

Case Report - Pathology

Clinical and Immunohistopathologic Profile of a Mediastinal Seminoma

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Background --- Malignant germ cell tumors of the mediastinum are unusual, accounting for approximately 10% of all mediastinal tumors. Histologically, the mediastinal seminomas are identical to its gonadal counterpart. We present a rare case of mediastinal seminoma negative for CD117, which is usually positive in most cases.

Case --- The patient is a 22 year old male who complained of a chest pain. Further evaluation with computed tomography of the chest revealed an anterior mediastinal mass. Surgical thoracotomy was performed to remove the mediastinal mass and the specimen submitted for histopathologic evaluation. Immunohistochemistry and special stains were performed.

Histopathologic Findings --- The mediastinal mass was received fragmented and partly encapsulated. Cut-sections showed tan-yellow, lobulated to nodular cut-surfaces. Microsections revealed a seminomatous lesion. Immunohistochemistry demonstrated a strong positive reaction of the tumor with Placental Alkaline Phosphatase (PLAP). CD117 was occasionally expressed in rare tumor cells while cytokeratin was focal and faint.

Conclusions --- Mediastinal seminoma is a rare, distinctive clinicopathologic entity with a wide range of treatment modalities. Its diagnosis, even in unusual sites, based on the typical histologic features is paramount given its very favorable prognosis. *Phil Heart Center J 2012; 16(2):75-83*

Key Words: Seminoma ■ Mediastinal Mass ■ Germ Cell Tumor

Extragenital areas, such as the thorax, retroperitoneal and intraabdominal cavity, accounts for less than 5-7% of germ cell tumors, and among these sites, the most common location is the mediastinum. How seminomas arise in this area is still undetermined.¹

Mediastinal germ cell tumors appear identical histomorphologically to germ cell tumors arising in the testis. All histologic subtypes seen in germ cells neoplasms from the gonads have also been observed and analyzed in the mediastinum.¹

The histomorphology can usually be confirmed by immunohistochemistry particularly Placental Alkaline Phosphatase (PLAP) and CD117 in achieving a definitive diagnosis.¹ In the absence of CD117

expression, the diagnosis can still be achieved with its classic morphology supported by special stains for glycogen as seen in our case.

Case

The patient is a 22 year-old male admitted for chest pain. Ten months prior to admission, his chest roentgenogram revealed a suspicious density anterior to the heart. He was advised chest Computed Tomography Scan (CT-Scan). Four months prior to admission, he began to have chest pain, described as dull in character, non-radiating, graded as 7/10 in intensity, accompanied by shortness of breath,

productive cough with whitish, nonbloody sputum and moderate grade fever.

Repeat chest x-ray revealed the same suspicious mediastinal density. Chest CT Scan revealed an anterior mediastinal mass and CT scan-guided biopsy was inconclusive. He was advised thoracotomy and referred to our institution. His admitting impression was mediastinal mass, probably lymphoma. He had no cervical lymphadenopathy or abdominal and gonadal abnormalities. On the second hospital day, thoracotomy was performed and the mass was submitted for histologic evaluation. Approximately 80 mL of pericardial fluid was aspirated during the procedure and cytologic assessment fluid was nonspecific with abundant red blood cells and few medium-sized lymphoid cells. Postoperatively, he had fever and crackles on the base of the left lung and he was treated with cefuroxime, salbutamol with tramadol and nalbuphine for pain. Pertinent laboratory examinations include carcinoembryonic

antigen (CEA) of 0.90 ng/mL (0 – 3.0), alpha fetoprotein (AFP) 0.87 IU/mL (0 – 2.0). He stayed in the hospital for 10 days and was discharged improved.

GROSS DESCRIPTION. The specimen is received in formalin and labeled as ‘mediastinal mass’. It consists of six (6) pieces of partly encapsulated tan-yellow to tan-brown irregular to ovoid rubbery tissues measuring in aggregate 6.0 cm x 4.5 cm x 1.0 cm with a total weight of 42 grams. The surfaces are inked black. The cut-sections show tan-yellow, lobulated to nodular cut-surfaces (Figure 1).

