

Case Report

Primary mediastinal yolk sac tumor: a case report and literature review

Fang Zhu, Lixia Wang, Xiaoli Zhai

Department of Pathology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine (Jinhua Municipal Central Hospital), Jinhua, Zhejiang Province, China

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Abstract: Primary mediastinal yolk sac tumors (YSTs) are rare and have a high degree of malignancy. This article reports a 42-year-old man with a primary mediastinal YST. The patient presented with chest tightness and shortness of breath. Using a contrast-enhanced computer tomography (CT) scan, the mediastinal space was found to be occupied by a mass shadow, about 10 cm × 8 cm with a clear boundary and low density. Serum alpha-fetoprotein (AFP) was elevated to 7169.66 ng/ml. The 5th day after hospitalization, a percutaneous biopsy of the mediastinal mass was performed. Malignant tumor cells were found by cytologic examination. According to the pathological morphology and immunohistochemical results, the tumor was diagnosed as primary mediastinal YST. Subsequently, the patient underwent five cycles of adjuvant chemotherapy including bleomycin, etoposide, and cisplatin (BEP) and surgical tumor removal. One month after operation, AFP was elevated to 252.96 ng/ml. CT examination showed that the tumor recurred. As of September 12, 2020, the patient has undergone four cycles of VIP (etoposide, ifosfamide, cisplatin) chemotherapy after relapse, and the patient's condition is currently in partial remission.

Keywords: Primary mediastinal yolk sac tumor, immunohistochemistry, chemotherapy

Introduction

Yolk sac tumors (YSTs), also known as endodermal sinus tumors, are highly malignant germ cell tumors that occur in the yolk sac, an extra-embryonic structure. Most of them occur in the gonads. Extragonadal YSTs are rare and often occur in the middle axis of the body, such as the brain, mediastinum, retroperitoneum, and sacrococcygeal [1]. Occasionally, tumors are localized to other body regions, such as the head and neck [2], or liver [3]. The age distribution of mediastinal YST shows a bimodal pattern, with most cases occurring in infancy and post-puberty [4]. For post-pubertal patients, onset age ranges from 14 to 63 years with an average of 30 years old [5], however, diagnosis is exceedingly rare in patients over 40 years old [6]. Originating from the mediastinum, primary mediastinal YSTs can pose diagnostic difficulties due to their morphologic spectrum and unusual site. Primary mediastinal YSTs are highly malignant and the prognosis is extremely poor, mainly due to the degree of tissue invasion and inability of complete resection at the

time of diagnosis [7]. YSTs grow rapidly and metastasize early, usually to the lungs, brain, and liver [7]. Here, we report the pathological diagnosis of a 42-year-old male patient with primary mediastinal YST, review the relevant literature, and discuss the clinical features, pathology, treatment, and prognosis.

Case report

Clinical history

A 42-year-old male patient was hospitalized with chest distress that had lasted for 3 days. The patient had a body temperature of 38.5°C at the time of physical examination. A routine blood examination showed leukocyte levels of $14.44 \times 10^9/L$, neutrophil levels of 81.8%, and lymphocyte levels of 13.6%. A computer tomography (CT) scan with contrast enhancement showed that the mediastinal space had a mass shadow, about 10 cm × 8 cm in size, with clear boundary, lower than average density, right bronchial compression and narrowness, and right pleural effusion (**Figure 1A**). After admis-

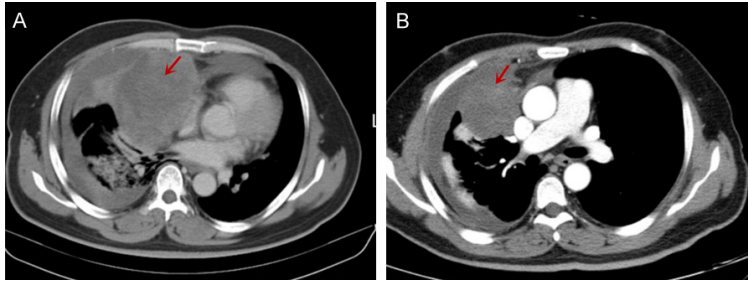


Figure 1. A. Enhanced CT scan on admission showed a mass shadow in the mediastinal space, about 10 cm × 8 cm in size. B. After 5 cycles of BEP chemotherapy, the tumor size decreased to about 6.0 cm × 5.1 cm.

