Original Article

Unusual lesions of the mediastinum

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ABSTRACT

Objectives: To study unusual lesions in the mediastinum, which do not originate from the thymus, lymph nodes, neural tissues or germ cells, and tissues that normally engender pathologic lesions in the mediastinum. **Materials and Methods:** Of the 65 cases seen, 12 unusual lesion were encountered in a 5½ year period from 2006 to 2011. **Results:** Two cases of nodular colloid goiter and one each of the mediastinal cyst, undifferentiated carcinoma, and Langerhans cell histiocytosis (LCH) affected the anterosuperior mediastinum. In the middle mediastinum, one case each of the mesothelioma, malignant gastrointestinal stromal tumor (GIST), squamous cell carcinoma (SCC), solitary fibrous tumor (SFT), and pleomorphic sarcoma (PS) was seen. One case of meningeal melanocytoma (Mme) and primary pleural liposarcoma (PL) involved the posterior mediastinum. Persistent disease was seen in LCH after 2 years. Of all the cases with malignant lesions, only the patient with SCC was alive after 1 year. **Conclusion:** The cases of primary and SCC, LCH, melanocytoma, liposarcoma and PS, and GIST are unexpected and very rarely have paradigms in the mediastinum. Radiologic impression and knowledge of the compartment where these lesions arose from hardly assisted in arriving at a definitive opinion as the lesions were not typical of this location. A high index of suspicion and the immunohistochemical profile facilitated the final diagnosis.

KEY WORDS: Langerhans cell histiocytosis, malignant gastrointestinal stromal tumor, mediastinum, meningeal melanocytoma, solitary fibrous tumor

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INTRODUCTION

Lesions of the mediastinum mostly arise from the unique motley of structures native to this well-constrained space. In the anterior mediastinum, lesions arising from the thymus, lymph nodes as well as germ cell tumors are more common. From the middle mediastinum, lesions of the lymph nodes, along with the incidence of metastases are common. The posterior mediastinum witnesses tumors of neural origin as well as lymph node lesions. Mediastinal cysts are, however, seen in both the middle mediastinum and posterior mediastinum. The classification of neoplasms arising in the mediastinum is difficult and uncertain due to the variability in their morphological appearance and clinical behavior. Yet, statistically, some lesions arise in the mediastinum with sufficiently low frequency. In a 5½-year study at our center, there were 12 such cases from a total of 65 which was unusual.

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MATERIALS AND METHODS

This study was conducted from January 2006 till June 2011 in the Department of Pathology, Kasturba Medical College, Mangalore, Karnataka, India. The patient's identification details were noted, along with the clinical history and laboratory investigations. The tissue was fixed in 10% buffered formalin, processed by paraffin embedding and stained with routine hematoxylin and eosin (H and E). Special stains and immunostains were done wherever necessary for evaluation and confirmation. A total of 12 unusual mediastinal lesions were collected and were identified based on morphology and special stains.

Immunohistochemistry (IHC) was performed on paraffin sections using a two-step process; first, the binding of the primary antibody to the antigen of interest and second, the detection of the bound antigen by a chromogen. Appropriate positive and negative controls were used. The various antibody markers utilized were cytokeratin (AE1 + AE3, Monoclonal, BioGenex, San Ramon CA, USA), S100 (Polyclonal, Dako Corporation, Carpintaria, CA, USA), and CD34 (Polyclonal, Dako Corporation, Carpintaria, CA, USA). The immunohistochemical stain used was EnVision detection kit from Dako Corporation with diaminobenzidine (DAB) as chromogen. The brief procedure for IHC is documented in the following steps:

1. Sections are taken on poly-L-lysin slides, incubated for 12 h at 37°C and for 15 min at 60°C
2. After treating the slides in xylene, methanol, and H_2O_2, tap water is run on the slide
3. The sections are treated with citrate buffer at pH 6 and the antigen is retrieved in a microwave, washed in tap water, and treated with working solution (Tris buffer at pH 7 and NaCl 0.9%)
4. Power block reagent and antibody are given for 1 h. This antibody is from the kit and needs no dilution
5. After washing with the working solution, "EnVision" is added and made to stand for 40 min
6. Washing with working solution is done and chromogen is added
7. Washing with working solution and tap water is done
8. Counterstaining with hematoxylin is done.