MICROSCOPIC DESCRIPTIONS. Microsections show lymphoid tissues, with preserved nodal architecture including germinal centers, one of which is infiltrated by large neoplastic cells arranged in sheets (Figure 2). In certain areas, the tumor cells are arranged as invasive nests within desmoplastic stroma with mild



Figure 1. Gross Specimen from a 22-year old male who presented with chest pain and mediastinal mass. Mediastinal mass consists of six (6) pieces of grossly of tan-yellow to tan-brown, irregular to ovoid rubbery tissues measuring 6x4.5x1.0cm in aggregate.

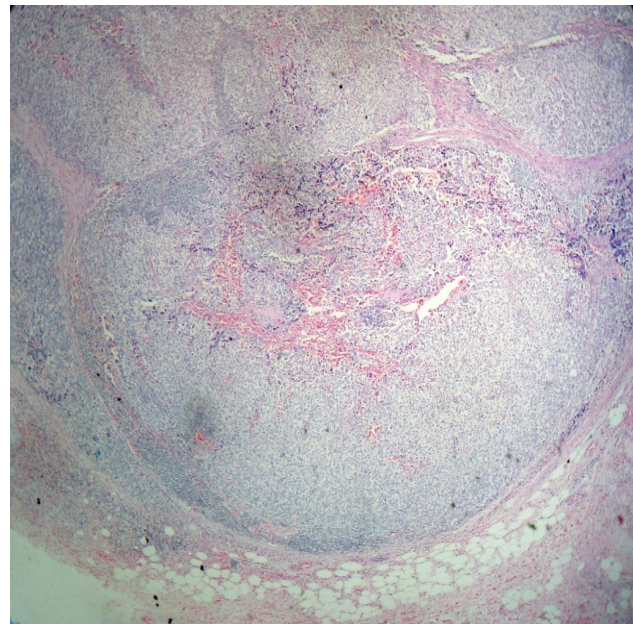


Figure 2. Microscopic view taken from mediastinal mass of a 22-year old male who presented with chest pain and mediastinal mass. A lymph node infiltrated by seminoma cells arranged in sheets (H&E 40X, scanning).

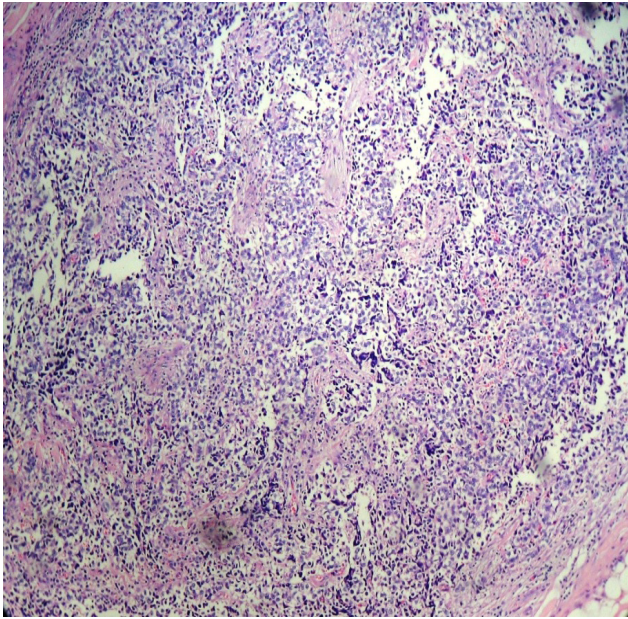


Figure 3. Microscopic view taken from mediastinal mass of a 22-year old male who presented with chest pain and mediastinal mass. The tumor cells are arranged as invasive nests within desmoplastic stroma with mild lymphocytic infiltrates (H&E, 100X).

lymphocytic infiltrates (Figure 3). The tumor cells are round to polygonal, fairly uniform in size with round to oval central nuclei and occasional prominent nucleoli. (Figure 4).

The tumor cells have abundant clear to lightly eosinophilic cytoplasm and distinct cell membranes. Mitosis is infrequent. Special stains with Periodic Acid Schiff (PAS) showed focal positivity highlighting glycogen content (Figure 5) while Mucicarmine stain for mucin is negative.

