Mediastinal Germ Cell Tumors

Updates in Diagnosis and Management

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KEYWORDS

• Germ cell tumors • Mediastinal tumors • Nonseminomatous germ cell cancer
• Thoracic surgery • Chemotherapy

KEY POINTS

- Primary mediastinal nonseminomatous germ cell tumors represent a rare but important malignancy that occurs in otherwise young and healthy patients.
- Treatment is challenging and involves cisplatin-based chemotherapy followed by surgery to remove residual disease.
- Avoiding bleomycin-containing chemotherapy in the treatment of primary mediastinal nonseminomatous germ cell tumors is important.
- Prechemotherapy and postchemotherapy pathology as well as postoperative serum tumor markers are independent predictors of long-term survival.

INTRODUCTION

The mediastinum is the most common site of extragonadal origin of germ cell tumors, with 5% to 10% of germ cell tumors arising primarily within the anterior mediastinum and accounting for 15% to 20% of all anterior mediastinal tumors.[1,2] Mediastinal germ cell tumors comprise 3 distinct histologic types: teratoma (mature and immature subtypes), seminoma, and nonseminomatous germ cell tumors (NSGCTs). Mature teratomas comprise 60% to 70% of mediastinal germ cell tumors and are considered benign, and surgical resection is curative. Immature teratomas behave more aggressively and have poor outcomes compared with their mature counterparts. Primary mediastinal seminomas represent about 40% of malignant mediastinal germ cell tumors. Seminomas are sensitive to chemotherapy and have excellent cure rates with

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cisplatin-based treatment. Primary mediastinal NSGCTs (PMNSGCTs) represent most malignant mediastinal germ cell tumors. These tumors are typically aggressive with a poor-risk profile, and overall 5-year survival is approximately 45%.[3–5] Treatment of PMNSGCTs consists of cisplatin-based chemotherapy followed by surgical resection of residual tumor mass. The diagnosis and contemporary multimodality strategy for the treatment of PMNSGCT are discussed here.

Pathogenesis

PMNSGCTs represent a rare but important malignancy, accounting for 1% of all mediastinal tumors and most of the malignant germ cell tumors of the mediastinum. These tumors occur almost exclusively in young adult men, most commonly between the ages of 20 and 40 years.

On histology, these neoplasms are typically mixed, and contain at least 1 nonseminomatous germ cell cancer subtype (yolk sac tumor, embryonal carcinoma, choriocarcinoma) as well as some form of teratomatous disorder, ranging from mature teratoma to teratoma with immature or atypical elements. Occasionally, frank malignant transformation of teratoma into so-called non–germ cell cancers (sarcomas and epithelial carcinomas) is found. The tumor admixture can contain variable proportions of these nonseminomatous histologies, as well as malignant seminoma.

DIAGNOSIS

Patients with PMNSGCTs are usually symptomatic on presentation. Clinical findings are consistent with a growing mediastinal mass, such as cough, shortness of breath, chest pain, or superior vena cava syndrome. Computed tomography (CT) imaging usually reveals a large heterogeneous mass in the anterior mediastinum (**Fig. 1**). These masses are aggressive tumors and local invasion into surrounding structures is a common finding at presentation. Metastatic disease was present at diagnosis in 32% of 244 patients in our recent institutional series, with lung being the most common site, followed by mediastinal and extrathoracic lymph nodes, liver, and central nervous system (CNS).[6] Chest and abdominal CT scans are standard imaging tests for staging, with other radiologic studies, including PET scan and MRI, acquired on a case-by-case basis.

Obtaining serum tumor markers (STMs) on a young man presenting with an anterior mediastinal mass is essential to establish a diagnosis of PMNSGCT. Any increase in alpha fetoprotein (AFP) level or significant increase in β-human chorionic gonadotropin (βHCG) greater than 100 unit/L is diagnostic of PMNSGCT. In patients with diagnostic increase in STM level, prompt cytologic confirmation can be obtained with CT-guided biopsy, if desired. Biopsy, either CT guided or surgical when CT-guided is not feasible, is obtained in cases where AFP level is normal and βHCG level marginally increased, potentially indicating seminoma.

