


ORIGINAL ARTICLE

Primary mediastinal germ cell tumors - A retrospective analysis of >30 years of experience in a single institution

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Abstract

Background: This study was performed to clarify the treatment outcome of patients with primary mediastinal germ cell tumors (PMGCTs), focusing on the clinical manifestations and management during definitive therapy and long-term follow-up.

Methods: In this study, we retrospectively reviewed the medical records of patients with PMGCTs treated at Shinshu University School of Medicine, and examined the clinical profiles and treatment outcomes of 22 patients (mean age of 29 years) with primary mediastinal GCTs treated at our hospital between 1983 and 2019.

Results: Five patients were diagnosed with pure seminoma and 17 had non-seminomatous GCT. A total of 21 patients were treated with cisplatin-based chemotherapy and 15 patients (68.2%) underwent thoracic surgery after chemotherapy. Although all cases of nonseminomatous GCT were negative for tumor markers after cisplatin-based chemotherapy, two cases showed variable GCT cells and two had somatic components (angiosarcoma and rhabdomyosarcoma) in resected specimens. Three relapsed soon after surgery. Growing teratoma syndrome developed during chemotherapy in four cases. Urgent thoracic surgery was performed in three patients, but one case was inoperable. The calculated 10-year overall survival rates were 100% in mediastinal seminoma and 64.7% in NSGCT. During follow-up, second non-GCT malignancies developed in three patients (colon cancer, 190 months; thyroid cancer, 260 months; non-small cell lung cancer, 250 months after the initial chemotherapy) and one patient with primary mediastinal seminoma was associated with multiple type I endocrine tumors.

Conclusions: Our experiences demonstrated that long-term survival and/or cure can be achieved with adequate chemotherapy followed by local surgical treatment even in patients with mediastinal GCTs. However, the clinical manifestations and biological behaviors during and/or after chemotherapy were complex and varied. In addition, the development of secondary malignancies should be taken into consideration for long-term follow-up. Clinicians should be aware of the various clinical features and secondary malignancies in primary mediastinal GCTs.

KEYWORDS

chemotherapy, germ cell, growing teratoma syndrome, mediastinal tumor, second malignancy

INTRODUCTION

Germ cell tumors (GCTs) are the most common cancers in young males and most GCTs originate in the testes. However, GCTs occasionally present in extragonadal sites, such as the mediastinum or retroperitoneum. Mediastinal GCTs represent nearly 2%–4% of all GCTs^{1–3} and account for 1%–4% of mediastinal tumors.^{3, 4} GCT is subdivided into seminoma and nonseminomatous GCT (NSGCT) and the prognostic factors have been identified by the International Germ Cell Cancer Collaborative Group (IGCCCG) classification.⁵ The outcome of GCT has improved markedly since the introduction of cisplatin-based chemotherapy,⁵ but the prognosis of NSGCT is generally poorer than that of seminoma.^{2,5–8} In addition, primary mediastinal GCT is histologically identical to gonadal GCT and both are also treated with cisplatin-based chemotherapy. However, the biology and prognosis of primary mediastinal GCT and gonadal GCT are substantially different. The five-year overall survival rate for patients with primary mediastinal GCT is generally worse than that of gonadal GCT.^{2,6–11} In particular, the treatment outcome in mediastinal NSGCT is poor and the five-year overall survival rate has been reported to be 27.3%–51%.^{2,6–13} Thus, primary mediastinal NSGCT has been classified as poor prognosis in the IGCCCG criteria and the treatment and management of this disease are still challenging for multidisciplinary teams.

In this study, we retrospectively reviewed our medical records of patients with primary mediastinal GCTs treated at Shinshu University School of Medicine. This study was performed to clarify the treatment outcomes of the disease, focusing on the clinical manifestations and management during definitive therapy and long-term follow-up.

METHODS

The medical records of 22 consecutive patients with primary mediastinal GCT diagnosed and initially treated at our institute between 1983 and 2019 were reviewed. The major inclusion criteria were histologically confirmed GCT, adequate medical records, and a primary mediastinal mass without evidence of testicular or ovarian abnormalities on physical and ultrasonographic (US) examinations. Data on clinicopathological characteristics and treatment outcomes were analyzed. Serum tumor markers, especially alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG), were measured in all patients. Patients were categorized into pure seminoma and NSGCT based on the IGCCCG classification.

