

PRIMARY GERM CELL TUMORS OF THE MEDIASTINUM: 10 YEARS OF EXPERIENCE IN A TERTIARY TEACHING HOSPITAL

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Germ cell tumors occur mostly in the gonad. Extragonadal germ cell tumors are rare, and most occur in the retroperitoneum and mediastinum. Primary mediastinal germ cell tumors are often found in the anterior portion of the mediastinum and include teratomas and non-teratomatous tumors. Non-teratomatous tumors include seminomas and malignant non-seminomatous germ cell tumors (MNSGCTs). MNSGCTs include yolk sac tumors, choriocarcinomas, embryonal carcinomas, and mixed type germ cell tumors. Teratomas are the most common germ cell tumors of the mediastinum, and seminomas are the most common non-teratomatous germ cell tumors of the mediastinum. Cases of primary mediastinal MNSGCT reported in the literature are rare. In this report, we review all primary mediastinal germ cell tumors from a 10-year period at the Chung-Ho Memorial Hospital of Kaohsiung Medical University. A total of 14 cases were reviewed, including 11 patients with mature teratomas, two with yolk sac tumors, and one with seminoma. We discuss the differences in clinical presentation, histopathologic characteristics, treatment, and prognosis.

Key Words: germ cell tumor, mediastinal mass
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Extragonadal germ cell tumors are rare and are usually located in the anterior mediastinum [1,2]. The most common germ cell tumors are teratomas [3]. Malignant germ cell tumors are extremely rare, comprising less than 1% of all mediastinal tumors. These germ cell tumors have different clinical presentations, histologic features, serologic markers, and immunohistochemical stain patterns [4–10]. Over the last decade, the prognosis of these malignant germ cell tumors, except for seminomas, has improved significantly because of the introduction of platinum-based chemotherapy [11].

We reviewed all primary mediastinal germ cell tumors from the past 10 years at Chung-Ho Memorial Hospital of Kaohsiung Medical University. We present these primary mediastinal germ cell tumor cases and discuss the differences in clinical presentation, histopathologic characteristics, and prognosis.

PATIENTS AND METHODS

We retrospectively reviewed primary germ cell tumors covering a period from 1993 to 2003. Case definition and diagnosis were identified from the files of the Department of Pathology. All cases were diagnosed by surgical resection.

Clinical findings were recorded separately for each patient. The data analyzed included gender and age at diagnosis, clinical findings, histologic findings, radiologic findings, therapeutic approaches, and follow-up regimen.

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RESULTS

There were 14 primary mediastinal germ cell tumors at Chung-Ho Memorial Hospital, occurring with equal frequency in male and female patients. The median age was 27 years (range, 1–44 years). Eleven patients had mature teratomas (Figures 1 and 2), one had seminoma, and two had yolk sac tumors (Table 1 and Figure 3). None of these

patients had a history of testicular neoplasm or tumors elsewhere.

The most common symptoms were dry cough (5 cases), chest pain (3 cases), fever (3 cases), and shortness of breath (3 cases) (Table 1). One patient with teratoma had massive left pleural effusion. Four patients were asymptomatic, with tumors encountered accidentally during health examinations. All asymptomatic patients had teratomas.



Figure 1. Case 4: chest X-ray of a 28-year-old man showing an anterior mediastinal mass.