TREATMENT

Chemotherapy

The treatment strategy for PMNSGCT is multimodal therapy with cisplatin-based chemotherapy as initial treatment followed by surgical resection of residual tumor. There is no role for radiation therapy in the treatment of PMNSGCT. Development of cisplatin-based combination chemotherapy for NSGCT has been responsible for vastly improved long-term survival rates compared with outcomes in the precisplatin era. Four courses of bleomycin, etoposide, and cisplatin chemotherapy have traditionally been considered the standard of care for patients with poor-risk NSGCT, including

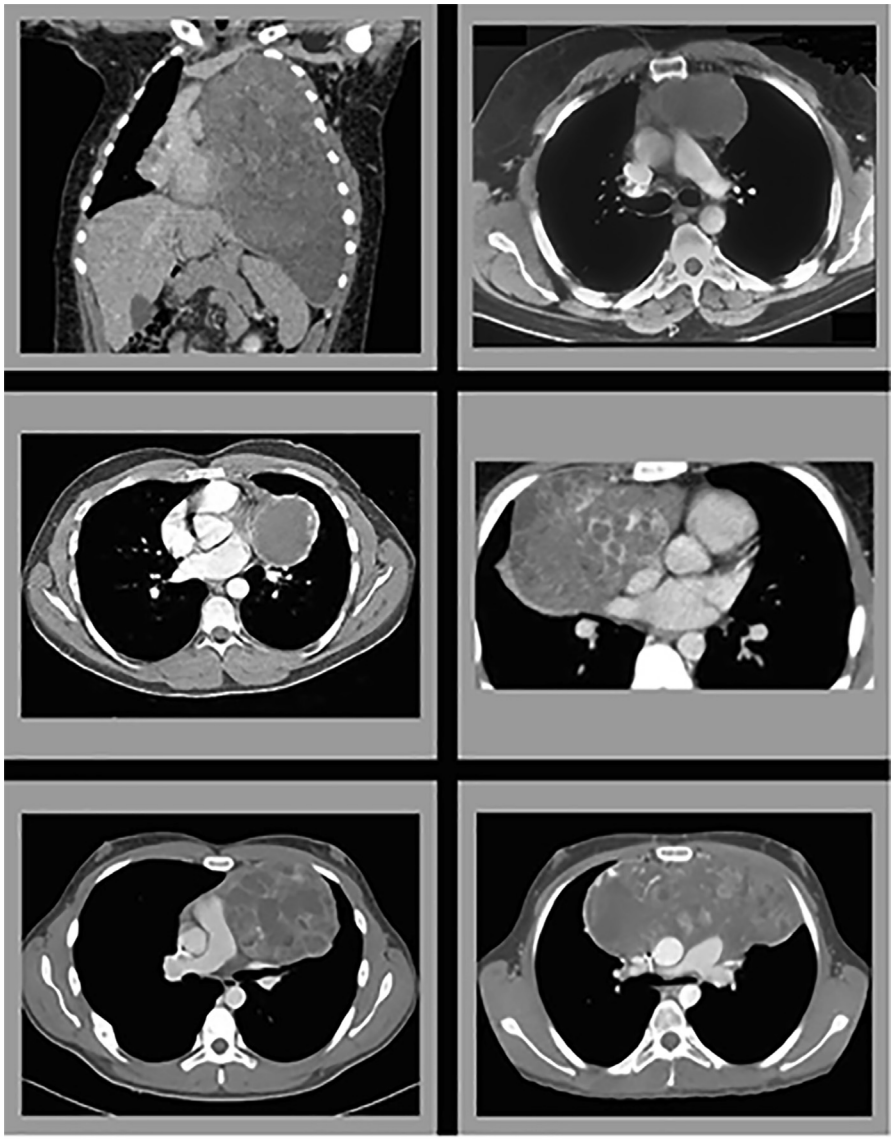

Fig. 1. Illustrative chest CT images of patients presenting with PMNSGCT, showing heterogeneous tumors arising from the anterior mediastinum.

