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Non-Seminomatous Germ Cell Tumor Presenting with Superior Vena Cava Syndrome

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient: Male, 24
Final Diagnosis: Non-seminomatous primary mediastinal germ cell tumor
Symptoms: Chest pain • dyspnea
Medication: —
Clinical Procedure: Chemotherapy
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Primary mediastinal non-seminomatous germ cell tumors (NSGCTs) are aggressive and carry a poor five-year disease free survival rate even with aggressive treatment. We describe a young adult male with primary mediastinal NSGCT presenting with airway obstruction and superior vena cava syndrome (SVCS).

Case Report: The patient presented with four weeks of nonproductive cough, weight loss, and right-sided pleuritic chest pain. Chest computed topography (CT) imaging demonstrated a right-sided mediastinal mass determined as a yolk sac tumor on biopsy. The patient underwent induction chemotherapy with etoposide and cisplatin for stage III NSGCT. In the interim, he developed SVCS warranting a second cycle of chemotherapy along with intravenous steroids, with notable improvement in symptoms. However, serial alpha-fetoprotein (AFP) measurements showed progressively increasing levels up to a maximum of 18,781 ng/mL indicating treatment failure. He is currently on salvage chemotherapy.

Conclusions: Obstruction of the SVC by external compression is often a manifestation of a malignant process in the thorax. SVCS is a medical emergency and occurs in 6% of patients with mediastinal GCTs. Historically, irradiation was initiated without a histologic diagnosis to relieve the life-threatening obstruction. However, newer data suggest that it is acceptable to defer therapy until a full diagnostic workup is completed. This case highlights the malignant nature of primary mediastinal NSGCTs. In addition, inasmuch as SVCS is dramatic in presentation, it is important to recognize that symptomatic obstruction often develops over weeks or longer. In a hemodynamically stable patient, an accurate histologic diagnosis prior to starting treatment is essential in guiding therapy.

MeSH Keywords: Endodermal Sinus Tumor • Mediastinal Neoplasms • Neoplasms, Germ Cell and Embryonal • Superior Vena Cava Syndrome • Yolk Sac

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/904855

Background

Non-seminomatous germ cell tumors (NSGCTs) of the mediastinum are aggressive neoplasms and carry a poor five-year disease free survival rate even with aggressive treatment [1,2]. These patients are often severely symptomatic on presentation [3]. We report the case of a 24-year-old male with primary mediastinal germ cell tumor of yolk sac histology presenting with signs of early airway obstruction and superior vena cava syndrome (SVCS).

Case Report

Our patient was a current every day smoker with a newly discovered mediastinal tumor. He initially presented with a four-week history of fever, night sweats, weight loss, progressive exertional dyspnea, and pleuritic chest pain. He was found to have a large mediastinal mass associated with right-sided pleural effusion causing compression atelectasis. A video-assisted thoracoscopic surgery (VATS) for drainage of the effusion and pleural biopsy was performed demonstrating high grade epithelial neoplasm with extensive necrosis and immunohistochemical stains that were consistent with a yolk sac tumor. His alpha-fetoprotein (AFP) level was 4,110 ng/mL (normal ≤10 ng/mL). Due to respiratory distress and compromise, he received inpatient chemotherapy with etoposide and cisplatin for his stage III [4] non-seminomatous mediastinal yolk cell tumor. He tolerated the regimen well without any significant side effects.

He was readmitted soon after with a two-week interval development of intermittent fever, headaches, hoarseness, orthopnea, and persistent non-exertional chest pain. He was normotensive with a blood pressure of 127/88 mm Hg, tachycardic at 125 beats per minute and tachypneic at a rate of 23 breaths per minute. The O2 saturation was 98% on 2 L of O2. His cortical function was intact. He had chemosis in the right eye without visual defects. There was significant unilateral right facial fullness, plethora, as well as prominent jugular veins and signs of right upper arm inflammation. Tactile fremitus and breath sounds were decreased in the right lower lung field and bibasilar dullness appreciated on percussion. Cardiovascular examination was normal except tachycardia. Laboratory evaluation results are shown in Table 1. The electrocardiogram revealed sinus tachycardia. The computed tomography (CT) of chest demonstrated a large intrathoracic and mediastinal tumor with mass effect on superior vena cava (Figure 1). Incidental thrombus within the right brachiocephalic vein was discovered. A cardiac magnetic resonance imaging (MRI) confirmed a mass in the cardiophrenic angle causing extrinsic compression of the right atrium and leftward displacement of the heart, and ruled out any cardiac invasion by tumor. There was a small pericardial effusion.

