Survival Outcomes of Patients With Primary Mediastinal Germ Cell Tumors: A Retrospective Single-institutional Experience

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Abstract. *Background/Aim: Primary mediastinal non-seminomatous germ cell tumors (PMNSGCTs) are occasionally complicated by a hematologic malignancy, as with somatic-type malignant tumors called germ cell tumors with somatic-type malignancy (GCTSTM) and are known to have a poor prognosis. Patients and Methods: Data obtained between September 1997 and February 2020 for patients with mediastinal germ cell tumor at our institution were retrospectively analyzed. Key outcome measures included survival rates and the clinical features of non-seminoma cases. Results: Of 16 patients, 9 had pure seminoma, and 7 had non-seminoma. At the median follow-up of 56.2 months, the 5-year survival rate was significantly higher in patients with seminoma (100%) than in those with non-seminoma (37%) (log-rank test, p=0.0153). Regarding PMNSGCT, two patients evolved into GCTSTM and three had concomitant hematological malignancies. Conclusion: Patients with PMNSGCTs, GCTSTM complications, and hematologic malignancies showed poor survival, suggesting the need for the development of treatment strategies.*

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Germ cell tumors (GCTs) make up 2% of human malignancies and are the most common malignancies in males aged 15-35 years. About 2%-5% of GCTs occur outside the gonads, usually in the midline of the body. Conventionally, 54% of extragonadal germ cell tumors are considered to occur in the mediastinum and 45% in the retroperitoneum (1). However, a recent study has shown that most purely retroperitoneal GCTs in adults represent metastases from an undiscovered or occult primary in the testicle (2). Primary mediastinal GCTs (PMGCTs) are rare, accounting for approximately 1%-3% of all germ cell tumors and represent 15% of all anterior mediastinal tumors in adults and 24% in children. The majority of malignant mediastinal GCTs occurs in male adolescent and middle-aged adult patients (3); 30%-40% of PMGCTs are seminoma, and 60%-70% are non-seminoma (4, 5). Patients with mediastinal seminoma are known to have a prognosis similar to those with metastatic testicular seminoma (6). In contrast, the clinical features of primary mediastinal non-seminomatous germ cell tumors (PMNSGCTs) differ from those of testicular non-seminomatous germ cell tumors (7, 8), and PMNSGCT has a poorer prognosis than primary non-seminomatous germ cell tumors at other sites (9).

Currently there is no specific therapeutic strategy for PMGCT. PMGCT cases are classified by prognostic category using the International Germ Cell Consensus Classification (IGCCC) and treated with cisplatin-based combination chemotherapy, similar to primary testicular GCTs. After chemotherapy and following confirmation of laboratory values negative for tumor markers, resection of the primary tumor is considered (10-13).

On the other hand, GCT with somatic-type malignancy (GCTSTM) is a very rare disease, with a 2% incidence of all GCTs in males. Primary GCTSTM, most likely to occur in the mediastinum, accounts for 25%-30% of cases. Almost all patients with GCTSTM are male, and the highest incidence is seen between the ages of 20 and 40 years. The prognosis for GCTSTM is very poor, with a median survival of 9 months (14). Studies have shown a malignant tumor with a sarcoma component, usually rhabdomyosarcoma, followed by angiosarcoma, leiomyosarcoma, liposarcoma, and undifferentiated sarcoma (15). Early detection is difficult, and almost all GCTSTM diagnoses are based on histopathology from the site of recurrent tumors resected after some type of chemotherapy, such as for the treatment of lung metastases (16). Because patients with GCTSTM are poorly responsive to cisplatin-based chemotherapy, physicians should consider somatic component-driven therapies (17).

Hematologic disorders are rarely associated with PMNSGCT but have been reported continuously since 1985 (18). The treatment-related acute leukemia that develops after chemotherapy for GCTs takes several years to develop, whereas acute leukemia associated with GCTs is present from the time of onset of PMNSGCT, and an association between isochromosome 12p in leukemic blasts and cytogenetic abnormalities in PMNSGCT has recently been demonstrated (19, 20).

Although there is only a small likelihood of these PMGCT comorbidities occurring, some strategic measures should be considered. In this article, in order to provide information about PMGCT and devise a treatment strategy for PMGCT, we report our institution's experience of patients who underwent chemotherapy or chemotherapy plus surgery for PMGCT.

Patients and Methods

A series of 16 patients with PMGCT treated at the Kanazawa University Hospital between September 1997 and February 2020 were retrospectively reviewed. The PMGCT diagnosis was made on the basis of germ cell tumors arising in the mediastinum, without demonstrable testicular or other abnormalities, as determined by physical examination, testicular ultrasonography, and computed tomography. Patients were divided into groups by prognostic category, according to the IGCCC, on the basis of histology, location of metastasis, and concentrations of serum tumor markers AFP, human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) at the time of diagnosis (21). Tumor response was classified as follows: complete remission (CR), defined as the complete disappearance of all clinical target lesions with normalization of tumor markers; pCR, defined as the absence of tumor lesions by histology; and surgical CR (sCR), defined as the existence of tumor lesion with viable cells by histology despite complete excision. A partial response (PR) was defined as a decrease of ≥30% in the sum of the products of the perpendicular diameters of measurable tumor lesions without the appearance of new lesions. In addition, serum tumor marker positivity and negativity were denoted as PRm+ or