PMNSGCT. However, postchemotherapy surgery for PMNSGCT is usually extensive and carries significant risk of pulmonary-related morbidity, including development of acute respiratory distress syndrome (ARDS). Pulmonary toxicity is a well-known consequence of bleomycin. In order to avoid the compounding effect of bleomycin on the postoperative pulmonary risk associated with mediastinal and intrathoracic resection, over the past 15 years, our institution has been using an etoposide, ifosfamide, and cisplatin (VIP) regimen as the chemotherapy of choice for PMNSGCT. The authors have experienced a relative reduction in postoperative respiratory failure rate

in patients with PMNSGCT with use of non–bleomycin-containing regimens, despite similar extent of surgery, including pulmonary resections.[7,8] We recently updated our institutional experience and showed a 14.8% rate of postoperative pulmonary failure, which carried 40.7% mortality in these otherwise young and healthy patients, after receiving bleomycin-containing regimens, compared with an incidence of 2.6% in patients who received VIP.[6] Postoperative pulmonary complications and ARDS carry significant associated morbidity. Therefore, following chemotherapy strategies that minimize the risks of ARDS remains important.

Surgery

Ideally, STM levels normalize after chemotherapy, or at least significantly decrease, and tumor dimension shrinks. However, there always remains a residual mediastinal mass, most of which contain residual disease for which surgical resection is indicated. Most residual tumor masses contain teratoma, persistent nonseminomatous germ cell cancer, and non–germ cell cancer cells, and complete tumor necrosis is found in only a minority of cases.[9] Surgery to remove residual disease is typically planned 4 to 6 weeks following chemotherapy to allow for patient recovery. The standard of care for patients with testicular NSGCT who relapse serologically shortly after first-line chemotherapy involves second-line chemotherapy, before considering surgery. However, response rates of standard cisplatin-based salvage chemotherapy for PMNSGCT are notoriously poor.[10] Moreover, although increased STM levels are diagnostic of PMNSGCT, postchemotherapy STM levels lack high sensitivity or specificity for residual NSGCT. In addition, the propensity of PMNSGCT to transform into non–germ cell cancers, which are typically STM negative as well as refractory to chemotherapy, further questions the role of second-line chemotherapy before surgery. Therefore, the authors subscribe to a policy of removing residual disease if deemed operable, regardless of STM status, because the overall results of surgical salvage in patients with residual malignancy after first-line chemotherapy seem to be superior to the response rates of second-line chemotherapy.[11,12]

Patients are rarely considered to be inoperable; however, extensive great vessel or middle mediastinal involvement may preclude safe resection. For patients with persistent metastatic disease after first-line chemotherapy, the authors use an individualized approach. In patients with normal STM levels after first-line chemotherapy, nonpulmonary and pulmonary metastases are resected when feasible, particularly if suspicious for teratoma. Extrathoracic metastases are typically removed as a staged procedure before or after mediastinal surgery. Surgery is undertaken for select patients with increased STM levels and limited areas of pulmonary metastases deemed resectable at the time of surgery to remove the residual mediastinal mass. For patients with increased STM levels after first-line chemotherapy and systemic or extensive pulmonary metastases, second-line chemotherapy, more recently in the form of high-dose chemotherapy with peripheral stem cell transplant, should be given before proceeding with surgery.[13] Patients with increased STM levels after first-line chemotherapy caused by an isolated CNS metastasis can be treated with stereotactic radiation and/or surgery with CNS disease control before removal of mediastinal disease. Rare patients show a so-called growing teratoma syndrome, defined by a rapidly growing symptomatic mediastinal mass with decreasing STM level before completion of 4 chemotherapy cycles.[14] In these cases, chemotherapy is discontinued and urgent surgery undertaken.

Surgery can be challenging, because chemotherapy results in fibrosis of mediastinal tissues surrounding residual disease. Our technique to remove residual mediastinal

tumor has been described.[15] We start by selecting an approach (median sternotomy, clamshell with transverse sternotomy, anterolateral thoracotomy, or sternotomy combined with separate thoracotomy) to optimize exposure of technically difficult areas anticipated during surgery. Surgical removal involves en bloc dissection of the residual mass and surrounding involved structure with an ultimate goal of obtaining an R0 resection (Table 1). A balanced surgical approach is used to spare critical structures such as phrenic nerves, main pulmonary arteries, great veins, and cardiac chambers where the residual mass abuts but does not grossly invade, using intraoperative frozen section for margin control. In cases where phrenic nerves are removed en bloc, prophylactic diaphragm plication can be performed on an individual basis. With respect to the great veins, reconstruction is done in all cases where en bloc superior vena cava resection is required. If 1 innominate vein is involved, ligation can be performed without reconstruction. A single vein reconstruction technique is used for cases that