IMMUNOHISTOCHEMISTRY: Placental alkaline phosphatase (PLAP) staining is diffuse and strong (Figure 6). Leukocyte common antigen (LCA) and CD30 are totally negative (Figures 7 & 8). CD117 is occasionally expressed in rare tumor cell while cytokeratin has focal faint staining (Figure 9).

Discussion

Primary extragonadal seminoma is a

rare disease occurring in 10–15% of all masses found in the mediastinum.^{2,3} Mediastinal seminomas have accounted for approximately 37% of all mediastinal germ cell tumors, second only to teratomas. It is morphologically indistinguishable from their gonadal counterparts. However, it has a different biologic and clinical behavior due to the difference in anatomical location.⁴

Presenting symptoms have a direct relationship to tumor size. Majority of symptoms, such as cough, hemoptysis, and/or dyspnea, are usually consequent to compression of adjacent structures. Another common symptom is chest pain as seen in this case. Superior vena cava syndrome may manifest as an acute process in some cases. This presentation has been documented in the past in 10-20% of cases.⁵

In most cases, mediastinal seminomas may be totally asymptomatic and may be an incidental finding on routine physical or radiographic examinations. Approximately 20% of the patients presented without any symptoms and the diagnosis

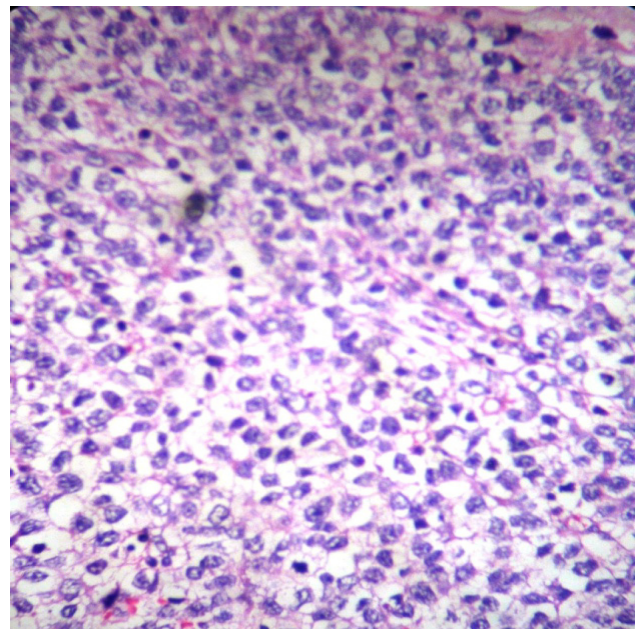


Figure 4. Microscopic view taken from mediastinal mass of a 22-year old male who presented with chest pain and mediastinal mass. Tumor cells are round to polygonal fairly uniform in size with round to oval central nuclei, occasional prominent nucleoli, and cytoplasmic clearing (H&E, 400X).