The patient had a complicated hospital course. He developed coagulase negative staphylococcal bacteremia secondary to central line associated bloodstream infection, and received antibiotic therapy. Rivaroxaban was started for the right brachiocephalic venous thrombosis and nonsteroidal anti-inflammatory drugs (NSAIDs) were given for acute pericarditis. Systemic steroids were also administered mainly for laryngeal edema and to mitigate the risk of airway compromise from superior vena cava syndrome (SVCS). He received a second cycle of chemotherapy with etoposide and cisplatin. The facial fullness and headache improved over the course of two weeks. Hemodynamics remained normal. However, serial AFP measurements showed progressively increasing levels up to a maximum of 18,781 ng/mL indicating treatment failure. As part of investigative workup of NSGCT, a scrotal ultrasound had been performed demonstrating a suspicious lesion in the left testicle, however, pathology was benign after radical left

Table 1. Laboratory evaluation results and reference range.

Hemoglobin 12.9	(14–18 g/dL)	Alk Phos 81	(30–130 IU/L)
WBC 10.3	(3.4-9.4 K/mm^3)	AST 25	(0–41 IU/L)
Neut 71%		ALT 34	(0–45 IU/L)
Lymph 14%		Total bilirubin 0.8	(0–1 mg/dL)
Mono 14%		Total protein 5.8	(6–8 g/dL)
Eos 1%		Albumin 3.2	(3.5–5.5 g/dL)
Platelets 643	(140–410 K/mm^3)	AFP 2,961, Peak 18,791	(<10 ng/mL)
S. Na 138	(133–142 mmol/L)	BHCG 1 (<5 mIU/mL in the nonpregnant)	
S. K 4.6	(3.6–5.1 mmol/L)	LDH 272	(90–200 IU/L)
S. Ca 9.3	(8.5–10.5 mg/dL)	Blood Cultures: CONS in 2 out of 2 sets	
BUN 23	(6–22 mg/dL)		
S. creatinine 0.8	(0.7–1.4 mg/dL)		

AF – alpha fetoprotein, BHCG – beta-human chorionic gonadotropin, LDH – lactate dehydrogenase, CONS – coagulase negative staphylococci.