Table 1
Anatomic structures removed en bloc with the residual mass after chemotherapy in 244 operative survivors with primary mediastinal nonseminomatous germ cell tumors

Variable (Total n = 244)	Number (%)
Organs removed, any	228 (93.4)
1	37 (15.2)
>1	191 (78.3)
Pericardium	195 (79.9)
Phrenic nerve	74 (30.3)
Right phrenic nerve	19 (7.8)
Left phrenic nerve	51 (20.9)
Diaphragm plication	15 (6.1)
Great vein, any	64 (26.2)
Right innominate	12 (4.9)
Left innominate	54 (22.1)
Superior vena cava	25 (10.2)
Inferior vena cava	1 (0.4)
Cardiac chamber	9 (3.9)
Right atrium	5 (2.2)
Left atrium	2 (0.9)
Left ventricle	2 (0.9)
Chest wall	9 (3.9)
Diaphragm	8 (3.5)
Pulmonary resection	165 (72.3)
Segment or wedge	77 (33.8)
Lobectomy	55 (24.1)
1	35 (15.4)
>1	20 (8.8)
Pneumonectomy	12 (5.3)

Data from Outcomes Following Surgery for Primary Mediastinal Nonseminomatous Germ Cell Tumors in the Cisplatin Era. Kesler, Kenneth A. et al. The Journal of Thoracic and Cardiovascular Surgery, Published online April 22, 2020

require bilateral innominate vein removal, preferably the right innominate to superior vena cava with ligation of the left innominate vein. Our conduit preference for great vein reconstruction is cryopreserved descending thoracic aortic allografts. Cardiopulmonary bypass capabilities should be made available for select patients with great vessel or cardiac involvement. Perioperative fluid and oxygen administration should be kept to a minimum, particularly in patients who may have received bleomycin before surgery.

Follow-up

Patients who present to surgery with increased STM levels should have the levels measured before hospital discharge and at 1 month postoperatively. Patients with pathologic evidence of viable NSGCT and normal postoperative STM levels should be given 2 additional cycles of etoposide/cisplatin. Current practice includes consideration of high-dose chemotherapy for patients with persistently increased postoperative STM levels and recurrent PMNSGCT.[13] Routine long-term follow-up includes chest radiographs and STM levels every 2 months for the first year, every 4 months for the second year, every 6 months in years 3 through 5, then annually. For patients who pathologically show a component of teratoma, CT imaging is also recommended during follow-up. Patients with recurrent disease are treated on an individual basis, with surgery favored for teratoma and limited areas of malignancy.

Outcomes

STMs seem to remain important from a prognosis standpoint. By univariate analysis, our recent study showed that preoperative increased AFP level, increased STM levels in general, and increasing STM levels were predictive of poor survival, whereas normal STM level was protective. Even though increased postchemotherapy STM levels did not remain statistically significant in the multivariate model, persistent increase of STM levels after surgery, likely indicating residual microscopic NSGCT, was predictive of adverse survival.[6] Our institutional approach now uses high-dose chemotherapy in patients with increasing postoperative STM levels with an expectation of low but improving cure rates.[13] A multicenter review of patients with extragonadal NSGCT, including 341 with PMNSGCT, identified pretreatment increased βHCG level and nonpulmonary visceral metastases as adverse risk factors for survival.[5] Of note, less than half of the patients with PMNSGCT in this study underwent postchemotherapy surgery. Although prechemotherapy tumor histology was not provided, it is plausible that increased βHCG level was a surrogate for the presence of choriocarcinoma, which was independently predictive in our recent series. In contrast, pure mediastinal seminomas have extremely high cure rates with cisplatin-based chemotherapy alone.[3,4] Although all patients in our recent series had serologic or pathologic evidence of NSGCT, it is perhaps not surprising that the subset of cases with tumors containing a malignant seminoma component had significantly improved survival.