Table I. *Clinical characteristics of the study population (n=16).*

Characteristics	Seminoma (n=9)	Non-seminoma (n=7)
Age, years		
Median (range)	27 (18-50)	21 (19-31)
Follow-up, months		
Median (range)	53.5 (12-149)	60.9 (6-200)
Tumor marker at initial treatment		
AFP, ng/ml		
Median (range)	4.0 (<1.0-<10)	1254 (269.6-188,530)
HCG, IU/l		
Median (range)	39.6 (<1.0-54.1)	169 (7.4-1,720)
LDH, IU/l		
Median (range)	269 (129-329)	308 (174-750)
IGCCC prognosis		
Good/intermediate	8/1	0/0
Poor	0	7
Type of treatment		
Chemotherapy only	6	2
Chemotherapy + surgery	3	5
Prior to chemotherapy	1	0
Post-chemotherapy	2	5

AFP: Alpha-fetoprotein; HCG: human chorionic gonadotropin; IGCCC: International Germ Cell Consensus Classification; LDH: lactate dehydrogenase.

PRm-, respectively. Progressive disease (PD) was defined as either an increase in tumor size of ≥25% or occurrence of new lesions. In this study, overall survival (OS) was defined as the time from initial diagnosis of PMGCT to death from any cause.

GraphPad Prism version 8.0.0 for Windows, (GraphPad Software Inc., San Diego, CA, USA) was used for data analysis and graphical illustration. Kaplan–Meier curves were used to compare survival times. Between-group differences in survival were assessed using the log-rank test. Differences with a p value less than 0.05 were considered statistically significant.

Results

Analysis of overall survival. Table I summarizes the characteristics of patients. Sixteen patients, including nine patients with pure seminomatous PMGCT and seven patients with PMNSGCT, were identified from our records. Alpha-fetoprotein (AFP) levels at initial treatment were within the normal range in all patients with seminomatous PMGCT. According to the IGCCC, nine patients belonged to the good or intermediate prognosis group and seven to the poor prognosis group. Because all patients in the poor prognosis group had non-seminomatous histologic types, a survival curve was analyzed only for differences in histologic types. All patients received three to four courses of standard bleomycin, etoposide, cisplatin (BEP) regimen as induction chemotherapy. The median follow-up duration was 57.2

months (range=6-94 months). The 5-year OS rates were 100% for patients with seminomatous and 37% for non-seminomatous, PMGCT (*p*=0.0153) (Figure 1).

Clinical courses of non-seminoma patients. Table II summarizes the clinical features and treatment outcomes of the seven patients with non-seminoma. Of the seven non-seminoma cases, we experienced two cases of GCTSTM, one case of histiocytic sarcoma, and two cases of acute megakaryoblastic leukemia (M7 leukemia) following chemotherapy for GCT. Both cases of GCTSTM were sarcoma proven by biopsy of the metastatic site after treatment for GCT.

GCTSTM. The patient in Case 1 who underwent resection of a mediastinal tumor following salvage chemotherapy showed viable cells. Despite tumor marker values within the normal range, multiple lung metastases appeared. A resection biopsy of lung metastases revealed germ cell with sarcoma components; the multiple lung metastases showed a good response to pazopanib (22).

In Case 5, the patient was administered induction chemotherapy. Because normalization of tumor markers was achieved, resection of PMGCT was performed. Although AFP concentration normalized postoperatively, there was tumor recurrence. Resection of recurrent tumor showed spindle and pleomorphic cell sarcoma. Because re-recurrent tumor in the right side of the mediastinum was not indicated for operation, doxorubicin was administered for eight cycles; however, radiologic evaluation showed regrowth of re-recurrent tumor. Next-generation sequencing showed the presence of the mutations TP53 R282W, SMO K575M, CDK4 (amplification) and loss of CDKN2A and CDKN2AB. Because the Japanese Ministry of Health, Labor and Welfare has not approved a CDK4/6 inhibitor for this condition under medical insurance, the patient was given pazopanib, which may be effective for sarcoma, as a next treatment, and he is currently alive with disease.

Histiocytic sarcoma. Case 6 was that of a patient with PMGCT with marked thrombocytopenia from the first visit. Although no definitive diagnosis was made by tumor biopsy, AFP was high, and induction chemotherapy was administered as for germ cell tumor. Induction and salvage chemotherapy normalized the patient's AFP level, and the tumor decreased in size once but showed regrowth. Respiratory surgeons considered tumor resection but had to abandon surgery because of the patient's persistent thrombocytopenia. Hepatic and splenic metastases then appeared and the patient died; on autopsy, the patient was diagnosed with histiocytic sarcoma (23).