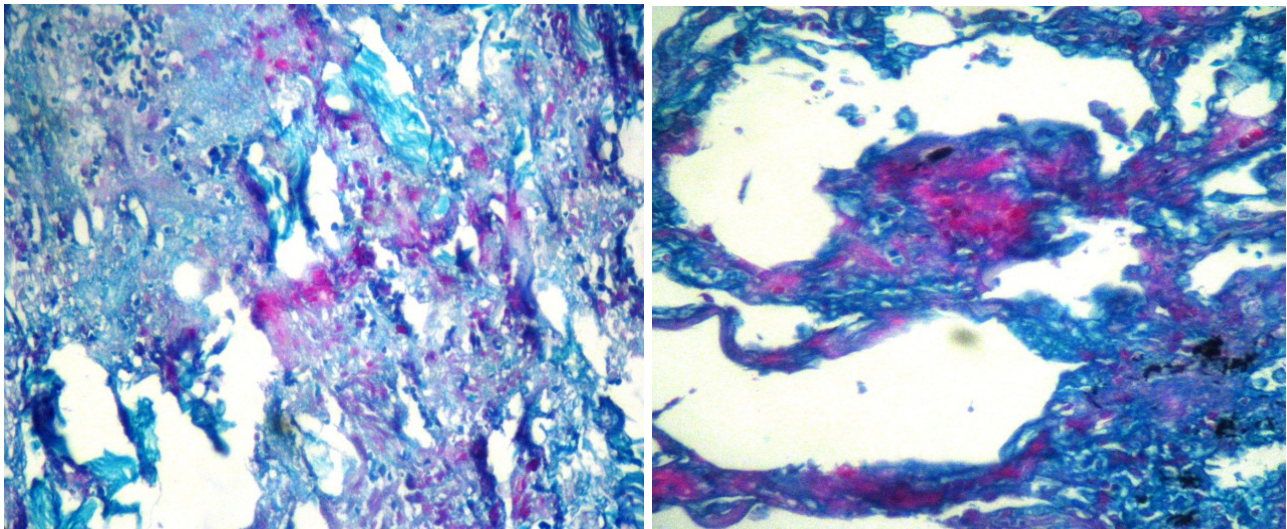


Figure 5. Special stain using Periodic Acid Schiff (PAS) of the mediastinal mass of a 22-year old male who presented with chest pain. Right figure shows a good working positive control (right) while the left shows a positive reaction for glycogen (left).

was made on a routine chest X-ray. Radiologically, these tumors are seen as bulky, well-circumscribed masses occasionally extending to both sides of the midline. On computed tomography scans, seminomas are large and coarsely lobulated, with homogeneous attenuation equal to that of soft tissue.⁶

Regardless of the pathologic subtype, the mediastinal germ cell tumors have a predilection for patients in the first three decades of life. Among the malignant germ cell tumors, males are affected far more commonly than females.⁷

The exact pathogenesis of germ cell tumors in the mediastinum is still uncertain. A number of theories have been presented to explain the etiology of extragonadal seminomas. Some authors have proposed that it may have come from primordial germ cells misplaced during their migration along the midline from the yolk sac to the embryonic gonadal ridge.⁸ Friedman proposed that mediastinal germ cell tumors originate from germ cells that were deposited in the thymus during embryogenesis. He also suggested that germ cells may be distributed widely to the thymus,

brain, liver and bone marrows during development.⁹ Some authors suggested that germinal cell tumors arise from a maldevelopment of the thymic gland during embryogenesis.¹⁰ More recently, Rosai et al suggested that mediastinal germ cell tumors may have originated from myoid cells that are normally present in the thymus.¹¹ Other authors have contended that the pathogenesis of these tumors is different from that of testicular tumors, based on results of ploidy studies by flow cytometry.¹² Although the exact histogenesis of mediastinal seminomas has still not been determined, recent data garnered from molecular studies appear to indicate that they may represent a distinctive and separate entity from gonadal seminomas.¹³

The median tumor size in the current series was 4.6 cm for mediastinal sites and 7.2 cm for retroperitoneal sites. Aggregate measurement of the gross specimen in this case is 6 cm x 4.5 cm x 1.0 cm. Primary extragonadal seminoma of the mediastinum and the retroperitoneum grow slowly and produce few symptoms during the initial stages making these tumors usually bulky at presentation. Symptoms are often