Although overall 5-year survival averages 45%, individual survival after surgery for PMNSGCT has been reported to range widely, with rates reported between 30% and 90%. Similar to prechemotherapy pathology, features identified in resected mediastinal masses can be variable and mixed, potentially containing elements of tumor necrosis, teratoma, and malignancy. Current and previous studies from our institution as well as a report from Memorial Sloan Kettering Cancer Center continue to show that the pathology features identified in the residual mass following chemotherapy is independently predictive of long-term survival and largely responsible for variable survival rates (**Fig. 2**).[6,7,16] Patients who show complete tumor necrosis have excellent long-term prognosis. Patients with pathologic evidence of teratoma, with or without tumor

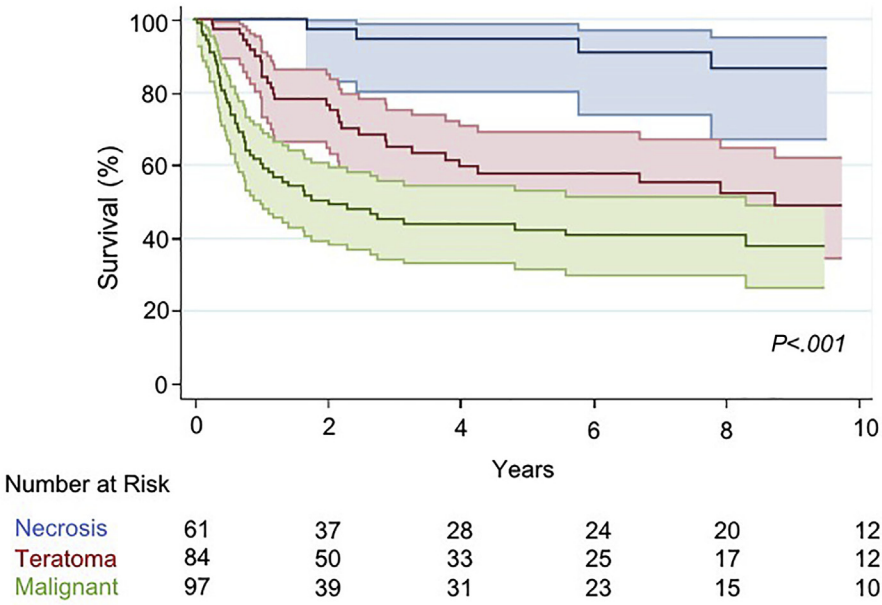

Fig. 2. Long-term survival in a series of 244 operative survivors with primary mediastinal nonseminomatous germ cell tumors based on the worst pathologic diagnosis microscopically identified in the residual mass (necrosis, teratoma, or malignant). (*Data from* Outcomes Following Surgery for Primary Mediastinal Nonseminomatous Germ Cell Tumors in the Cisplatin Era. Kesler, Kenneth A. et al. The Journal of Thoracic and Cardiovascular Surgery, Published online April 22, 2020.)

necrosis, show intermediate survival. The poorer prognosis of PMNSGCT compared with testicular NSGCT is caused not only by a relative resistance to cisplatin-based chemotherapy but also by a higher propensity of teratoma in PMNSGCT to undergo malignant transformation into nongerm cancers.[17,18] Teratoma with stromal atypia arguably represents the precursor to non–germ cell cancer. Although sarcomas predominate, the spectrum of non–germ cell disorders in residual mass lesions is a testimony to the pluripotent nature of these tumors. Interestingly, the subset of patients who pathologically show teratoma with stromal atypia have long-term survival similar to patients with residual malignancy, which diminishes overall survival in the teratoma category. We speculate that pathologic sampling error in large residual masses where small areas of frank non–germ cell cancer are missed, or perhaps observer variability (severe atypia vs frank non–germ cell cancer), could be contributing factors to this finding.

Surgery has the ability to salvage patients with pathologic evidence of malignancy in the form of either viable NSGCT and/or non–germ cell cancers with poor but possible long-term survival. Impressively, patients with less than 50% of the residual mass containing viable malignancy have been shown to have long-term survival equivalent to the overall survival of patients whose worst disorder was teratoma. However, survival significantly diminishes when 50% or more of the residual mass contains viable malignancy.[6,7]

SUMMARY

PMNSGCTs represent a challenging group of malignant germ cell tumors. Avoiding bleomycin-containing chemotherapy before these major thoracic surgical procedures is important. Prechemotherapy and postchemotherapy pathology, as well as postoperative STM levels, are independent predictors of long-term survival. Although overall PMNSGCT survival remains inferior to testicular NSGCT, an aggressive surgical approach can be justified in these otherwise young and healthy patients.

DISCLOSURE

The authors declare no conflict of interest. There was no external funding source.

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