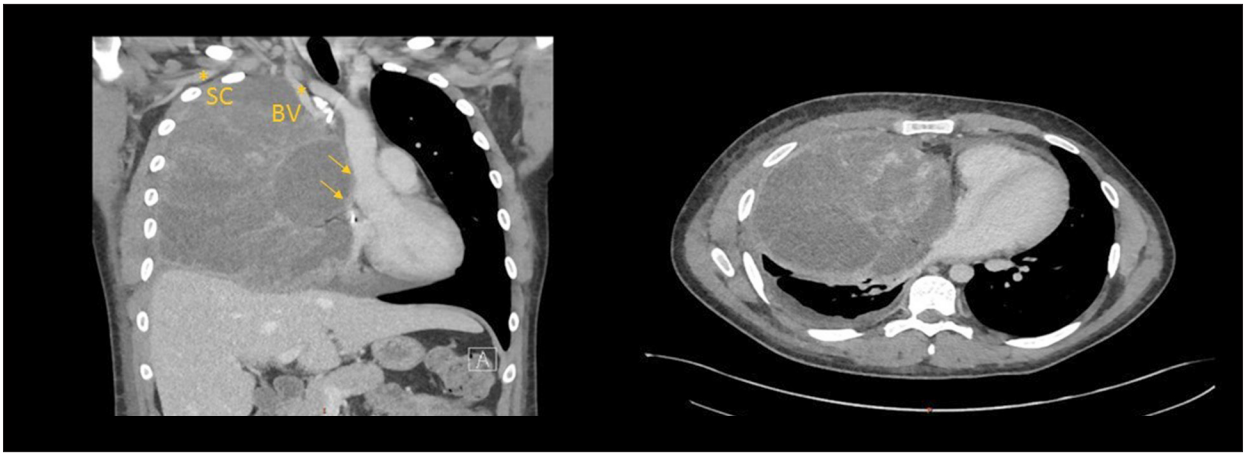

Figure 1. Coronal and transverse view chest CT. Lobulated, heterogeneous yolk sac tumor within the mediastinum and right hemithorax with mass effect causing marked narrowing of the SVC (arrows) and distal left brachiocephalic vein (BV), subclavian vein (SC), right atrial and ventricular compression.

orchiectomy. He is currently on salvage chemotherapy with etoposide, ifosfamide, and cisplatin, planned for four courses. His AFP level trended down to 2,961 ng/mL.

Discussion

In a patient presenting with mediastinal mass, localizing the mass to the specific mediastinal compartment is helpful in developing a differential diagnosis. In the anterior compartment, the most commonly encountered masses are the Terrible Ts (thymoma, terrible lymphoma, teratoma/germ cell, and thyroid tissue) [5]. In this case, both thymoma and a thyroid mass were ruled out radiographically. The elevated AFP and low lactate dehydrogenase (LDH) suggested the presence of an NSGCT.

Germ cell tumors (GCT) arise from the gonads (ovaries and testes) [6]. They are uncommon neoplasms, contributing to 1–4% of all mediastinal tumors [7–9]. These extragonadal germ cell tumors (EGCT) histologically contain the same components as their gonadal counterparts, but may have different biologic behaviors, clinical characteristics, and poor overall prognoses [6]. They can be divided into two broad groups: seminomas and NSGCT. Seminomas are radiosensitive and carry good prognosis [10]. NSGCTs have poor prognosis [11], and the five-year overall survival rate of mediastinal NSGCT is much lower than that of gonadal NSGCT [6,12]. Since the testicular biopsy of a suspicious lesion found on ultrasound did not show evidence of malignancy in our patient, it was designated as an EGCT. EGCTs are a result of a malignant transformation of arrested germ cells along the urogenital ridge during embryogenesis. This aberrant tissue is located along the craniocaudal axis in adult life, thus giving rise to tumors along the midline of the body (pineal gland, mediastinum, retroperitoneum, and presacral areas) [13,14]. The most common location in adults is the anterior mediastinum [15] as observed in our patient.

True for 90% of the EGCTs [3], our patient was severely symptomatic on presentation. SVCS are reported in 6% of these cases [16,17]. Historically, SCVS was considered a life-threatening emergency requiring immediate radiation therapy (RT) to relieve the obstruction [18,19]. The pattern of elevated AFP in a young adult male with a mediastinal mass is so characteristic that in some institutions, it was accepted as de facto evidence of an EGCT and treatment was oftentimes initiated without a tissue diagnosis [19–21]. However, in a study illustrating 107 cases of SVCS, it was shown that, providing that the patient was clinically stable, deferring therapy until a timely and full diagnostic workup was completed did not pose a significant risk in the interim [22]. In unstable patients presenting with severe symptoms, rapid palliation with the use of an endovenous stent was a viable option [23]. Furthermore, Loeffler et al. reported that RT prior to biopsy may obscure tissue histology, and diagnosis could not be established in 42% of cases [24]. Current management guidelines stress the importance of accurate histologic diagnosis prior to starting therapy [25]. The oncologists in our institution also stand by this principle.

In our case, the yolk sac histology was confirmed on pleural biopsy. The high grade epithelial neoplasm with extensive necrosis is shown in Figure 2. Immunohistochemistry revealed a positive reaction with AFP, cytokeratin AE1/3, WT11, CD11, and glypican 3 consistent with a yolk sac tumor. Tumor cells stained negatively for CK5/6, calretinin, HBME1, TTF1, CD31, CD34, moc31, napsin-A, CK7, CK20, CD68, CD3, CD20, ALK-1, CD15, and CD30, which confirmed the diagnosis of a yolk sac tumor [26] (Figure 3).