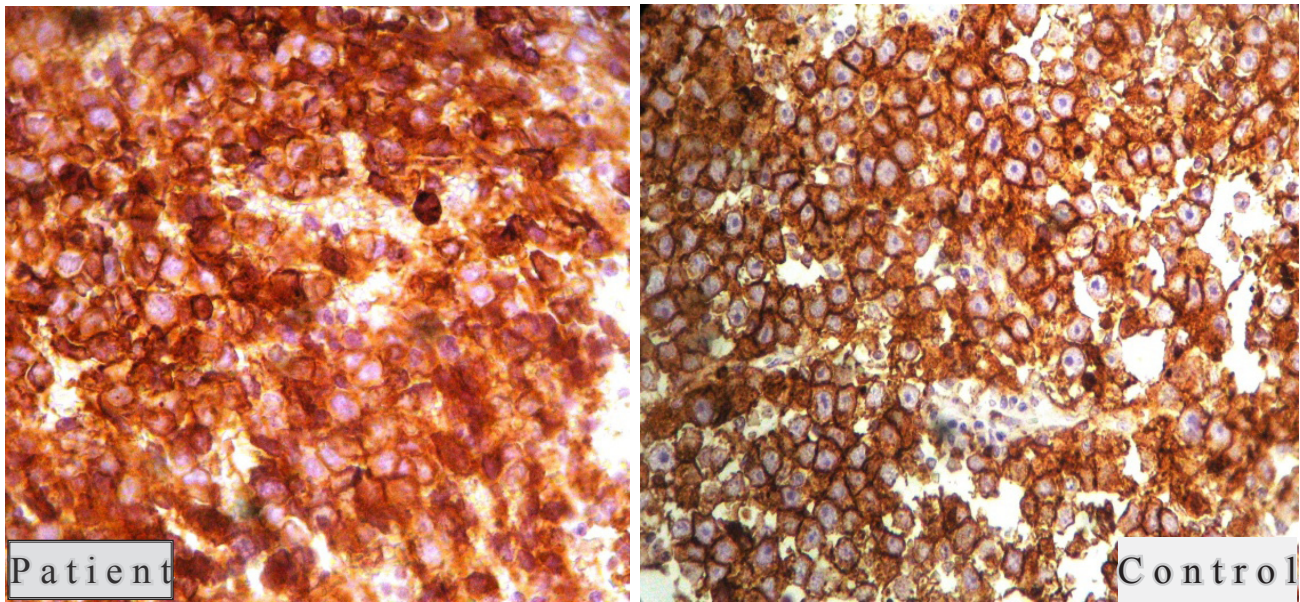


Figure 6. Immunohistochemistry using PLAP of the mediastinal mass of a 22-year old male who presented with chest pain. Right figure shows a good working positive control while the left figure showed epithelioid cells as strongly positive.