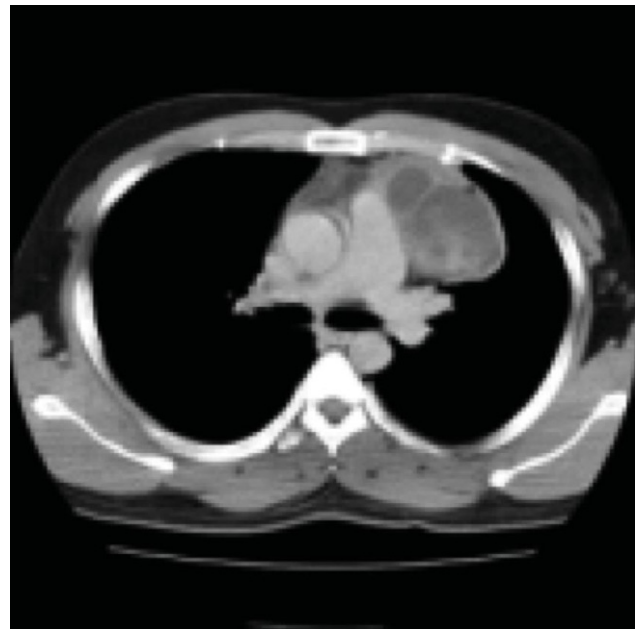


Figure 2. Case 4: chest computed tomography revealing an anterior mediastinal mass with a fat-containing soft-tissue mass.

Table 1. Primary germ-cell tumors of the mediastinum at Chung-Ho Memorial Hospital, Kaohsiung Medical University, from 1993 to 2003

Case	Gender	Age (yr)	Initial presentation	Diagnosis
1	F	37	Chest pain for 1 year	Mature teratoma
2	F	1	Asymptomatic	Mature teratoma
3	M	5	Cough, fever for 2 weeks	Mature teratoma
4	M	28	Chest pain, cough	Mature teratoma
5	F	36	Asymptomatic	Mature teratoma
6	F	2	Fever, cough for 1 week	Mature teratoma
7	F	20	Cough for 3 months	Mature teratoma
8	F	30	Exertional dyspnea, pleural effusion	Mature teratoma
9	M	20	Asymptomatic	Mature teratoma
10	M	44	Asymptomatic	Mature teratoma
11	F	19	Cough, hemoptysis	Mature teratoma
12	M	30	Sudden chest pain	Seminoma
13	M	23	Fever, dry cough, weight loss	Yolk sac tumor
14	M	24	Intermittent chest pain, cough, weight loss	Yolk sac tumor

All cases were diagnosed through surgical resection. Interestingly, both patients with yolk sac tumors presented with elevated α -fetoprotein (AFP). Surgical specimens stained positive for AFP (Figure 4), but had previously been misdiagnosed as having undifferentiated adenocarcinomas by a local hospital. The misdiagnosis was according to fine needle aspiration biopsy (FNAB) and histologic features.

All germ cell tumors were located in the anterior mediastinum and demonstrated typical widened mediastinum on chest X-rays. Malignant non-teratomatous tumors were observed in three cases (Table 2). The patient presenting with seminoma responded well to radiotherapy after completion of surgical resection, showing no evidence of recurrence after 8 years. Both patients with yolk sac tumors underwent radical resection and received postoperative platinum-based chemotherapy. Both patients lived for more than 10 months after surgery.

DISCUSSION

Germ cell tumors include teratomatous lesions and non-teratomatous lesions. Teratomatous lesions consist of mature teratomas, immature teratomas (containing fetal tissue), and teratomas combined with other malignant components [1,2]. Non-teratomatous lesions include seminomas and non-seminomatous tumors, such as yolk sac tumors, embryocarcinomas, choriocarcinomas, and mixed types. The most frequent germ cell tumors are teratomas [1–3], and the most common non-teratomatous tumors are seminomas. Eleven cases of teratoma were diagnosed at our hospital over the 10 years, and there were only three cases (21%) of non-seminomatous germ cell tumors. All of the primary mediastinal germ cell tumors were located in the anterior mediastinum.

The most common symptoms among these cases of

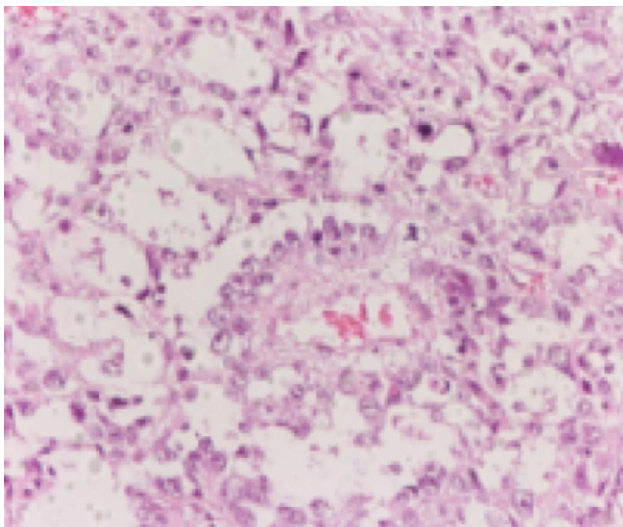


Figure 3. Case 13: typical Schiller-Duval body in a yolk sac tumor (hematoxylin & eosin stain, $\times 200$).