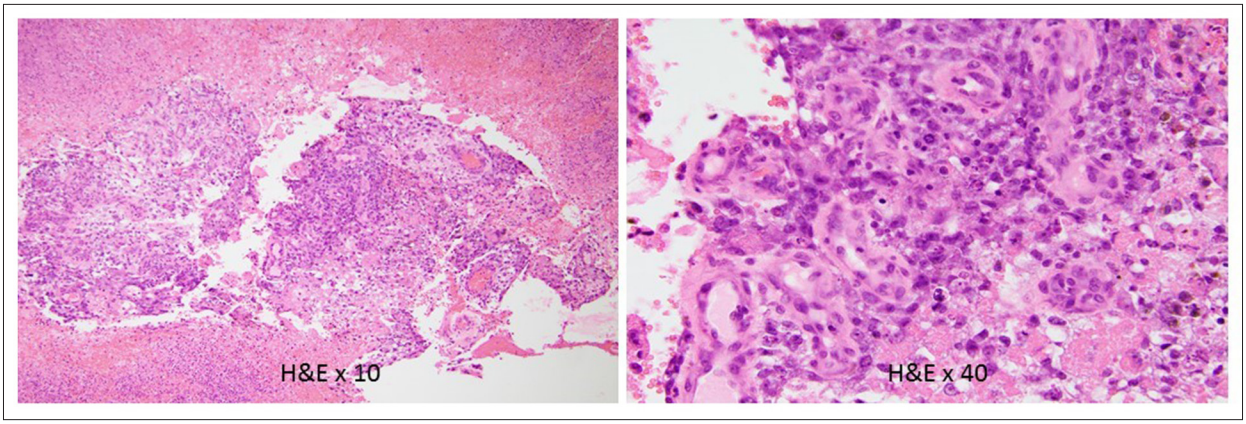

Figure 2. Histopathology. H & E sections show a high grade epithelial neoplasm with extensive necrosis. The tumor cells have high nuclear-cytoplasmic ratio, irregular nuclear contour, and prominent nucleoli.