sion, the patient received anti-infection treatment due to persistent low fever. During this period, pleural effusion puncture and drainage were performed with no identification of tumor cells in the hydrothorax. An examination of blood tumor markers revealed that alpha-feto-protein (AFP) levels were elevated to 7169.66 ng/ml (reference level, <10 ng/ml), CA125 was 1921.8 U/ml (reference level, <35 U/ml), and CYFRA21-1 was 123.2 ng/ml (reference level, <3.3 ng/ml). The 5th day after hospitalization, a percutaneous biopsy of the mediastinal mass was performed under the guidance of a CT scan. Based on the results of histomorphology and immunohistochemical staining, the tumor was diagnosed as primary mediastinal YST. After exclusion of contraindications, BEP (bleomycin, etoposide and cisplatin) chemotherapy was performed on the third day (2020-2-11) after diagnosis, with supportive treatments such as liver protection, stomach protection, and antiemetic. Four cycles of chemotherapy were subsequently carried out on March 5, March 27, April 18, and May 8, 2020. During chemotherapy, enhanced CT scan showed that the tumor gradually reduced to 6.0 cm × 5.1 cm on May 9, 2020 (**Figure 1B**). On May 9, 2020, serum AFP levels dropped into the normal range (8.55 ng/ml). Subsequently, the patient underwent surgical tumor removal. More than one month after operation, serum AFP was elevated to 252.96 ng/ml. Enhanced CT examination showed that the tumor recurred. Due to the lack of bleomycin, the patient could not undergo BEP chemotherapy after surgery and switched to VIP (etoposide, ifosfamide, cisplatin) chemotherapy for alternative treatment. As of September 12, 2020, the patient has undergone four cycles of VIP chemotherapy after relapse, and the patient's condition is currently partial remission.

Pathological examination

Cytologic examination of biopsy specimen: Under cytologic examination, several colonies of abnormal epithelioid cells were observed. Abnormalities included unclear cell boundary, rich cytoplasm, large nucleus, irregular shape, high ratio of nucleus to the cytoplasm, thick chromatin, nucleolus, and a small amount of necrosis (**Figure 2A**). As a

result the patient was diagnosed with a malignant tumor.

Histopathologic examination of biopsy: The tumor cells were arranged in a network, with unclear cell boundary, vacuolated cytoplasm (**Figure 2B**), mucin, eosinophilic bodies, irregular nuclei, mitotic figures, and much necrosis (**Figure 2C**). Envision method was used for immunostaining, and the positive signals of all antibody IHC were brown-yellow granules. IHC results showed that the tumor cells expressed pan-cytokeratin (**Figure 2D**), SALL4 (**Figure 2E**), AFP (**Figure 2F**), GPC3 (**Figure 2G**), CD99, D2-40, CD117; but S-100 protein, cytokeratin 5/6, CD56, CD5, CD20/L26, CD30 (**Figure 2H**), ALK, Desmin, SMA, Synaptophysin, TTF1, P63, HMB45 and Oct3/4 were negative.

Histopathological examination of resected specimen: The size of the removed tumor was 6.3 cm × 6.0 cm × 5.2 cm, and the outer layer was covered by a capsule. The tumor sections were grayish-yellow, mostly hard, and a few areas with necrosis were soft (**Figure 3**). Under microscopic examination, we found extensively necrotic tissue and small remnants of the YST in the resected tumor specimen (**Figure 4A, 4B**). The results from the immunohistochemical stains of the resected tumor were consistent with those of the biopsies. We confirmed the prior diagnosis of a primary mediastinal YST.