Acute megakaryocytic leukemia (M7 leukemia). The patient in Case 3 had PMGCT with an abnormally high AFP value, and tumor biopsy was suspicious for teratocarcinoma. AFP
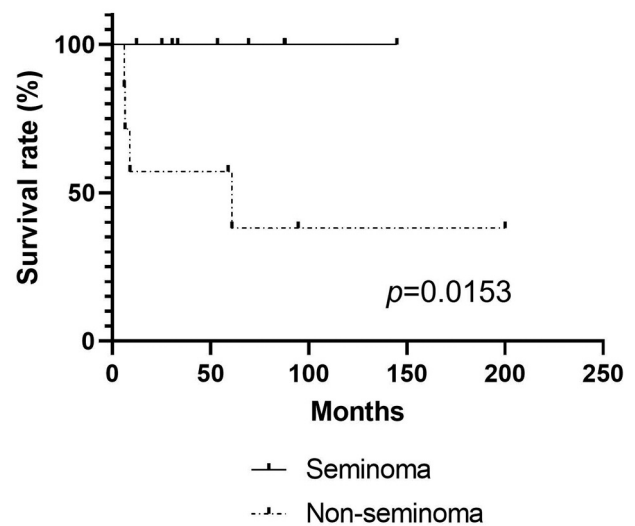

Figure 1. *Overall survival of patients with primary mediastinal germ cell tumor according to histological types.*

normalized after four courses of induction chemotherapy, and because radiologic evaluation showed stable disease, resection of the primary tumor was performed. Histopathologic findings of the excised specimens were mainly immature teratoma, but many viable cells were also found. However, at this point, the tissue type of the viable cells could not be confirmed by immunohistochemical staining. Because it was considered to be a curative resection, the patient was followed up. However, 6 months after the operation, the patient experienced sudden low back pain and was admitted to another hospital. A scrutiny was also considered, but his general condition deteriorated rapidly and he died. On autopsy, a biopsy revealed that he had M7 leukemia (Figure 2A and B), and the primary lesion was reevaluated. Immunohistochemical staining revealed CD42b-positive atypical cells, which were strongly suspicious for the presence of leukemia cells showing differentiation into megakaryocytes (Figure 2C).

Case 7 was similar to Case 3. The patient in Case 7 was comprehensively diagnosed, including *via* tumor biopsy, with non-seminoma with an abnormal high AFP value. After four courses of induction chemotherapy, the patient's AFP normalized, and radiologic evaluation showed stable disease. The patient underwent radical resection of the tumor with lymph node dissection, and histopathologic findings revealed immature teratoma. The patient was discharged on the 10th postoperative day without problems. However, he came to the emergency department of our institution with low back pain 10 days after discharge. Blood tests showed marked pancytopenia and abnormally high LDH levels. Recurrence of the germ cell tumor was initially suspected, but immunohistochemical staining of the mediastinal tumor,

Table II. *Clinical features and treatment outcomes of seven non-seminomatous patients.*

Case no.	Age	Histology (biopsy)	Histology (resection/ autopsy)	Histology (excision biopsy of metastatic site)	CTx	AFP (ng/ml)	HCG (IU/l)	LDH (IU/l)	Course	Observation period (months)	Outcome
1	19	Y	IT	Undifferentiated sarcomatous components	BEP(4), VeIP(1), TIP(3), Paz	879	1720	750	PD	94	AD
2	20	IT+Y	IT+Y	ND	BEP(8), VIP(4), HDCT(2), TIP(2), CPT-11/N(3)	1254	N/A	<230	Elevation of HCG	61	Dead
3	18	Y+T with malignant	AML	ND	BEP(4)	3307	N/A	391	CR	6	Dead
4	31	Y	Viable cell(–)	ND	BEP(4), HDCT(2)	188530	N/A	<230	PRm-	200	NED
5	21	Y+ sarcomatous area	IT	Spindle and pleomorphic cell sarcoma	BEP(4), ADM(8), Paz	2928	169	202	PRm+	61	AD
6	25	Suggestive of T	HS	ND	BEP(3), TIP(1), VeIP(1)	269.6	N/A	174	PRm-	9	Dead
7	31	EC+T	AML	ND	BEP(4), IDR + Ara-C	1178	7.4	308	CR	6.5	Dead

AD: Alive with disease; ADM: doxorubicin; AFP: alpha fetoprotein; AML: acute megakaryocytic leukemia; BEP: bleomycin, etoposide, cisplatin; CPT-11/N: irinotecan, nedaplatin; CR: complete remission; CTx: chemotherapy; EC: embryonal carcinoma; HDCT: high-dose chemotherapy; HCG: human chorionic gonadotropin; HS: histiocytic sarcoma; IT: immature teratoma; LDH: lactate dehydrogenase; N/A: not available; ND: not done; NED: no evidence of disease; Paz: pazopanib; T: teratoma; TIP; paclitaxel, iphosphamide, cisplatin; VeIP: vinblastine, iphosphamide, cisplatin; VIP: etoposide, iphosphamide, cisplatin; Y: yolk sac tumor.

based on the experience in Case 3, revealed CD42b-positive cells (Figure 3A). Furthermore, a bone marrow biopsy was also positive for CD42b (Figure 3B), and the patient was diagnosed with M7 leukemia and transferred to the Department of Hematology at our institution. Induction chemotherapy with idarubicin and Ara-C was administered promptly, but the patient developed pneumonia and required intensive care. A bone marrow examination on day 29 revealed that the patient had not reached remission, and he continued to have severe, prolonged respiratory dysfunction. Therefore, it was decided to provide palliative care. His respiratory condition gradually deteriorated, and he died 1.5 months after being diagnosed with M7 leukemia.