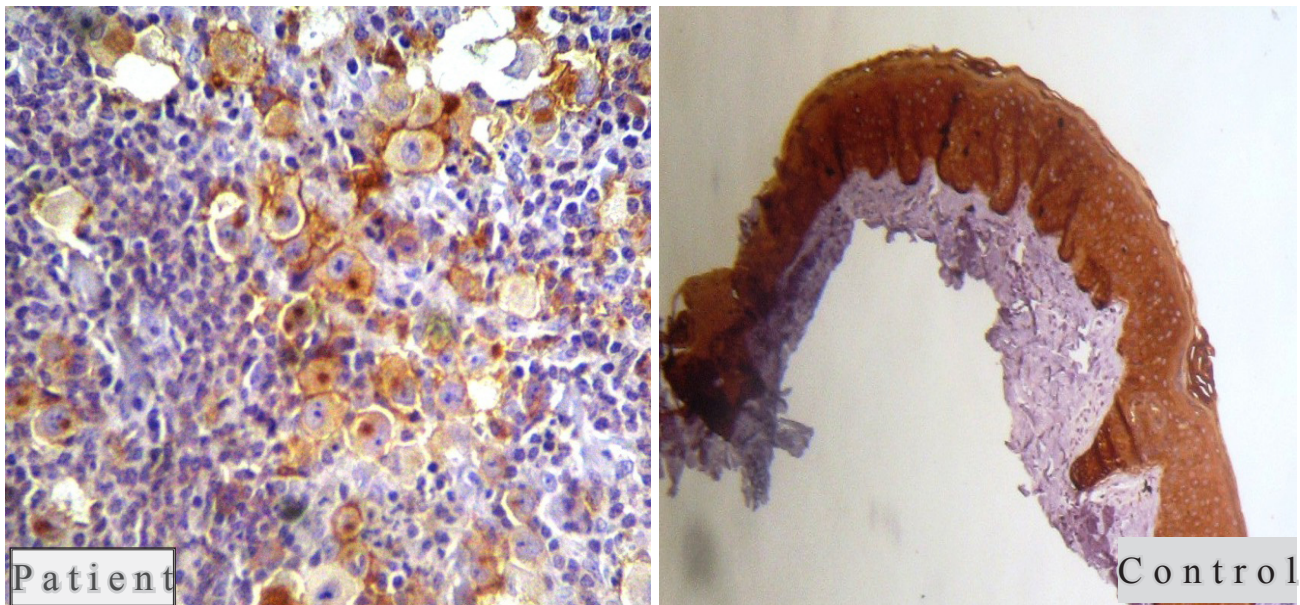


Figure 7. Immunohistochemistry using pancytokeratin proteins AE1-AE3 of the mediastinal mass of a 22-year old male who presented with chest pain. Right figure shows a good working positive control while the left showed focal faint staining.

due to invasion of surrounding structures as these tumors enlarge. No major difference in the frequency of distant metastases is noted between retroperitoneal and mediastinal tumors. Infrequently distant metastases have been reported at the time of presentation.^{2,14} Retroperitoneal tumors are

generally considered to be metastatic coming from gonadal lesions, whereas the origin of primary mediastinal and pineal lesions has been unresolved.¹⁵ Microscopically, the mediastinal germinoma is histologically identical to testicular germi-nomas. It is seen forming sheets of medium

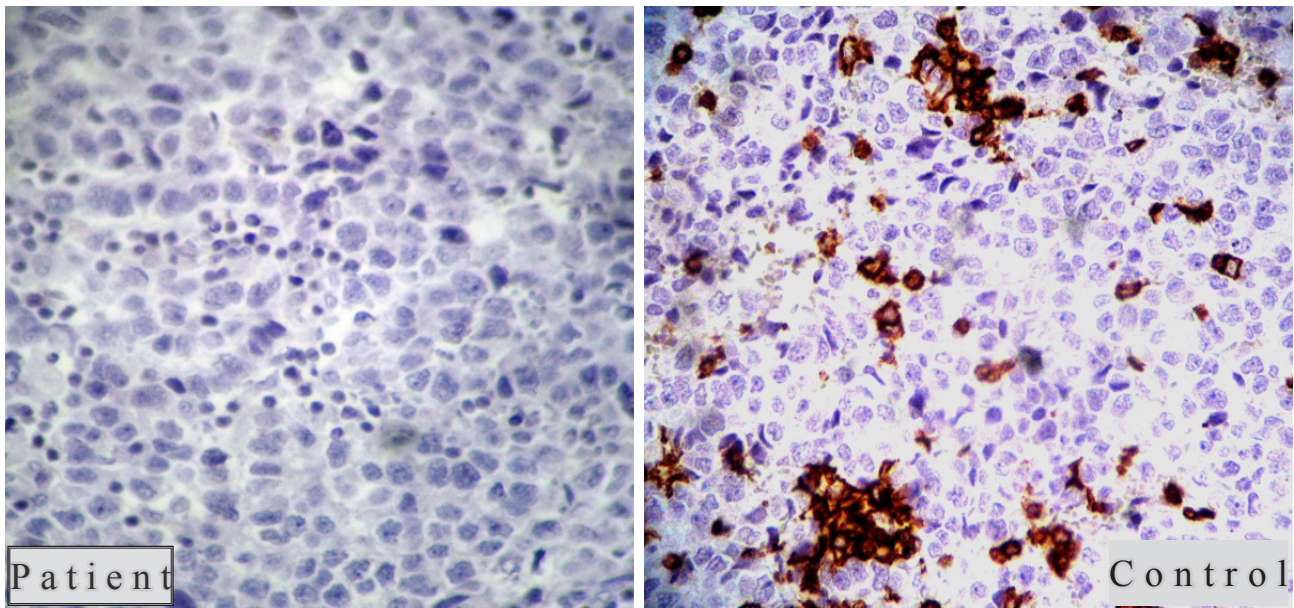


Figure 8. Immunohistochemistry using CD30 of the mediastinal mass of a 22-year old male who presented with chest pain. Right figure shows a good working positive control while the left showed negative reaction.