Discussion

According to histologic analysis, mediastinal germ cell tumors are classified as seminoma, non-seminoma, mature teratoma, and immature teratoma. YSTs are a non-seminomatous germ cell tumor, accounting for 15% of diagnosed mediastinal germ cell tumors [7]. At present, the prevailing theory holds that YSTs

Case of primary mediastinal yolk sac tumor

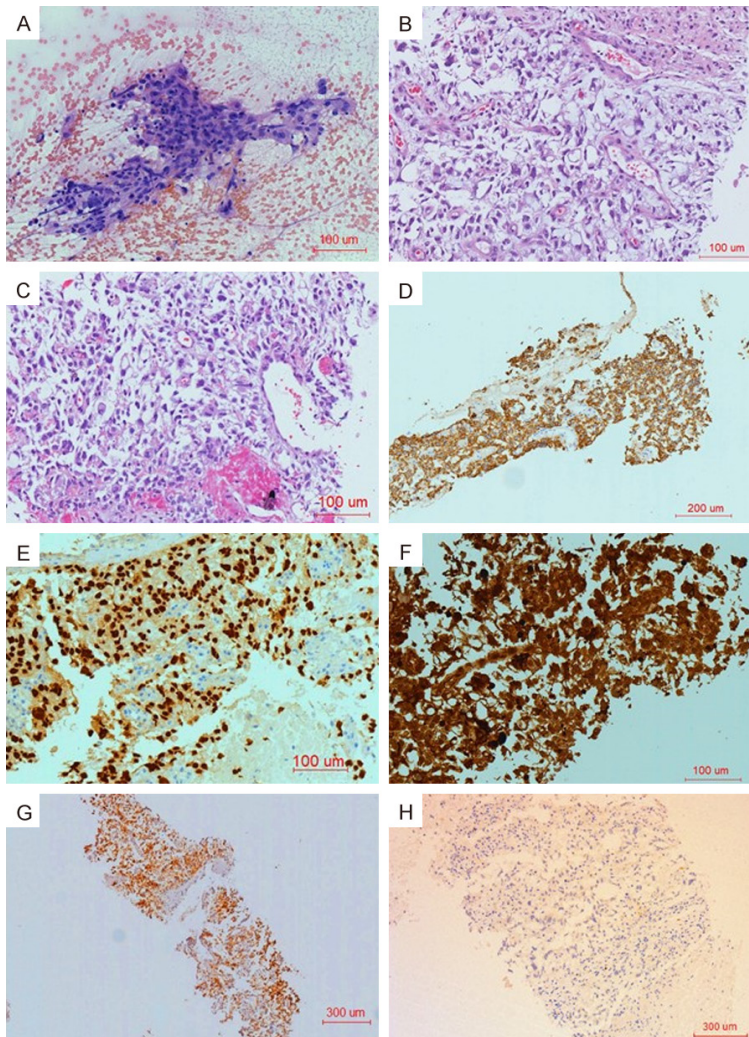


Figure 2. A. Abnormal epithelioid cells with a high ratio of nucleoplasm to cytoplasm and thick chromatin were observed upon cytologic examination (H&E, 200 ×). Morphologic and immunohistochemical characteristics of tumor tissue in biopsy specimens: B. The tumor cells are arranged in a network and the cytoplasm is vacuolated (H&E, 200 ×). C. The tumor cells contain mucus, eosinophils, and irregular nuclei (H&E, 200 ×). D. Positive expression of pan-cytokeratin (100 ×). E. Positive expression of SALL4 (200 ×). F. Positive expression of AFP (200 ×). G. Positive expression of GPC3 (100 ×). H. Negative expression of CD30 (100 ×).

are caused by malignant transformation in the process of gonadal embryonic cell migration. Moreover, the occurrence of YSTs in the mediastinum is the result of blocked reproductive cell migration from the yolk sac to the reproductive ridge or by abnormal migration [1].