RESULTS AND OBSERVATIONS

The usual lesions were thymic (15 neoplastic and seven nonneoplastic), nodal (i.e. of lymph nodes; four each of Hodgkin and non-Hodgkin lymphomas, and 11 nonneoplastic lesions), of germ cell origin (seven neoplastic lesions), and neural (four benign and one malignant tumor). The various unusual lesions encountered are shown in Table 1. The age of the patients ranged from 1½ years to 65 years. Most of the lesions were in males with male: female (M: F) ratio being 2:1. The cases of goitre, meningeal melanocytoma (Mme) and solitary fibrous tumor (SFT) occurred in females. The malignancies occurred mostly in the elderly age group with the exception of malignant mesothelioma in a 21-year-old male and a sarcoma in a 30-year-old male. The lesions belonging to the anterior mediastinum were the retrosternal goiters (RGs), mediastinal cyst, poorly differentiated carcinoma (PCa), and Langerhans cell histiocytosis (LCH). The middle mediastinum contained the lesions of mesothelioma, malignant epithelioid GIST, squamous cell carcinoma (SCC), SFT, adenocarcinoma, and pleomorphic sarcoma (PS). The cases of Mme and primary pleural liposarcoma (PL) were found in the posterior mediastinum. All the cases with lesions presented with chest symptoms of breathlessness or pain or both. The case of SCC unpredictably and the Mme expectedly exhibited upper thoracic spine pain radiating to the upper limbs and there was pinprick sensation with lower limb paresis in Mme. Pleural effusion without any diagnostic cells was observed in the cases of PS and mesothelioma. Computed tomography (CT) scans showed tumors in the various compartments where these tumors were located. Not only was the diagnosis not provided by radiology but also the biological behavior, that is, whether the lesion was benign or malignant could not be surmised in cases of most of these tumors. The case of mediastinal cyst displayed smooth circumscription, whereas Mme showed a dumbbell-shaped tumor parted into the intraspinal and paraspinal extensions. While both the cases of liposarcoma and SFT produced collapsed lung, the SFT due to its widespread nature added to necrosis in the lung parenchyma, thus paradoxically suggesting malignancy. The patient with LCH also suffered from fever and mild hepatosplenomegaly at the outset.

The pathological features of goiter were typically that of multinodular type [Figure 1] and the mediastinal cyst had a thin wall with attenuated cuboidal lining.

In two patients in their mid-60s with carcinoma, one poorly differentiated and the other with SCC were discovered. The patient with PCa had diaphragmatic palsy and a fungating, unresectable mass. Pleomorphic cells in sheets were observed on histopathology. Cytokeratin positivity on IHC confirmed the diagnosis of PCa. The patient died within 3 months. The patient with SCC was

Table 1: Distribution of the mediastinal lesions

Anterosuperior mediastinum	
Nodular colloid goiter	2
Mediastinal cyst	1
Carcinoma (undifferentiated)	1
LCH	1
Middle mediastinum	
Mesothelioma	1
Malignant epithelioid GIST	1
Squamous cell carcinoma	1
SFT	1
PS	1
Posterior mediastinum	
Mme	1
Primary pleural liposarcoma	1

LCH: Langerhans cell histiocytosis, GIST: Gastrointestinal stromal tumor, SFT: Solitary fibrous tumor, PS: Pleomorphic sarcoma