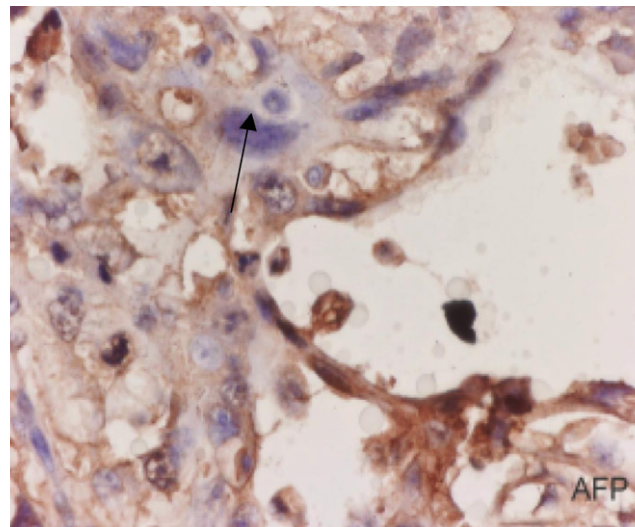


Figure 4. Case 13: positive staining with α -fetoprotein supports the diagnosis of yolk sac tumor (α -fetoprotein stain, $\times 200$).

Table 2. Characteristics and prognosis of malignant germ cell tumors

Case (diagnosis)	Serum marker	Immunohistochemical staining	Survival
12 (seminoma)	AFP 0 IU/mL; β -hCG 0 IU/L	All stains negative	Postoperative radiotherapy and no relapse for 8 years
13 (yolk sac tumor)	AFP 2,533 IU/mL; β -hCG 0 IU/L; CEA 1.92 ng/mL; LDH 456 U/L	AFP positive, β -hCG negative	Alive 10 months after diagnosis
14 (yolk sac tumor)	AFP 1,842 IU/mL; β -hCG 0 IU/L; CEA 1.31 ng/mL; LDH 268 U/L	AFP positive, β -hCG negative	Alive 9 months after diagnosis

Normal range: serum α -fetoprotein (AFP) < 20 IU/mL; serum and urine β -human chorionic gonadotropin (β -hCG) < 0.01 IU/L in males; serum carcinoembryonic antigen (CEA) < 5 ng/mL; serum lactate dehydrogenase (LDH) 289–497 U/L.

mature teratomas were chest pain, cough, and fever. Interestingly, one case with teratoma showed exertional dyspnea because of massive pleural effusion. Pleural effusion is generally thought to be related to the rupture of teratomatous cysts [3]. Four of our cases (36%) were asymptomatic at the time of presentation, and the tumor was found from abnormal chest X-ray findings during health examinations. All cases showed a well-circumscribed anterior mediastinal mass. Fat, fluid, and calcification on chest computed tomography (CT) are the characteristics of teratomas. Radical surgical removal leads to resolution in all patients with teratomas [3].

Seminomas are the second most common germ cell tumors of the mediastinum and almost exclusively affect men. Approximately 25% of all reported cases are asymptomatic [4,5]. The typical presentations from chest X-rays are well-circumscribed masses extending to one or both lungs. Importantly, seminomas are lobulated with homogeneous attenuation on chest CT. Seminomas are typically composed of uniform polygonal or round cells with distinct cell borders, granular or clear cytoplasm, and centrally located nuclei. The cells may occur in sheets or form small lobules separated by fibrous septa [4,5]. Because seminomas are radiosensitive, radiotherapy is used as the primary postoperative therapy. One of our patients had seminoma. He presented with chest pain and was diagnosed at complete surgical resection, then received postoperative radiotherapy. No evidence of recurrence was noted during 8 years of follow-up.