Clinical features

Primary mediastinal YSTs are typically located in the anterior mediastinum. These tumors are usually large and easily invade adjacent tissues

and organs, such as the vena cava and pericardium [8]. In the early stages of tumor development, most patients have no obvious symptoms. However, once the tumor enlarges or compresses surrounding organs, chest distress, chest pain, and superior vena cava syndrome (SVCS) may occur. Additionally, some patients may have a fever [9]. Rapid tumor growth and early metastasis are clinical features of YSTs. In YST cases, metastases are commonly found in the lungs, liver, brain, and bone [10]. YSTs also have endocrine clinical characteristics including elevated serum AFP. Since only YST cells in mediastinal tumors can produce AFP, the determination of the AFP blood value is used as a key indicator during the diagnostic and prognostic evaluation of YSTs [11]. In the case presented here, serum AFP levels were as high as 7169.66 ng/ml at the time of the initial diagnosis. However, AFP levels decreased after 4 cycles of chemotherapy to 8.55 ng/ml.

Pathology

After surgical removal, most of the primary resected mediastinal YST remained intact, with a cystic and solid morphology on the cut surface. Cystic structures had an almost exclusively honeycomb morphology and

solid structures were generally gel or mucus-like. A huge YST is often accompanied by bleeding and necrosis. The histopathologic structures of YSTs are relatively complicated and include reticular, endodermal sinusoid, adenoid, and solid structures. Reticular structures are sieve-like and consist of loosely distributed star shaped cells. Endodermal sinus-like structures have unique characteristics and contain glomerular-like Schiller-Duval (S-D) bodies. The relatively rare adenoid structure is lined by columnar or cuboid tumor cells as glandular



Figure 3. Gross examination of resected specimens: The outer layer of the tumor is covered by a capsule; the sections are grayish-yellow and mostly hard, and a few areas with necrosis are soft.

ducts. In addition to these morphologic hallmarks, IHC is used as an important method for the detection and diagnosis of YSTs. The three most sensitive diagnostic indicators in IHC are AFP, glypican-3 (GPC3), and SALL4 [4]. Co-expression of CAM5.2, SALL4, GPC3, and AFP provides strong evidence of YST differentiation [12]. In this patient, the tumor was positive for AFP, SALL4, GPC3, and cytokeratin (AEI/E3). Extensive necrosis in postoperative tumor specimens may be related to tumor cell necrosis caused by chemotherapy.

Differential diagnosis

Primary mediastinal YSTs must be distinguished from other germ cell tumors in the mediastinum, such as seminoma and embryonal carcinoma. Mediastinal seminomas are often composed of round or polygonal tumor cells with uniform morphology, rich cytoplasm, and clear cell membranes, and they lack any reticular structure or S-D bodies. In addition, immunohistochemical staining is an important method to distinguish the two tumors. The positive expression of OCT-4 and the negative expression of pan-cytokeratin are shown in seminomas, while those in YSTs are the opposite. Mediastinal embryonal carcinomas are mainly composed of primordial polymorphic large mononuclear cells that may be accompa-

nied by eosinophilic hyaline cells and syncytiotrophoblasts. The tumors also lack S-D bodies and/or eosinophilic basement membrane-like substances. Clinically, mediastinal embryonal carcinomas may be accompanied by endocrine abnormalities, and β -human chorionic gonadotropin (β -hCG) reactivity is positive in the majority of cases, but β -hCG reactivity is negative in YSTs. In addition to the above mediastinal germ cell tumors, primary mediastinal YSTs also need to be differentiated from thymic cancer, mediastinal metastatic lung cancer, and mediastinal lymphoma.