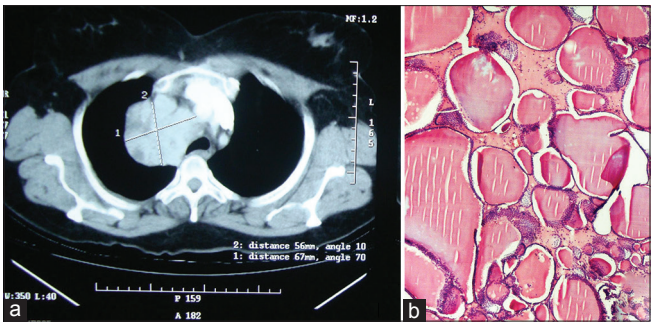

Figure 1: (a) Computed tomography scan - large soft tissue mass in the superior mediastinum extending anteriorly. (b) (H and E, ×100) goiter showing variably sized colloid filled follicles

treated with combination radio and chemotherapy and was alive at 1-year follow-up. In both the cases, the tissue of origin remained obscure.

LCH was presumptively diagnosed in an 18-month-old child on CT-guided fine-needle aspiration (FNA) [Figure 2] of the mediastinal mass followed by confirmation with Trucut biopsy and IHC for S100 protein. Biopsy of the liver demonstrated concentric periductal fibrosis resembling primary sclerosing cholangitis but Langerhans cells were inconspicuous. Biopsy from a few skin lesions revealed unequivocal histology of LCH. The bone marrow examination did not disclose any evidence of involvement. At 2 years of follow-up, the child had received three cycles of chemotherapy but there was persistent hepatosplenomegaly.

Malignant mesothelioma (sarcomatoid variant) was diagnosed in a resected mass measuring 18 cm × 10 cm × 6 cm with variegated and necrotic areas in a 21-year-old man. Mildly pleomorphic spindle cells

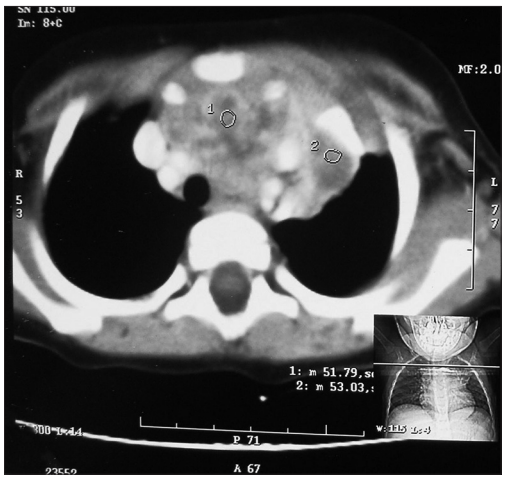

Figure 2: Computed tomography scan - large heterogenous mass lesion in anterosuperior mediastinum contiguous with small nodule in the inferior left lobe of thyroid

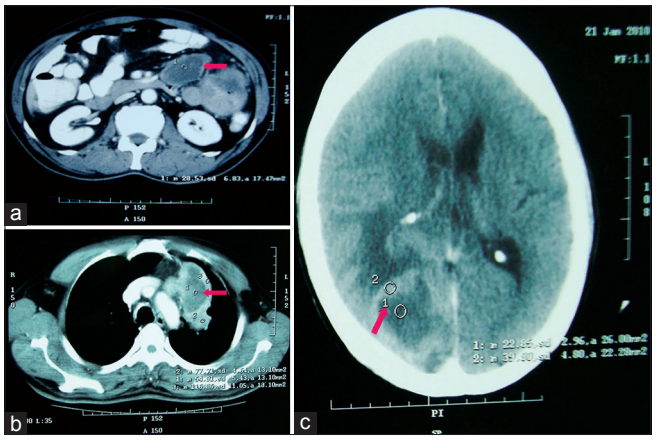

Figure 4: Computed tomography scans. (a) Tumor attached to small intestine. (b) Tumor metastatic to the left mediastinum (NOT lymph node). (c) Tumor metastatic to the brain

in indistinct fascicles, an imprecise storiform pattern, a few mitotic figures, and abundant areas of necrosis were evident in the tissue sections [Figure 3]. IHC showed cytoplasmic positivity for calretinin and cytokeratin.

Metastatic malignant epithelioid GIST was diagnosed on tru-cut biopsy of the mediastinal mass showing hyperchromatic malignant cells preponderantly in sheets positive for CD117. The initial small intestinal mass had shown a similar morphology. The patient expired 1 month later with brain metastases [Figure 4].