Discussion

In the present study, the 5-year OS rate of patients with primary mediastinal seminomatous GCTs was 100%, which was an excellent result. In contrast, the 5-year OS rate of patients with PMNSGCT was only 37%. As for the primary mediastinal seminomatous GCT, our treatment outcome was comparable to those reported previously (3, 21, 24-27).

van Dijk *et al.* reviewed 10 articles describing cases since 1989 and performed a meta-analysis of 1,775 cases of non-seminomatous GCT. They found that the 5-year survival rates of the good, intermediate, and poor prognosis groups were 94%, 83%, and 71%, respectively, indicating that the prognosis of the poor prognosis group has been significantly improved by recent advances in chemotherapy (28). However, only risk-specific data are included in the IGCCC, which does not mention the primary site.

Related to this report, the 5-year survival rate of patients with IGCCC poor-risk testicular germ cell tumors in a relatively large cohort in Japan was 83% in the 2000s (29).

In a retrospective analysis of a cohort of extragonadal GCTs in Taiwan, the 2-year survival rate was 29.6% for mediastinum, 79.1% for central nervous system, and 33.3% for retroperitoneum (30). In other words, the outcomes of patients with mediastinal GCTs were reported to be worse than those with central nervous system or retroperitoneal GCTs. It has also been reported that 35% and 24.3% of patients with PMNSGCT were alive at 1 year and 2 years, respectively, in the low- to middle-income setting in India (31).

Finally, a review from the Indiana University, a large facility with extensive experience with GCTs, revealed that the OS rate for PMNSGCT was 40%-50% (32).

In the present study, the 5-year survival rate of patients with poor prognosis IGCCC (*i.e.*, PMNSGCT) was only 37%, which differs from the report by van Dijk *et al.* (28), suggesting the poor prognosis of PMNSGCT, as described previously.

Regarding these points, although GCTSTM has been reported to have a poor median survival time of 9 months
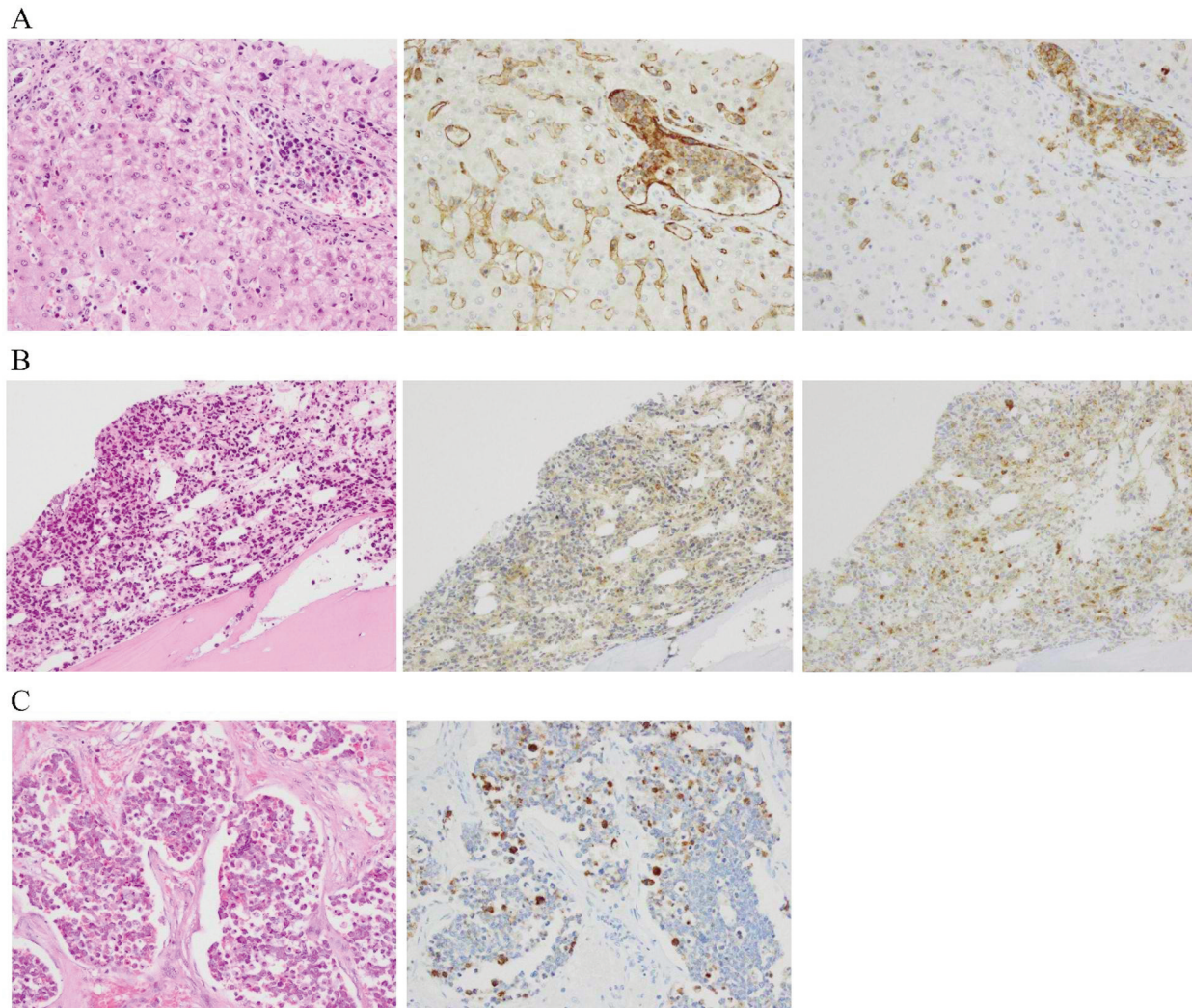
Figure 2. *Immunohistopathological images from specimens obtained by a corpse biopsy and radical resection of the primary tumor. (A) Microscopic findings of a corpse biopsy of the liver (HE: left, CD31: middle, CD42b: right). Immunohistopathological staining showed positivity for CD31 and CD42b, which strongly indicated acute megakaryocytic leukemia cells (magnification ×400). (B) Microscopic findings of a corpse biopsy of bone marrow (HE: left, CD31: middle, CD42b: right). Immunohistopathological staining also showed positivity for CD31 and CD42b (magnification ×200). (C) Immunohistopathological staining of primary mediastinal tumor following initial diagnosis (HE: left, CD42b: right). Immunohistopathological staining showed positivity for CD42b after all (magnification ×400).*