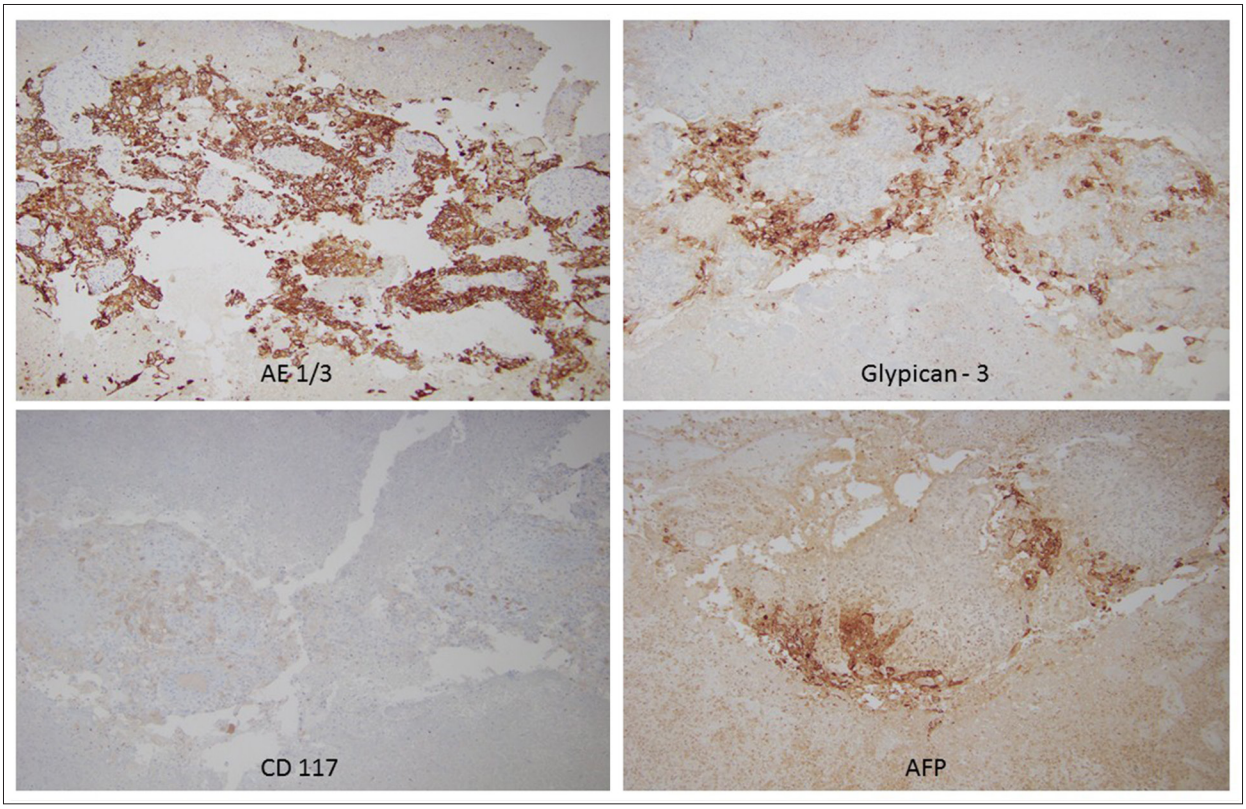

Figure 3. Immunohistochemical staining. Immunostaining showed that the tumor cells positively stained for CKAE1/3, glypican-3, CD117, and AFP.

Establishing accurate histologic diagnosis is very important as the choice of therapy differs remarkably depending on the underlying etiology. SVCS may result from an EGCT including seminomas which are radiosensitive or NSGCTs which respond well to chemotherapy [27]. In addition, it is important to rule out other malignancies which can cause SCVCS such as small cell lung cancer, non-Hodgkin lymphoma, plasmacytoma, and nonmalignant etiologies including mediastinal fibrosis and benign mediastinal tumors such as teratoma. [28,29]

After disease staging, the standard course of etoposide, and cisplatin (EP) was started for the patient's stage IIIC NSGCT. Bleomycin was not given due to pulmonary compromise. In 1997, the International Germ Cell Cancer Collaborative Group proposed a classification for patients with metastatic GCT as good, intermediate, or poor [30] (Table 2). Due to a mediastinal primary mass and extremely high levels of AFP reaching a peak level of 18,781 ng/mL; our patient was categorized as a poor risk candidate. Both of these two factors are validated

Table 2. Non-seminoma germ cell tumor risk classification.

Good risk group	AFP <1000 ng/mL hCG <5000 mIU/mL LDH <1.5×ULN Nonpulmonary visceral metastases absent Gonadal or retroperitoneal primary site
Intermediate risk group	AFP 1000–10000 ng/mL hCG 5000–50000 mIU/mL LDH 1.5–10×ULN Nonpulmonary visceral metastases absent Gonadal or retroperitoneal primary site
Poor risk group	Mediastinal primary site Nonpulmonary Visceral metastasis present (e.g., bone, liver, brain) AFP >10,000 ng/mL hCG >50,000 mIU/mL LDH >10×ULN

Reference [30]: hCG – human chorionic gonadotropin; LDH – lactate dehydrogenase; AFP – alpha fetoprotein; ULN – upper limit of normal range.

prognostic factors of poor disease-free survival [31]. The three-year progression-free survival in recent series is estimated at 48% to 54% [2,12,32,33].

Our patient relapsed during surveillance. His AFP level was elevated above 10,000 ng/mL and attempt at salvage chemotherapy with etoposide, ifosfamide, and cisplatin is ongoing. Several salvage regimens have been proposed in the literature [34–38]. Unfortunately, long-term survival rates for patients with relapsed mediastinal GCTs are less than 10% [15,39–41]

Conclusions

This case highlights the malignant nature of primary mediastinal NSGCTs. In addition, inasmuch as SVCS is dramatic in presentation, it is important to recognize that symptomatic obstruction often develops over weeks or longer [22]. In a hemodynamically stable patient, obtaining an accurate histologic diagnosis prior to starting treatment is essential in guiding therapy.

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