All patients were treated with cisplatin-based chemotherapy, i.e., VAB-6 (cyclophosphamide, vinblastine, actinomycin D, bleomycin, and cisplatin),¹⁴ PE (cisplatin and etoposide), or BEP (cisplatin, etoposide and bleomycin). The chemotherapy regimen was sequentially used throughout the study period according to the standard or recommended therapy for testicular GCT. These regimens were repeated every 3–4 weeks. As salvage chemotherapy, GEMOX (gemcitabine and oxaliplatin) or TIN (paclitaxel,

ifosfamide, and nedaplatin) were used. Partial response was defined as >50% reduction in bidimensional tumor measurements. In this study, “growing teratoma syndrome (GTS)”^{15–18} was defined as tumor growth during chemotherapy despite decreases in serum tumor marker levels.

Management of residual masses following planned chemotherapy was performed by the treating physician’s team, including thoracic surgeons. In NSGCT, surgical removal of residual mass was essentially planned if surgical operability was possible. In seminoma, treatment policies, including surveillance or salvage surgery, were considered. Thoracic surgery was performed approximately 4–5 weeks from the date of last chemotherapy. Operative reports were also reviewed and complete resection was defined as no macroscopic or microscopic residual tumor. Post-chemotherapy resected specimens were evaluated according to the histological types of viable cells, and only necrosis without any viable cells was regarded as no viable cells (none).

The overall survival time was measured from the first day of chemotherapy to the date of death or last follow-up. The survival curves were calculated using the Kaplan–Meier method. This retrospective study was approved by the institutional review board of Shinshu University School of Medicine (approval number # 4840).

RESULTS

Patient characteristics

The characteristics of the 22 patients included in the study are listed in Table 1. The study population consisted of 21 men and one woman with a median age of 29.3 years (range: 17–55 years) at the time of diagnosis. A total of 17 patients (77.5%) had a diagnosis of NSGCT and five patients (22.5%) had pure seminoma. Most cases presented symptoms related to the large mass in the mediastinum, including cough (32%), dyspnea (23%), chest pain (23%), fever (23%), and facial edema (14%) due to superior vena cava (SVC) syndrome, etc. Three patients in the NSGCT group (Cases 2, 4, 12) and one patient (Case 20) in the seminoma group were asymptomatic and were detected by chest radiographic screening. In NSGCT group, 14 patients had mediastinum-localized disease at presentation, and three patients had extra-mediastinal involvement; the metastatic sites in these cases at initial presentation were the liver (Case 9), bone (Case 13), and lung (Case 17). The pathological diagnosis in most cases was made by percutaneous computed tomography (CT) or US-guided needle biopsy, but Case 9 was diagnosed by liver biopsy.

Initial treatments and related complications

NSGCT

Among NSGCT patients, one patient (Case 4) initially underwent surgical resection, because the tumor showed

TABLE 1 Patient characteristics

Nonseminomatous germ cell tumor in the mediastinum											
Cases	Age	Sex	Initial symptoms	Diagnosis	Chemotherapy	Total cycles	Operations	Histology of viable tumor in the resected mass	Additional therapy or salvage chemotherapy	Survival time (months)	Others
1	25	M	Cough, dyspnea	US guided biopsy	VAB-6	3	(+)	Yolk sac	PE	13 (died)	
2	22	M	Chest X-ray survey	US guided biopsy	VAB-6 x1, PE x 3	4	(+)	Yolk sac	PE	19.5 (died)	
3	20	M	Chest pain	None	VAB-6	3	(+)	None		384	
4	22	M	Chest X-ray survey	CT guided biopsy	None	0	(+)	Teratoma	VAB-6 2 courses after operation	395	Spontaneous regression before operation
5	34	M	Cough	US guided biopsy	PE	3	(+)	None		350	Second malignancy (colon cancer)
6	22	F	Cough	CT guided biopsy	PE	4	(+)	Teratoma		240	GTS, Secondary malignancies (thyroid cancer)
7	23	M	Dyspnea, facial edema	CT guided biopsy	PE	4	(+)	Yolk sac		120	
8	19	M	Chest pain	CT guided biopsy	BEP	4	(+)	None		120	
9	31	M	Fever, general fatigue, abdominal pain	CT guided biopsy (liver)	BEP	8	(+)	Sarcoma		185	Somatic tumor (Rhabdomyosarcoma)
10	17	M	Fever, chest pain	CT guided biopsy	BEP	4	(+)	Teratoma		137.5	
11	43	M	Neck tumor, dyspnea	Transcutaneous biopsy (neck mass)	BEP	4	(+)	None	RT for primary tumor (20Gy)	142	GTS
12	55	M	Chest X-ray survey	CT guided biopsy	BEP	2	(-)		TIF, GEMOX	29 (Daed)	
13	49	M	Cough	CT guided biopsy	BEP	4	(-)			96	
14	19	M	Cough, fever	CT guided biopsy	BEP	5	(-)		GEMOX, TIF	13 (Daed)	
15	23	M	Cough chest pain Facial edema	CT guided biopsy	BEP	3	(+)	Teratoma		23.5	
16	26	M	Fever	CT guided biopsy	BEP	3	(+)	None	Paclitaxel	16 (Dead)	GTS, Somatic tumor (angiosarcoma)
17	21	M	Dyspnea chest pain	US guided biopsy	BEP	4	(-)			15 (Dead)	GTS
18	34	M	Chest pain, facial edema	CT guided biopsy	PE	2	(-)	RT for primary tumor (60Gy) after chemotherapy	280 (Daed)	Second malignancy (non-small cell lung cancer)	