(14), long-term survival of 59 months and 94 months was achieved in the present study in both patients with sarcomatous components. One of the reasons for this long-term survival was that tissue-directed therapy became possible by performing more accurate histologic diagnosis by excision of the primary lesion and excisional biopsy of the metastatic lesion. However, in the patient diagnosed with histiocytic sarcoma, histologic diagnosis was hindered by persistent thrombocytopenia. In such cases, next-generation sequencing using liquid biopsy material might be useful (33).

It should be noted that in both cases in which the patient was diagnosed with M7 leukemia, the high AFP values normalized, and the patients achieved complete remission once due to resection of the primary lesion. Actually, in both M7 leukemia cases in the present study, the IGCCC corresponded to poor prognosis, and four courses of induction chemotherapy were performed. As a result, it was confirmed that the tumor marker had become negative, and the respiratory surgeons deemed the tumors resectable. Therefore, the tumors were removed, and there was no evidence of disease after the operation. Despite having no evidence of disease, the patient in Case 3 suffered from M7 leukemia and died of the disease 6 months after surgery. In Case 7, the patient was aware of symptoms 2 weeks after discharge
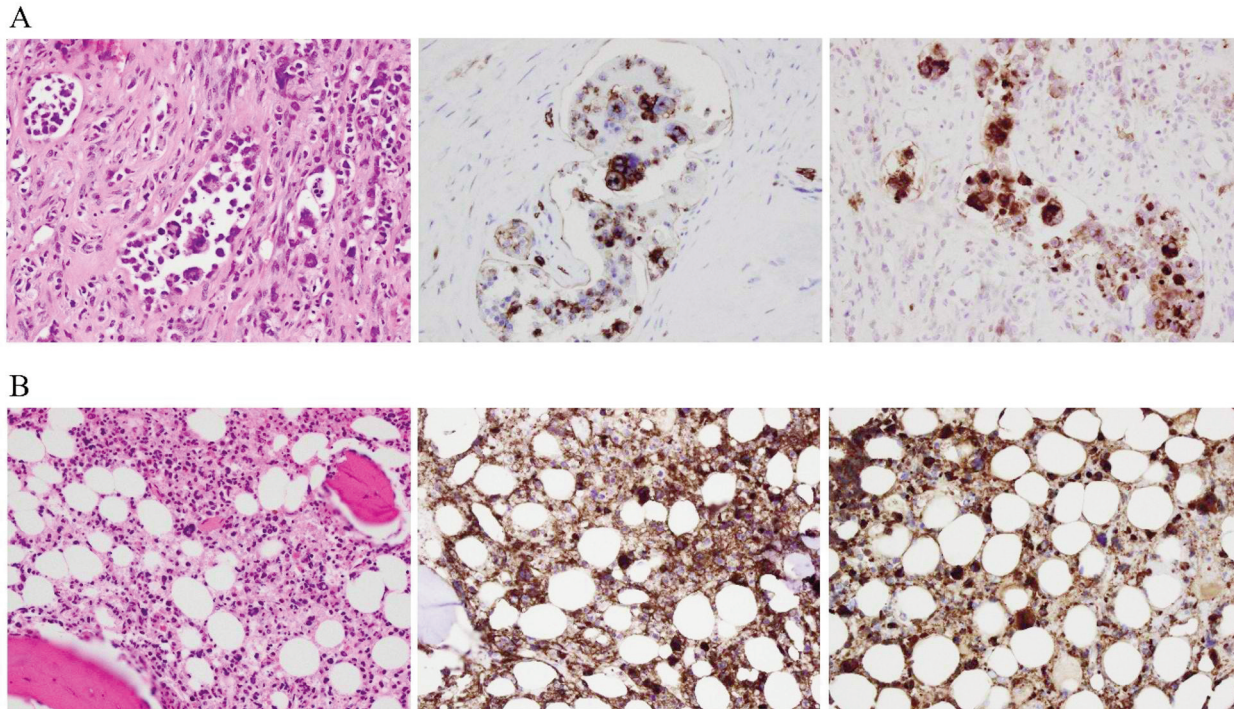
Figure 3. *Immunohistopathological images from specimens obtained by radical resection of the primary tumor and a bone marrow biopsy. (A) Microscopic findings of primary mediastinal tumor (HE: left, CD31: middle, CD42b: right). Immunohistopathological staining showed positivity for CD31 and CD42b, which strongly indicated acute megakaryocytic leukemia cells. (B) Microscopic findings of biopsy of bone marrow (HE: left, CD31: middle, CD42b: right). Immunohistopathological staining also showed positivity for CD31 and CD42b (magnification ×400).*