SFT [Figure 5] was seen intraoperatively attached to the visceral pleura of the left lung compressing it. The solid-cystic mass on microscopy demonstrated dark, elongated, and somewhat hyperchromatic nuclei in ill-defined fascicles, prompting a diagnosis of neurofibroma. The characteristic

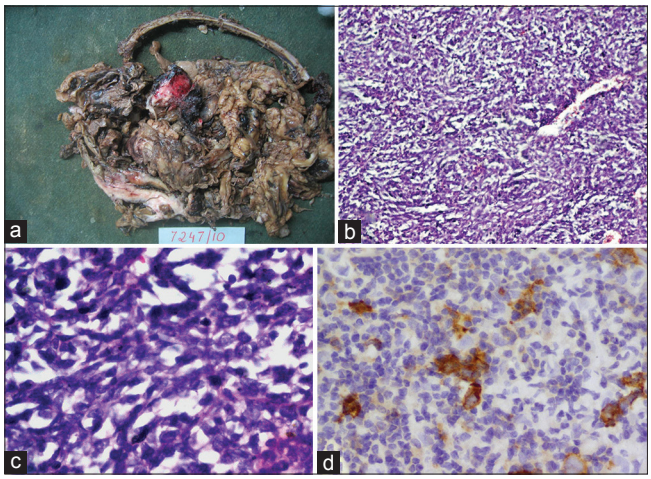

Figure 3: (a) Gross - Variegated tumor attached to membranous tissue with part of rib. (b and c) (H and E, ×100 [a], ×400 [c]) spindle shaped cells in sheets, vague fascicles and mitotic figures. (d) (×400) calretinin positivity in some cells

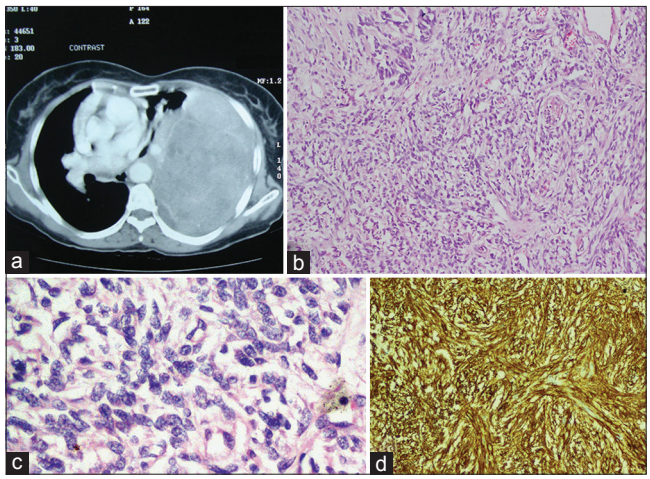

Figure 5: (a) Computed tomography scan - soft tissue density mass 21 × 0.5 cm with areas of heterogenous nodular enhancement and necrosis in the entire left hemithorax. (b and c) (H and E, ×100 [b], H and E, ×400 [c]) elongated cells with oval nuclei in patternless pattern. (d) (×100) diffuse, strong positivity with CD34

vascular pattern was seen on review. CD34 positivity and S100 negativity favored the final verdict of SFT. The patient was alive and without disease at 1-year follow-up.

The woman with lower limb weakness had a resected brown black nodular mass measuring 4.5 cm × 3 cm × 2 cm sent for microscopy. A cellular tumor composed of nests and whorls of heavily pigmented meningothelial cells with oval nuclei, granular chromatin, and distinct nucleoli in most of the cells was seen that decolorized with melanin bleach. The morphology was similar to its initial presentation. A reticulin stain done on the earlier tumor showed accentuation of reticulin fibers surrounding the nests of cells. Both the preliminary and the recrudescent tumor exhibited lack of mitoses, necrosis, or neural parenchymal invasion. IHC done on the original tumor demonstrated positivity for S100 and HMB45. Thus, a diagnosis of Mme was delivered [Figure 6]. Relapse of the disease was possibly due to inadequate excision of the primary tumor. After discharge, she was immediately lost to follow-up.