Treatment

Primary mediastinal YSTs are sensitive to chemotherapy and typically unresponsive to radiotherapy, but successful treatment by radiotherapy has occasionally been reported [13]. Chemotherapy is a treatment used to kill cancer cells. It involves taking one or more drugs that interfere with the DNA of fast-growing cells. Currently, surgery followed by adjuvant chemotherapy with BEP is considered the standard for YST treatment [14]. Surgery plays an important role in primary mediastinal YST treatment. Under otherwise healthy physical conditions and technical feasibility, the patient should undergo surgery to remove any residual lesions after chemotherapy. In the current study, a BEP chemotherapy regimen was utilized. After five cycles of chemotherapy, the residual tumor was excised, but after more than a month of tumor resection, the tumor quickly recurred. It may be because the tumor has extensive invasion and adhesion to surrounding tissue structures, including pericardium, superior vena cava, right upper lung, phrenic nerve, vagus nerve, and thymus. Therefore, although the tumor and thymus have been removed, tumor cells may remain in adjacent tissues, leading to tumor recurrence. In addition, delayed chemotherapy after surgery and the high degree of malignancy and rapid growth of the tumor may also be causes of rapid recurrence. After the surgery, the patient switched to VIP chemotherapy due to the lack

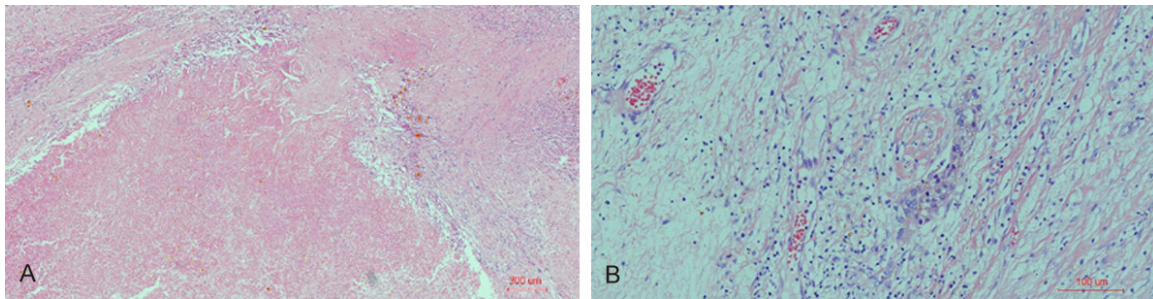


Figure 4. Histology of tumor tissue from surgically resected specimens. A. Extensive necrotic tissues, cholesterol crystals, and hyperplasia of surrounding fibrous tissue (H&E, 40 ×). B. Residual yolk sac tumor cells (H&E, 200 ×).

of bleomycin. Compared with other chemotherapy regimens, BEP appears to be the most effective first-line option for primary, metastatic, or recurrent disease [4]. It has also been reported that reliable diagnosis and immediate multimodal treatments are necessary for patients with primary mediastinal YST [15].

Prognosis

Since tumors attach to vascular structures, complete resection is often difficult [16]. Moreover, in advanced cases, the tumor volume is too large to be surgically removed [7]. Therefore, complete tumor resection, before or after chemotherapy, is the most important prognostic indicator [4]. At present, some studies indicate that serum AFP levels after preoperative chemotherapy, the pathologic status of residual mass, and presence or absence of lung metastasis are considered to be related closely to prognosis [7, 17]. Geng et al. investigated the clinical characteristics, survival, and risk factors of 569 male YST patients based on the surveillance, epidemiology, and end results (SEER) program. The results of the study showed that the 3-year and 5-year cancer-specific survival were 70.0%, 56.5% vs. 97.2%, 96.0% for the mediastinal and testicular YST patients, respectively, indicating that primary site of mediastinum is an independent adverse risk factor [18].

In summary, primary mediastinal YST is a rare tumor with high malignancy and poor prognosis. The clinicopathologic features, such as tumor location, range, histopathologic type, tumor stage, and serum tumor markers, are necessary conditions for predicting and formulating further treatment plans [19].

Disclosure of conflict of interest

None.

Address correspondence to: Fang Zhu and Lixia Wang, Department of Pathology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine (Jinhua Municipal Central Hospital), 365 Renmin East Road, Jinhua, Zhejiang Province, China. E-mail: zjzhufang@sina.com (FZ); wlxmyw@163.com (LXW)

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