(Continues)

TABLE 1 (Continued)
Nonseminomatous germ cell tumor in the mediastinum

Cases	Age	Sex	Initial symptoms	Diagnosis	Chemotherapy	Total cycles	Operations	Histology of viable tumor in the resected mass	Additional therapy or salvage chemotherapy	Survival time (months)	Others
19	26	M	Cough, fever	CT guided biopsy	PE	4	(+)	None		207	
20	20	M	Chest X-ray survey	CT guided biopsy	BEP	4	(+)	None		122	
21	28	M	Dyspnea	CT guided biopsy	BEP	4	(-)			133	
22	46	M	Fever, hemothorax	US guided biopsy	BEP	3	(-)			168	MEN 1 type

Abbreviations: BEP, cisplatin, etoposide and bleomycin; CT, computed tomography; GEMOX, gemcitabine and oxaliplatin; GTS, growing teratoma syndrome; MEN 1 type, multihormonal tumor type 1; PE, cisplatin and etoposide; TIN, pachitaxel, ifosfamide, and nedaplatin; US, ultrasonographic; VAB-6, cyclophosphamide, vincristine, actinomycin D, bleomycin, and cisplatin.

spontaneous regression after a biopsy procedure, resulting in normalization of tumor markers. The pathological findings from the resected specimen showed NSGCT (teratoma). The other patients were initially treated with cisplatin-based chemotherapy according to the regimens shown in Table 1: VAB-6 in 1983–1988 (3 cases), PE in 1988–2002 (3 cases), and BEP after 2002 (10 cases). Partial response to chemotherapy was observed in 12 cases (75%) after chemotherapy, but four cases showed enlargement of the tumor on radiographic examination despite normalization of the tumor markers, suggesting GTS. For the cases of GTS, urgent surgical intervention was performed in three cases. Enlarged mediastinal masses were successfully removed in Cases 6 and 11, but removal was incomplete in Case 16. The histological specimens in Case 16 revealed massive necrosis without any viable cells. However, the residual mass continued to grow and subsequent surgical resection was achieved. The final pathological findings revealed angiosarcoma. In the remaining case of GTS (Case 17), a gradually enlarging and huge mass caused cardiopulmonary compression.

Residual tumor resection was performed in 13 cases (76.5%). Among them, incomplete resection was performed in one case (Case 16), but complete resection was performed in the others, including lobectomy or pulmonary wedge resection, pericardium, SVC, or innominate vein and phrenic nerve resection were performed. Surgery was not performed in four cases. Two of these patients (Cases 12 and 14) showed partial response and tumor markers were also normalized after chemotherapy, but the residual tumor rapidly presented regrowth with rising tumor marker levels before scheduled surgery. The other two patients (Cases 13 and 17), who were inoperable, initially had metastatic lesions and/or presented with GTS. Case 9 had hepatic metastasis and a diagnosis of NSGCT was made by liver biopsy. After eight cycles of BEP chemotherapy, the hepatic lesion had almost disappeared, but the mediastinal mass showed only slight reduction in size. Thoracic resection was performed and the resected specimen revealed a somatic component (rhabdomyosarcoma).

The values of AFP and HCG before and after chemotherapy in patients with NSGCT are summarized in Table 2. Measurements of AFP and HCG after cisplatin-based chemotherapy were made preoperatively or approximately four weeks after the date of the last chemotherapy. In patients with NSGCT, tumor markers on admission were markedly increased (Table 2), with the median AFP level (8934.9 ng/ml; range, 1.7–60 500) and with the median serum HCG level (630.0 mIU/ml; range, <1.0–2300). After cisplatin-based chemotherapy, these increased tumor marker levels decreased markedly and most cases showed normal levels.