Primary malignant non-seminomatous germ cell tumors (MNSGCTs) are extremely rare. For example, primary mediastinal yolk sac tumors have been reported in only 104 cases in the English literature until 1994. The most common age of patients with MNSGCTs is from the 20s to 40s. Males predominate, and almost all MNSGCTs are located in the anterior mediastinum [1,2,7–9]. MNSGCTs are uniquely associated with hematologic malignancies, and approximately 20% of patients have Klinefelter's syndrome [10]. The most common symptoms of MNSGCT include chest pain, cough, dyspnea, weight loss, fever, and superior vena cava (SVC) syndrome. Some cases are asymptomatic and are encountered on routine chest X-ray. We had two patients with primary yolk sac tumors, and they both presented with chest pain, weight loss, and cough. One patient also showed signs of SVC syndrome.

Chest X-rays of MNSGCTs often show a large smooth contour or lobulated anterior mediastinal masses, with or without local lung invasion. An inhomogeneous soft-tissue attenuation is frequently noted on chest CT. Contrast-

enhanced chest CT shows enhanced margins and central attenuation or diffusely inhomogeneous enhancement [5,6]. In yolk sac tumors, the most pathologic presentations are reticular patterns. A lacelike appearance, Schiller-Duval bodies, and intra- and extracytoplasmic hyaline globules are the characteristics of the reticular pattern [5,7]. Both our mediastinal yolk sac tumors showed the typical histologic pattern in surgical specimens. Serologic investigations of yolk sac tumor are elevated AFP (often > 20 ng/mL), possibly combined with carcinoembryonic antigen or lactate dehydrogenase elevation. The most reliable immunohistochemical marker of yolk sac tumors is AFP staining, which is often positive to a variable degree. On the other hand, serum β -human chorionic gonadotropin is elevated and stains in choriocarcinoma [1,2,7,8]. Under assisted and immunohistochemical analysis, FNAB for diagnosis of MNSGCT is established with a high degree of accuracy in the literature. Unfortunately, inappropriate sampling and negative results on immunohistochemical staining will lead to misdiagnosis [12]. Both our cases of mediastinal yolk sac tumors were misdiagnosed as undifferentiated adenocarcinomas according solely to CT-guided FNAB at local hospitals. We did not have any primary mediastinal choriocarcinomas or embryonal carcinomas in the 10-year period at Chung-Ho Memorial Hospital.

Cisplatin-based chemotherapy has become the standard therapy for mediastinal MNSGCT. Overall, complete remission rates of 50–70% are obtained in most case series, and 5-year survival is approximately 45% [10]. Combined platinum-based chemotherapy followed by surgical resection for primary germ cell tumors is the best approach for improving results. Radiotherapy produces modest benefits for these MNSGCTs [4,10,11]. Currently, patients receiving platinum-based chemotherapy are still alive 10 months after diagnosis.

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原發之縱膈腔生殖母細胞瘤 — 一所醫學中心之十年經驗

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生殖母細胞瘤 (germ cell tumors) 絕大部份原發於生殖腺，少數會有原發於生殖腺外，其中以縱膈腔內為常見，大多是在前縱膈腔。發生年齡層以年輕人居多。生殖母細胞瘤包括最常見的畸胎瘤 (teratoma) 及惡性非畸胎瘤 (non-teratomatous tumors) — 包含了精母細胞瘤 (seminoma) 及惡性非精母細胞瘤 (non-seminomatous tumors)，後者又包含了卵黃囊瘤 (yolk sac tumor)、絨毛膜瘤 (choriocarcinoma)、胎芽性癌 (embryonic carcinoma) 及混合型 (mixed type)。只有極少數原發性惡性縱膈腔非精母細胞瘤被報告過。本文回顧十年來高雄醫學大學附設醫院所有原發於縱膈腔之生殖母細胞瘤—共有畸胎瘤十一例，精母細胞瘤一例，卵黃囊瘤兩例，討論其臨床表徵、細胞型態、治療方式及預後。

關鍵詞：生殖母細胞瘤，縱膈腔塊
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