Table III. *The incident rates of hematologic malignancies accompanied with PMGCT.*

	PMNSGCT cases	Hematologic malignancies (%)	The median time from the diagnosis of the PMNSGCT to the diagnosis of the hematologic malignancies (months)
Hartmann *et al*. (19)	287	17 (5.9)	6
Sowithayasakul *et al*. (36)	8	5 (62.5)	<12
Our case series	7	2 (28.5)	6

(*i.e*., 1 month after surgery) and immediately underwent chemotherapy for M7 leukemia; however, he died of the disease 1.5 months after initiation of treatment. Therefore, two out of seven cases of PMNSGCT developed M7 leukemia and died early, which contributed to the decrease in the survival rate of PMNSGCT in the present study.

These results indicate that cisplatin-based chemotherapy may not be sufficient as induction chemotherapy for PMNSGCT with M7 leukemia, and that when we encounter patients with PMNSGCT, the decision on induction chemotherapy should be taken after confirming that they are not associated with malignant hematologic disorders.

It is clear from previous reports that BEP combination chemotherapy is insufficient for PMNSGCT with M7 leukemia component. In a review of 26 cases of PMNSGCT and M7 leukemia by Mukherjee *et al*., all 26 were classified as Stage III according to American Joint Committee on Cancer classification. PMGCT occurred prior to the diagnosis of M7 leukemia in 46% of cases and concomitantly in 31% of cases; conversely, M7 leukemia was never reported prior to the appearance of PMGCT. Of the 23 patients whose treatment regimens were available, platinum-based chemotherapy directed toward management of the GCTs was used initially in 21 patients and leukemia-directed treatment was used initially in only two patients. Median time to death from the initial diagnosis of PMGCT was 6 months. The authors concluded that patients with a history of PMGCT are at higher risk of developing M7 leukemia (34).

Hiramatsu *et al*. reported a case of PMNSGCT with M7 leukemia. After performing bone marrow biopsy and mediastinal tumor biopsy followed by leukemia treatment with the addition of cisplatin, they subsequently performed cord blood transplantation followed by resection of mediastinal tumor to obtain long-term survival (35). Although it is a case report, this treatment strategy of performing a bone marrow biopsy at the first visit to check for leukemia cells might be useful when considering treatment strategy for PMNSGCT.

However, as shown in Table III, the incidence of hematological malignancies accompanied with PMNSGCT remains uncertain (19, 36), and further investigation is warranted.

Based on these facts, when encountering PMNSGCT, clinicians should first consider making an exclusion diagnosis by immunostaining for hematologic malignancies in the tumor biopsy or bone marrow aspiration, depending on the situation, and if detected, should consider performing chemotherapy for hematologic malignancies from the beginning of the treatment. Therefore, all physicians treating mediastinal GCTs need to be aware that hematologic malignancies may be present in PMGCT.

This study has several limitations, including single-center, retrospective study design, small sample size, and selection bias. However, when considering a treatment strategy for PMNSGCT, which is a heterogenous tumor, our results contribute to a future direction.

In conclusion, PMGCT is a rare and diverse disease with the potential for sudden outcomes. While primary mediastinal seminomatous germ cell tumor achieved excellent prognosis, PMNSGCT showed poor prognosis. Although it is easy to develop in young men, the treatment results are still poor with regard to PMNSGCT, and it is urgently desired to establish a treatment strategy.

Conflicts of Interest

Authors' Contributions

Acknowledgements

References

1 Bokemeyer C, Nichols CR, Droz JP, Schmoll HJ, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Kanz L, Einhorn L and Hartmann JT: Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol 20(7): 1864-1873, 2002. PMID: 11919246. DOI: 10.1200/JCO.2002.07.062

2 McKenney JK, Heerema-McKenney A and Rouse RV: Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. Adv Anat Pathol 14(2): 69-92, 2007. PMID: 17471115. DOI: 10.1097/PAP.0b013e31803240e6

3 Weissferdt A: Mediastinal Germ Cell Tumors. Diagnostic Thoracic Pathology. New York, Springer, pp. 939-969, 2020.

4 Childs WJ, Goldstraw P, Nicholls JE, Dearnaley DP and Horwich A: Primary malignant mediastinal germ cell tumours: improved prognosis with platinum-based chemotherapy and surgery. Br J Cancer 67(5): 1098-1101, 1993. PMID: 8494705. DOI: 10.1038/bjc.1993.201

5 Moran CA, Suster S, Przygodzki RM and Koss MN: Primary germ cell tumors of the mediastinum: II. Mediastinal seminomas – a clinicopathologic and immunohistochemical study of 120 cases. Cancer 80(4): 691-698, 1997. PMID: 9264352. DOI: 10.1002/(sici)1097-0142(19970815)80:4<691::aid-cncr7>3.0.co;2-q

6 Bokemeyer C, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Schmoll HJ, Kanz L, Einhorn L, Nichols CR and Hartmann JT: Extragonadal seminoma: an international multicenter analysis of prognostic factors and long term treatment outcome. Cancer 91(7): 1394-1401, 2001. PMID: 11283942.