Seminoma

There were five male cases of seminoma and both AFP and HCG levels were normal (data not shown) in the present

study population. Case 18 received two cycles of PE chemotherapy followed by a total of 60 Gy of thoracic radiotherapy. The other four cases were treated with three or four cycles of BEP chemotherapy. Two patients underwent surgical resection for residual disease. Case 22 with mediastinal seminoma developed multiple endocrine neoplastic type 1 (MEN1) due to the subsequent development of hypercalcemia and his family history. Following parathyroidectomy, resection of the pancreatic neuroendocrine tumor was performed. However, the patient was treated with chemotherapy for the relapsed pancreatic neuroendocrine tumor.

Clinical outcomes and prognosis

The mean follow-up period in all cases was 142 months (range, 13–395 months). Survival rates are shown in FIGURE 1. The calculated 10-year overall survival rates were 100% in patients with mediastinal seminoma and 64.7% in patients with NSGCT.

Six patients with NSGCT in our case series died. Two patients (Cases 1 and 2) with viable tumor cells in the resected specimens despite normalization of serum tumor markers relapsed soon after thoracic surgery. Several salvage chemotherapies failed to prolong survival in both patients. The poor response to salvage chemotherapy were similar in Cases 12 and 14 who were refractory to prior chemotherapy before thoracic surgery. The remaining two patients who died showed somatic components in resected specimens (Case 16) and presented with GTS (Case 17), respectively.

Secondary malignancy developed in three patients (two in the NSGCT group and one in the seminoma group) over the follow-up period in the present study. In two patients with NSGCT, colon (Case 5) and thyroid (Case 6) cancer were detected at 190 and 260 months after the initial chemotherapy, respectively. Both cases underwent radical resection and there have been no recurrences since. In the mediastinal seminoma group, Case 18 developed advanced non-small cell lung cancer at 250 months after initial therapy and died of the disease at 280 months. During our observation period, there were no hematological disorders in our series. In addition, the subsequent development of testicular cancer (referred to as metachronous testicular cancer) was not observed in our case series.

DISCUSSION

This report summarized our experience with treatment of primary mediastinal GCTs in our institute. As shown in previous clinical studies,^{2,5–13} whereas patients with mediastinal seminoma showed a good response to chemotherapy and favorable prognosis, patients with NSGCT showed a biphasic survival pattern; patients with NSGCT underwent successful thoracic surgery after cisplatin-based chemotherapy and showed a plateau in the survival curve, suggesting a cure from their disease.

In the present study, three (17.6%) patients with mediastinal NSGCT had metastatic disease, which was lower than the rates in studies performed in other institutions.^{8–13} Our 10-year survival rate was 64.7%, which was higher than in other reports,^{2,5–13} and may have been due to the smaller population of subjects initially presenting metastatic disease in our study. However, Bokemeyer et al.² reported that the rates of tumor marker normalization with PR plus complete response to chemotherapy were 64% and that 49% of patients with mediastinal NSGCT underwent secondary surgery of residual tumor masses after chemotherapy. Sakurai et al.⁸ reported that 38.5% of patients with mediastinal GCT underwent surgery after chemotherapy. In our study, tumor markers were normalized after planned chemotherapy in most cases and that 13 patients with NSGCT (76%) received subsequent thoracic surgery. Thus, the superior survival in the present study also may have been due to the higher rate of surgical treatment and normalization of tumor markers after chemotherapy. Therefore, the survival outcome in patients with mediastinal NSGCT is dependent on both chemotherapy and surgical skill. We would like to emphasize the significance of adequate chemotherapy leading to no variable tumor and/or negative tumor markers. In addition, close cooperation with thoracic surgeons and the appropriate timing of the surgery are essential for the therapeutic strategy in patients with primary mediastinal NSGCT.