Intraoperatively, a large, fungating mass in the middle mediastinum straddling the lungs and pleura bilaterally could not be totally enucleated in both the sarcomas. In one case, bizarre pleomorphic spindled cells in vague storiform pattern in a myxoid background urged us to afford the diagnosis of PS since the morphology resembled its soft tissue counterpart. In the other, pleomorphic spindled tumor cells, along with numerous lipoblasts were spotted containing single to multiple vacuoles. The background was myxoid and included areas with branched capillaries. A diagnosis of mixed liposarcoma (myxoid with well differentiated areas) was offered [Figure 7]. Both the patients had expired at 3 months follow-up.

DISCUSSION

The reason for inclusion of mediastinal goiter and cyst among unusual lesions is the fact that thyroid is a gland situated in close apposition to the laryngeal cartilages. It coming down in the mediastinum, though rare, is definitely unusual and a suitable explanation for the migration is still wanted. The mediastinal cyst apparently did not have an organ of origin. The tempting proposal of an enterogenous/bronchogenous[1] cyst needed evidence but the attenuated lining and the fibrous wall precluded any further investigation and the fact that the patient attained symptomatic remission deterred immunohistochemical investigation on this specimen. Mediastinal cysts may be found at any age, though gastric cysts are more common in childhood.[1]

In a very large series consisting of 2,263 thyroidectomies, 355 cases were mediastinal goiters without any mention of malignancies in this unexpected position.[2] Thus, the mediastinal position may not significantly aggravate the risk of malignancy. Another peculiarity of this lesion is its propensity to cause tracheomalacia that a goiter in a normal position is not associated with.[3] In the present study, there was one case of "forgotten goiter;"[3] a mediastinal goiter with a previous history of thyroidectomy. "All Mediastinal goiters should be removed, for the fact that they are mediastinal is proof that they show a tendency to grow."[4] Such expedition is not required in the case of a goiter in the normal position where a delay extending for months to years may be accepted. These patients mostly belonged to the adult age group below 50 years of age,[2,4] as did our patients (age group of 30-40 years)

In a comparable Indian scenario, two and one of 56 cases had retrosternal thyroid and cyst, respectively. The ages are not mentioned.[5]

In most cases, LCH presents in older children and adults as a unifocal disease that typically affects the bone and less commonly the lymph node, skin, or lung. Multifocal disease commonly affects young children and can be either unisystem or multisystem.[6] Isolated extraosseous disease is far less common.[7] In children, LCH can present from the newborn period to 15 years, with a peak incidence at the age of 1-4 years, and males are more commonly affected than females.[6] The presentation of LCH in an 18-month-old male child was

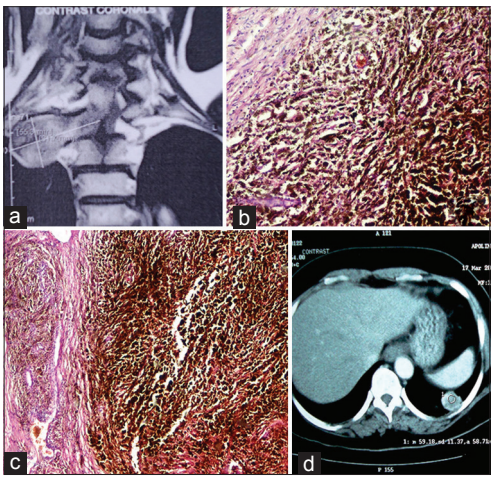

Figure 6: (a) Computed tomography scan showing dumb-bell shaped tumor at initial presentation (file picture). (b and c) (H and E, ×100). (d) CT scan of the paraspinal tumor