7 Takeda S, Miyoshi S, Ohta M, Minami M, Masaoka A and Matsuda H: Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. Cancer 97(2): 367-376, 2003. PMID: 12518361. DOI: 10.1002/cncr.11068

8 Weidner N: Germ-cell tumors of the mediastinum. Semin Diagn Pathol 16(1): 42-50, 1999. PMID: 10355653.

9 Kumar N, Madan R, Dracham CB, Chandran V, Elangovan A, Khosla D, Yadav BS and Kapoor R: Primary mediastinal germ cell tumors: Survival outcomes and prognostic factors - 10 years experience from a tertiary care institute. Rare Tumors 12: 2036361320972220, 2020. PMID: 33282160. DOI: 10.1177/2036361320972220

10 Schmidt AH, Høyer M, Jensen BFS and Agerbaek M: Limited post-chemotherapy retroperitoneal resection of residual tumour in non-seminomatous testicular cancer: complications, outcome and quality of life. Acta Oncol 57(8): 1084-1093, 2018. PMID: 29537330. DOI: 10.1080/0284186X.2018.1449249

11 Heidenreich A, Haidl F, Paffenholz P, Pape C, Neumann U and Pfister D: Surgical management of complex residual masses following systemic chemotherapy for metastatic testicular germ cell tumours. Ann Oncol 28(2): 362-367, 2017. PMID: 27831507. DOI: 10.1093/annonc/mdw605

12 Daneshmand S, Albers P, Fosså SD, Heidenreich A, Kollmannsberger C, Krege S, Nichols C, Oldenburg J and Wood L: Contemporary management of postchemotherapy testis cancer. Eur Urol 62(5): 867-876, 2012. PMID: 22938868. DOI: 10.1016/j.eururo.2012.08.014

13 Riggs SB, Burgess EF, Gaston KE, Merwarth CA and Raghavan D: Postchemotherapy surgery for germ cell tumors – what have we learned in 35 years? Oncologist 19(5): 498-506, 2014. PMID: 24718515. DOI: 10.1634/theoncologist.2013-0379

14 Travis WD, Brambilla E, Muller-Hermelink HK and Harris CC (eds.): World Health Organization Classification of Tumors, Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart, 1st ed. Lyon, IARC Press, 2004.

15 Motzer RJ, Amsterdam A, Prieto V, Sheinfeld J, Murty VV, Mazumdar M, Bosl GJ, Chaganti RS and Reuter VE: Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol *159(1)*: 133-138, 1998. PMID: 9400455. DOI: 10.1016/s0022-5347(01)64035-7

16 Malagón HD, Valdez AM, Moran CA and Suster S: Germ cell tumors with sarcomatous components: a clinicopathologic and immunohistochemical study of 46 cases. Am J Surg Pathol *31(9)*: 1356-1362, 2007. PMID: 17721191. DOI: 10.1097/PAS.0b013e318033c7c4

17 Scheckel CJ, Kosiorek HE, Butterfield R, Ho TH and Hilal T: Germ cell tumors with malignant somatic transformation: a Mayo Clinic experience. Oncol Res Treat *42(3)*: 95-100, 2019. PMID: 30820020. DOI: 10.1159/000495802

18 Nichols CR, Hoffman R, Einhorn LH, Williams SD, Wheeler LA and Garnick MB: Hematologic malignancies associated with primary mediastinal germ-cell tumors. Ann Intern Med *102(5)*: 603-609, 1985. PMID: 2984971. DOI: 10.7326/0003-4819-102-5-603

19 Hartmann JT, Nichols CR, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Fizazi K, Einhorn L, Kanz L and Bokemeyer C: Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. J Natl Cancer Inst *92(1)*: 54-61, 2000. PMID: 10620634. DOI: 10.1093/jnci/92.1.54

20 Taylor J, Donoghue MT, Ho C, Petrova-Drus K, Al-Ahmadie HA, Funt SA, Zhang Y, Aypar U, Rao P, Chavan SS, Haddadin M, Tamari R, Giralt S, Tallman MS, Rampal RK, Baez P, Kappagantula R, Kosuri S, Dogan A, Tickoo SK, Reuter VE, Bosl GJ, Iacobuzio-Donahue CA, Solit DB, Taylor BS, Feldman DR and Abdel-Wahab O: Germ cell tumors and associated hematologic malignancies evolve from a common shared precursor. J Clin Invest *130(12)*: 6668-6676, 2020. PMID: 32897884. DOI: 10.1172/JCI139682

21 International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol *15(2)*: 594-603, 1997. PMID: 9053482. DOI: 10.1200/JCO.1997.15.2.594