to large round-to-polygonal cells in a loose fibrovascular stroma. A mild-to-moderate lymphoid infiltrate in the stroma or among the tumor cells is seen in all the cases.¹⁶ Seminomas of the mediastinum, however, may display some distinct histopathologic characteristics not seen in their gonadal counterparts. In approximately 27% of the cases, remnants of thymic tissue within the tumor or at the periphery of the mass can be identified. Another distinguishing feature of mediastinal seminomas, observed in approximately 10% of our cases, was prominent cystic change simulating a multilocular thymic cyst.⁴

Immunohistochemical stains demonstrate a strong positive reaction with Placental Alkaline Phosphatase (PLAP) in 80% of the tumors. A marked dot-like pattern of staining was noted in 75% of cases with CAM 5.2 low-molecular-weight keratins and 70% of cases showed weak cytoplasmic staining with a broad-spectrum keratin. Focal cytoplasmic positivity was observed in scattered seminoma cells in 70% of the cases. In about 5% of cases, HCG

was found to be focally positive in single isolated mononuclear seminoma cells. Antibodies against CEA, EMA, or AFP are negative for staining.⁴

CD117 positivity in a cell membrane or paranuclear Golgi pattern is common.¹⁷ A helpful adjunct to the differential diagnosis of tumor in this location is a weak cytoplasmic immunostaining observed with antibodies against broad-spectrum keratins seen in about 70% of cases. This keratin reaction displayed by these tumors should not be misinterpreted as frank epithelial differentiation, as in thymoma or thymic carcinoma. It is recommended that immunostains in this context should be applied in the form of a panel that also includes germ cell tumor markers and other markers of differentiation. Ultimately, the peculiar paranuclear dot-like pattern of staining with CAM 5.2 low-molecular-weight keratin antibodies, a feature that is not associated with thymoma or thymic carcinoma, should alert the pathologist to the possibility that she or he is dealing with a seminoma.⁴

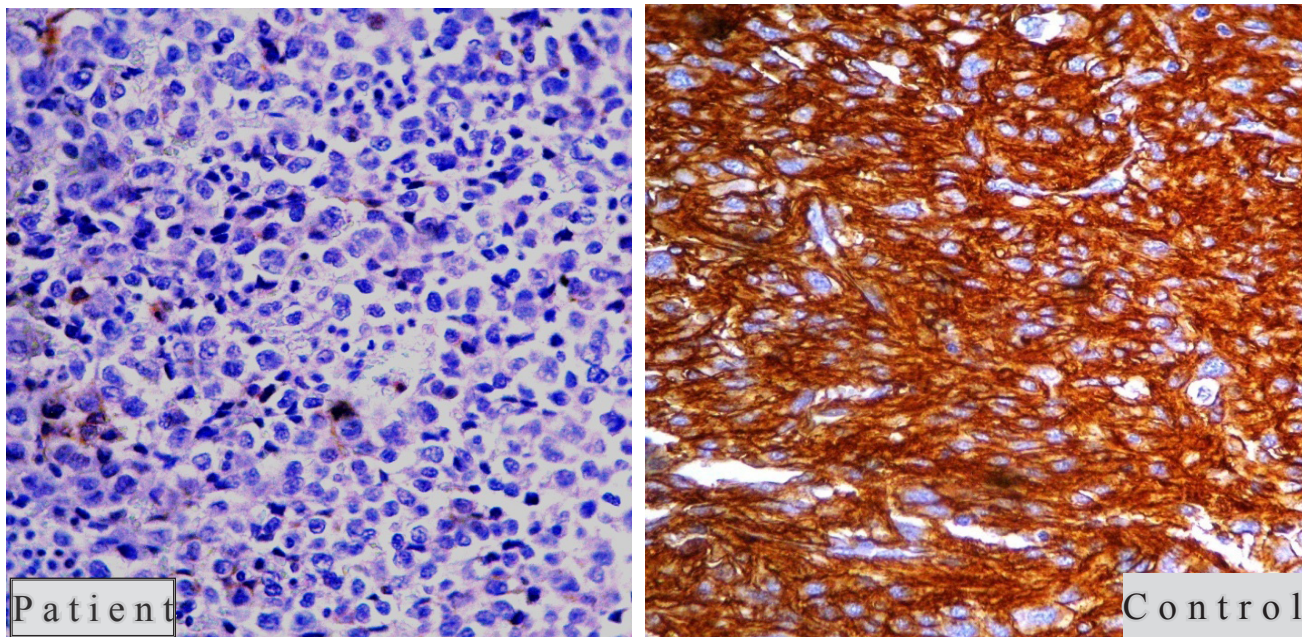


Figure 8. Immunohistochemistry using CD117 of the mediastinal mass of a 22-year old male who presented with chest pain. There is a good working positive control (right) is occasionally expressed in rare tumor cells (left).

