggression is more likely due to the underlying aggressive nature of the non-GCTs malignant transformation components, especially sarcoma[36]. It has been previously provided that GCTs with SM, especially with sarcoma malignant transformation, had a poor response to cisplatin-based chemotherapy[17, 39].

Orizi A et al[40] found that hematopoietic stem cells could exist in mediastinal GCTs which might cause hematologic derangements and it was associated with nontreatment-related blood malignance[41]. Garnick MB[42] et al also found that primary mediastinal GCTs were associated with thrombocytopenia. This might explain the continued reduction of platelet occurred in our patient. Another explanation for this phenomenon might be myelo-suppression caused by chemotherapy or radiotherapy before surgery but we failed to conduct a bone marrow biopsy to further find out the pathogeny of this phenomenon. It is worth noting that GCTs may induce thrombotic events, especially during chemotherapy, and pulmonary embolism (PE) might be suspected when a sudden hemoptysis occurred[43].

Currently, the standard treatment for nonseminoma GCTs is chemotherapy followed by surgical resection of residual mass, however, radiotherapy is not recommended for it is invalid in treating primary mediastinal nonseminoma GCTs. The recommended chemotherapy is 4 courses of bleomycin, etoposide, and cisplatin(2). Given the poor sensitivity to chemotherapy, immature teratoma with SM is hardly to be eradicated by cisplatin-based chemotherapy, and an aggressive surgical resection is recommended whenever possible for it may offer a better survival[44]. Nonetheless, Teratomas with SM presented in the mediastinum essentially have an aggressive course, high recurrence rate, and poor prognosis and are always fatal within a few months after initial diagnosis[15]. As our case demonstrated, the tumor was resistant to standard chemotherapy and showed progression in size after chemotherapy, therefore a primary mediastinal GCT with SM might be suspected[15] and surgical intervention instead of any other treatments should be considered firstly whenever possible.

Generally, primary mediastinal teratomas with SM have an extremely poor prognosis for the malignant transformation components in term of chemotherapy resistance, high recurrence and more invasiveness and sometimes even sudden death[20, 45]. Several indicators may relate with poor prognosis for GCTs which included as follow: (1) persistent germ cell tumor in the residual mass; (2) elevated LDH; (3) GCTs with thrombocytopenia; (4) somatic-type transformation; (5) post-chemotherapy AFP level greater than 1001 ng/ml[46, 47]. Our patient had a number of poor indicators, including elevated LDH, thrombocytopenia and somatic-type transformation. Even though complete resection of the tumor had been achieved, he finally died after 5 months after the initial diagnosis, which was consistent with previous study[15].

Conclusion

In summary, primary mediastinal immature teratoma with somatic-type malignancy is extremely rare with extremely poor prognosis. When laboratory and imaging findings are conflicting for patients with immature teratoma after chemotherapy, somatic-type malignancy should be considered. Due to its rarity, comprehensive reporting of clinical, radiological and pathological features is needed for a diagnosis of an immature teratoma with SM. We reported a primary giant mediastinal immature teratoma with sarcoma and squamous malignant transformation which was resistant to chemotherapy and radiotherapy but resected completely. Rare as it is, additional cases of this pathology are needed to add to the literature for a better understanding of somatic-type malignancy and management of this disease.

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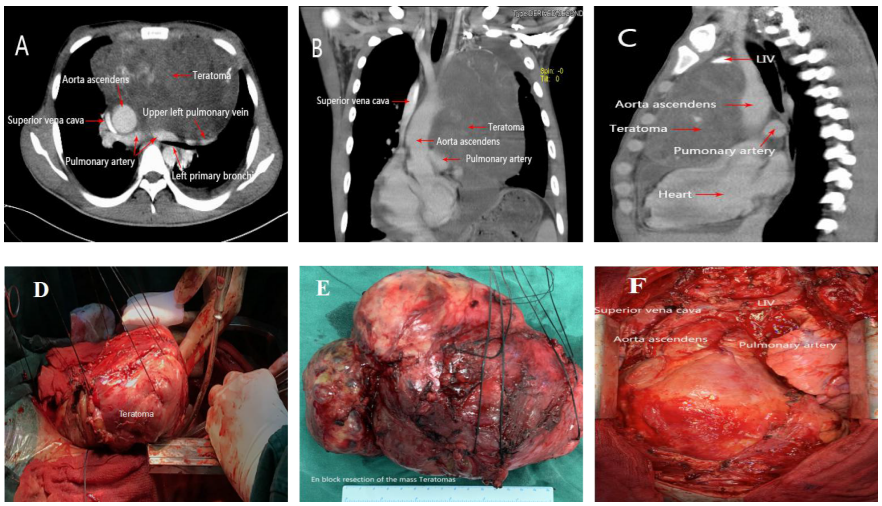
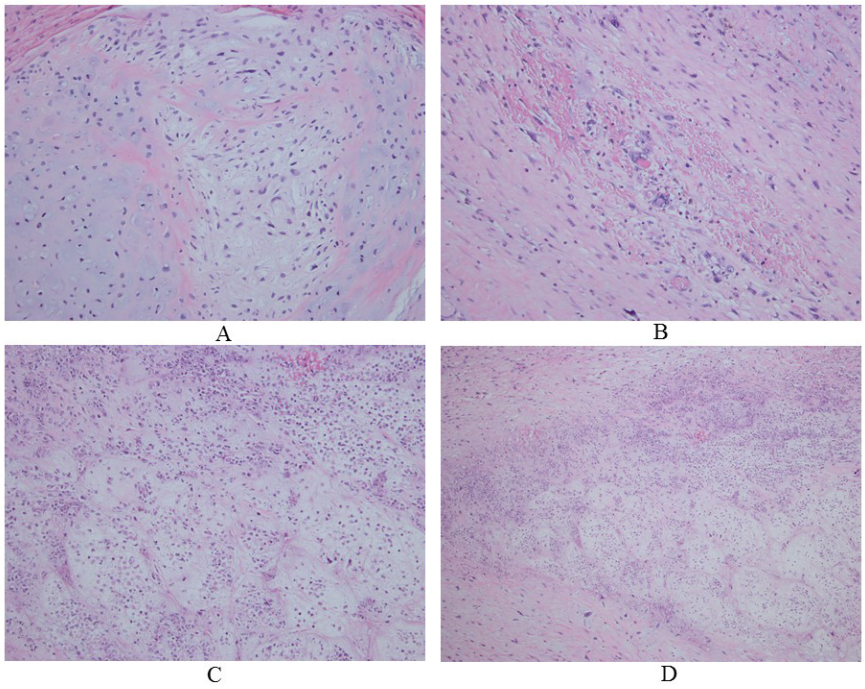
Figure Legends

Figure 1 A-C: Contrast-enhanced CT indicated a large mass in the anterior mediastinum with well-defined margin and the important structures in the mediastinum were compressed and surrounded by the tumor; D-F: an en bloc resection of the large solid tumor with intact capsule via a median sternotomy.

Figure 2 HE stain of somatic-type malignancies components showing: (A) rhabdomyosarcoma; (B) chondrosarcoma; (C) fibrosarcoma; (D) poorly differentiated carcinoma. Magnification ×200.





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