22 Takezawa Y, Yaegashi H, Iijima M, Kawaguchi S, Nohara T, Shigehara K, Izumi K, Kadono Y, Ikeda H and Mizokami A: Durable response achieved using Pazopanib for germ tumor cells: A case report. Mol Clin Oncol *14(3)*: 48, 2021. PMID: 33604038. DOI: 10.3892/mco.2021.2210

23 Yaegashi H, Kato Y, Nohara T, Izumi K, Kadono Y, Miyagi T, Nakashima T, Yoshimura K, Sato Y, Harada K and Mizokami A: Histiocytic sarcoma following combination chemotherapy for primary mediastinal germ cell tumor: a diagnostic dilemma. Int Cancer Conf J *10(2)*: 144-148, 2021. PMID: 33786289. DOI: 10.1007/s13691-020-00467-7

24 Hartmann JT, Nichols CR, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Kanz L, Einhorn L and Bokemeyer C: Prognostic variables for response and outcome in patients with extragonadal germ-cell tumors. Ann Oncol *13(7)*: 1017-1028, 2002. PMID: 12176779. DOI: 10.1093/annonc/mdf176

25 Sakurai H, Asamura H, Suzuki K, Watanabe S and Tsuchiya R: Management of primary malignant germ cell tumor of the mediastinum. Jpn J Clin Oncol *34(7)*: 386-392, 2004. PMID: 15342665. DOI: 10.1093/jjco/hyh062

26 Géczi L, Budai B, Polk N, Fazekas F, Bodrogi I and Biró K: Neutrophil-to-lymphocyte ratio in primary mediastinal germ cell tumors: A retrospective analysis of >20 years single institution experience. Curr Probl Cancer *44(4)*: 100537, 2020. PMID: 31980147. DOI: 10.1016/j.currproblcancer.2020.100537

27 Dechaphunkul A, Sakdejayont S, Sathitruangsak C and Sunpaweravong P: Clinical characteristics and treatment outcomes of patients with primary mediastinal germ cell tumors: 10-years' experience at a single institution with a bleomycin-containing regimen. Oncol Res Treat *39(11)*: 688-694, 2016. PMID: 27855414. DOI: 10.1159/000452259

28 van Dijk MR, Steyerberg EW and Habbema JD: Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: An update based on meta-analysis. Eur J Cancer *42(7)*: 820-826, 2006. PMID: 16574403. DOI: 10.1016/j.ejca.2005.08.043

29 Kojima T, Kawai K, Tsuchiya K, Abe T, Shinohara N, Tanaka T, Masumori N, Yamada S, Arai Y, Narita S, Tsuchiya N, Habuchi T and Nishiyama H: Identification of a subgroup with worse prognosis among patients with poor-risk testicular germ cell tumor. Int J Urol *22(10)*: 923-927, 2015. PMID: 26094715. DOI: 10.1111/iju.12844

30 Hsu YJ, Pai L, Chen YC, Ho CL, Kao WY and Chao TY: Extragonadal germ cell tumors in Taiwan: an analysis of treatment results of 59 patients. Cancer *95(4)*: 766-774, 2002. PMID: 12209720. DOI: 10.1002/cncr.10738

31 Joel A, Mathew N, Andugala SS, Daniel S, Gnanamuthu BR, John AO, Georgy JT, Chacko RT, Irodi A, Yadav B, John S and Singh A: Primary mediastinal germ cell tumours: real world experience in the low middle income (LMIC) setting. Ecancermedicalscience *15*: 1186, 2021. PMID: 33777179. DOI: 10.3332/ecancer.2021.1186

32 Albany C and Einhorn LH: Extragonadal germ cell tumors: clinical presentation and management. Curr Opin Oncol *25(3)*: 261-265, 2013. PMID: 23422328. DOI: 10.1097/CCO.0b013e32835f085d

33 Liu Q, Tomaszewicz K, Hutchinson L, Hornick JL, Woda B and Yu H: Somatic mutations in histiocytic sarcoma identified by next generation sequencing. Virchows Arch *469(2)*: 233-241, 2016. PMID: 27259537. DOI: 10.1007/s00428-016-1965-2

34 Mukherjee S, Ibrahimi S, John S, Adnan MM, Scordino T, Khalil MO and Cherry M: Non-seminomatous mediastinal germ cell tumor and acute megakaryoblastic leukemia. Ann Hematol *96(9)*: 1435-1439, 2017. PMID: 28578457. DOI: 10.1007/s00277-017-3037-3

35 Hiramatsu H, Morishima T, Nakanishi H, Mizushima Y, Miyazaki M, Matsubara H, Kobayashi M, Nakahata T and Adachi S: Successful treatment of a patient with Klinefelter's syndrome complicated by mediastinal germ cell tumor and AML(M7). Bone Marrow Transplant *41(10)*: 907-908, 2008. PMID: 18223696. DOI: 10.1038/sj.bmt.1705991

36 Sowithayasakul P, Sinlapamongkolkul P, Treetipsatit J, Vathana N, Narkbunnam N, Sanpakit K and Buaboonnam J: Hematologic malignancies associated with mediastinal germ cell tumors: 10 years' experience at Thailand's National Pediatric tertiary referral center. J Pediatr Hematol Oncol *40(6)*: 450-455, 2018. PMID: 29864110. DOI: 10.1097/MPH.0000000000001233