The histomorphology of this mediastinal tumor may mimic other lesions in the area notably tumors of thymic origin such as thymoma as mentioned above particularly of WHO type B3 and thymic carcinomas with residual intratumoral lymphocytes. The thymic tumors usually are strongly cytokeratin positive, PLAP negative and CD117 negative. Our case showed an immunoprofile of being strongly PLAP positive indicating its germ cell nature and nonsignificant staining for pancytokeratin. Furthermore, the characteristic cytoplasmic clearing seen in seminomas cell are present in this case. The peculiarity of the current case is its negative reaction for CD117, which is usually positive for a majority of cases. The tumor cells are focally positive for glycogen (PAS- positive, mucarmine-negative), which is supportive for seminoma.⁴

The largest data gathered regarding prognosis of mediastinal seminoma was provided by the International Germ Cell Consensus Classification (IGCCCG). There are 41 patients with primary mediastinal seminoma and 45 patients with retroperitoneal seminoma out of 5000 patients with

malignant germ cell tumor were included, yielding 5-year progression-free and overall survival rates of 80% and 88% compared with rates of 85% and 88%, respectively. However, the IGCCCG analysis did not provide a separate prognostic report in patients with extragonadal seminoma. Nonpulmonary visceral metastases are the only prognostic factor identified for all patients with metastatic seminoma. No significant differences in progression and overall survival exists between patients with mediastinal and retroperitoneal disease sites. The factors that were identified in a univariate analysis as associated with poor prognosis are: liver involvement, more than two sites of metastatic disease, and the presence of nonpulmonary visceral metastases. The presence of nonpulmonary visceral metastases corresponds to the “intermediate prognosis” criteria.²

Conventional therapy has been surgical biopsy or debulking initially followed by radiotherapy for localized disease. One-third of patients relapsed, following radiotherapy, with distant metastases or marginal recurrences despite being known

as radiosensitive.¹⁸ In patients with extragonadal seminoma, a 5-year survival rate of 90% is achieved with adequate chemotherapy with cisplatin. Present data shows that there is no difference in long-term survival between patients with non-seminomatous extragonadal germ cell tumor to that of primary retroperitoneal or mediastinal seminoma location.² Complete surgical excision of Stage I, well-circumscribed mediastinal seminomas (without invasion into adjacent organs) followed by local radiation therapy would be the optimum treatment for these patients. A more aggressive therapeutic approach for adequate local control and prevention of metastases is needed for more advanced disease.⁴ For this case, a thoracotomy was performed with subsequent improvement of condition. In majority of cases, patients with mediastinal seminomas have a good prognosis regardless of the treatment approach. The role of surgical resection as primary management is evolving.¹⁹

Conclusion

Mediastinal seminoma is a rare, distinctive clinicopathologic entity with a very favorable prognosis with a wide range of treatment modalities. Parenthetically, the diagnosis of seminomatous lesions, even in unusual sites, based on the typical histologic features is paramount. The histomorphology can usually be confirmed by immunohistochemistry, particularly LAP and CD117 in achieving a definitive diagnosis. In the absence of CD117 expression, the diagnosis can still be achieved with its classic morphology supported by special stains for glycogen is seen in our case. When complete excision is not possible, a biopsy is performed to confirm the diagnosis and an alternative treatment is started. Because these tumors are quite responsive to radiation, performing high-risk surgery (with its potential for injuring mediastinal structures) maybe unnecessary if a definitive diagnosis of mediastinal seminoma is established, given its good prognosis and excellent response to a variety of treatment options.

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