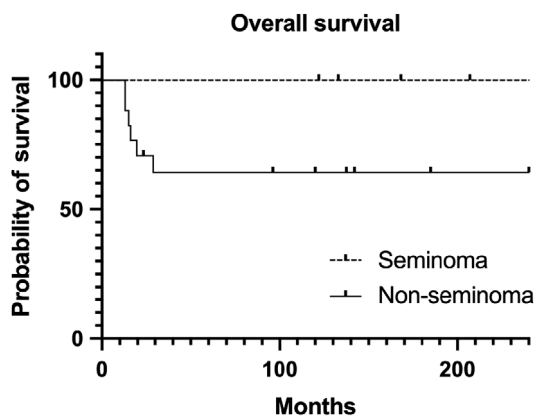
GTS is a rare but well-known phenomenon in patients with GCT.^{15–18} We encountered four cases of GTS in the present study. Based on the previous case series and case reports of mediastinal GTS, the development of GTS generally occurred during chemotherapy in mediastinal NSGCT and required emergency surgical resection or transbronchial stent implantation to preserve airway patency.^{15–18} In addition, the surgically resected mass did not always demonstrate only mature teratoma.^{17, 19} The pathology revealed only massive necrosis or mixed with nongerm cell cancer, such as sarcoma, in previous reports.^{15, 17} Furthermore, the sarcoma component coexisted or may have developed after a short latent interval from the initial development of mediastinal GCT.¹⁹ Kesler et al.¹³ described five cases of primary mediastinal GTS requiring urgent surgery because of cardiopulmonary deterioration. They reported that the frequency was 2.6% among mediastinal GCT treated in their institute.¹³ There was one case of surgery-related death and two patients had short survival periods of 1.7 and 2.2 years, respectively. The surgical pathology in these cases was mixed with angiosarcoma and pure mature teratoma, respectively. The clinical and pathological findings in our cases were also consistent with those in previous case series. Thus, mediastinal GTS is pathologically complex, and consists not only of mature teratoma. The optimal timing of the surgical approach for GTS is still challenging. However, we should recognize the presence of GTS during chemotherapy and should carefully monitor the radiographic and serological responses to chemotherapy in patients with NSGCT.

We presented long-term follow up data in our case series. It is noteworthy that three patients developed second

TABLE 2 Serum tumor markers at initial diagnosis and after chemotherapy (just before thoracic surgery)

Case	On admission		After chemotherapy	
	AFP (ng/ml)	HCG (mIU/ml)	AFP (ng/ml)	HCG (mIU/ml)
1	4318	<1.0	17.2	<1.0
2	8454	<1.0	6.2	<1.0
3	948	6	11.9	<1.0
4	<5.0	20	<5.0	<1.0
5	207.8	4	<5.0	<1.0
6	5120	NE	10	NE
7	5780	NE	24.7	NE
8	22074	<1.0	18.6	<1.0
9	20.7	2300	<1.0	<5.0
10	2355	4.9	7	<1.0
11	2749	NE	1	NE
12	60500	<1.0	5.6	<1.0
13	1.7	1804.8	NE	<0.5
14	4876.2	<0.5	7.3	<0.5
15	170.6	283.5	1.8	<0.5
16	711.8	2	1.1	<0.1
17	11586.9	10.64	6.9	<0.5
Mean	8934.9	630.0		

Abbreviations: AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin.

**FIGURE 1** Overall survival curve in the present study by Kaplan-Meier method

non-GCT malignancies. Two patients in the mediastinal NSGCT group underwent radical surgery for papillary thyroid cancer and colon cancer, respectively. However, one patient in the mediastinal seminoma group developed advanced non-small cell lung cancer 250 months after initial chemotherapy and died of the disease at 280 months. Although the patient had a history of smoking (30 pack years), chemotherapy and thoracic radiotherapy (60 Gy) were performed. Several studies indicated that patients with GCT have an increased risk of developing a second malignancy after treatment.^{20–22} The relative risk was significantly

related to the application of radiotherapy. For example, Kier et al.²⁰ reported increased risk of secondary malignancies in patients with GCT treated with BEP (hazard ratio [HR], 1.7), radiation (HR, 1.8) and more than one line of treatment (MTOL) (HR, 3.7). In addition, excess mortality due to secondary malignancies increased by 1.3 times after BEP, 2.1 times after radiation, and 5.8 times after MTOL. To our knowledge, no specific relative risk data are available in patients with mediastinal GCT. However, the increased risk of secondary lung cancer after chemotherapy and radiotherapy for mediastinal non-Hodgkin lymphoma has been reported.²³ Therefore, care is required regarding the development of secondary malignancies in patients with mediastinal GCT, and periodic check-up to detect malignancy should be started earlier in such patients.

In summary, patients with primary mediastinal GCT could exhibit a variety of clinical features, including GTS during chemotherapy, the coexistence and/or development of somatic malignancy during and/or after chemotherapy. In addition, secondary malignancies should be considered after definitive therapy. Although long-term survival can be achieved by adequate chemotherapy with and without local surgical treatment, the biological characteristics and clinical behaviors in patients with primary mediastinal germ cell tumors should be recognized.

CONFLICT OF INTEREST

The authors confirm that there are conflicts of interest.

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