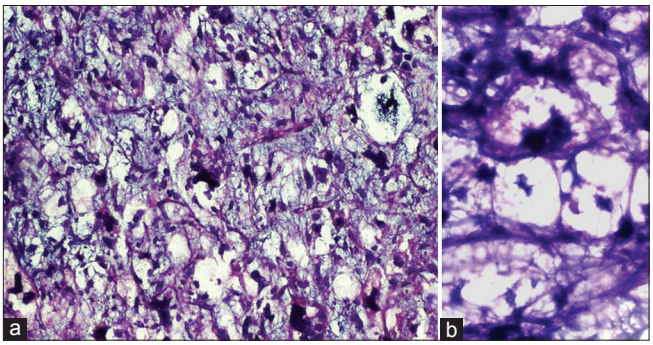

Figure 7: (a and b) (H and E, ×100, a; ×400, b) Characteristic vacuolated lipoblasts in a loose, myxoid background

thus, concordant with this observation. Though lymph node enlargement is observed in approximately 30% of symptomatic patients, involvement of hilar nodes is relatively uncommon.[7] Rare reports of anterior mediastinal masses observed in histiocytosis are also present in the literature.[8] Sclerosing cholangitis in the liver, coupled with the skin lesions, with concurrent mediastinal node involvement designate this disease as multisystem LCH. In one large Indian series consisting of 69 children whose age ranged from 2 months to 12 years, 21 cases had lymphadenopathy and 37 had multisystem involvement with some form of organ dysfunction. Mediastinal involvement was not reported though a variety of lung pathologies, including pleural effusion, was observed in 19 patients.[9] Immunostaining with cluster of differentiation 1a (CD1a) is the definitive criterion[9] but since these cells also stain with S100, it was done to support the diagnosis as CDIa was not available.

The sarcomatoid mesothelioma does not shed cells in the pleural fluid unlike the epithelioid variant.[10] The other variants are the biphasic and the extremely rare small cell, clear cell, and deciduoid, lymphohistiocytoid, and pleomorphic[11] Alistair *et al.* noted the connection of asbestos exposure to the progression to malignant mesothelioma to be 90%.[12] The spontaneous rate (without asbestos exposure) of development of malignant mesothelioma is around 1 per million[13] but the age adjusted rate is 5 per million in the 40-50-year age group and 17 per million for men in their 70s and 80s.[14] In the present study, the mediastinal involvement of malignant mesothelioma was World Health Organization (WHO) stage T3[15] and this event adds another facet of extreme infrequency to this rare case. Furthermore, any occupational history was missing. The immunohistochemical profile in the sarcomatoid variant consists of cytokeratin (AE1/AE3), podoplanin and calretinin (55%), and CK7 (100%) among others.[11]

SFT rarely occurs in the mediastinum in adults (28-74 years). It may represent either an extension from primary pleural tumor or occur primarily, derived from the mediastinal (including thymic) stroma. On an average, it accounts for 15% of all SFTs and 25% of all extrapleural SFTs but morphologically as well as immunophenotypically (CD34+ in greater than 90% tumors), pleural and extrapleural SFTs are alike.[16,17] In a study carried out by Magdeleinat *et al.* out of 60 resected SFTs of the pleura, the mediastinal relation was obtained in as rare as two cases.[18] The prognosis of benign SFTs of the pleura is excellent after surgery. However, individual studies have pointed out to the high possibility of recurrence.[19,20] Thus, follow-up for a prolonged period is prescribed to the treating surgeon.[20] In the present study too, the SFT arose from the pleura and the patient was doing well at 1-year follow-up. The immunophenotype of SFT consists of diffuse CD34 and CD99[21] positivity and CD34 positivity was seen in the present case. The differential diagnoses prominently are hemangiopericytoma, benign fibrous histiocytoma, synovial sarcoma, and dermatofibrosarcoma protuberans. Fibrosarcoma can rarely be confused with SFT but it has a herring bone pattern of its fascicles, along with no specific markers even though CD34 may be positive, particularly in cases arising with SFT. The conspicuous vascular pattern should be missing, along with the absence of variable cellularity and hyalinization throughout the lesion.[21]

Mme is a benign lesion arising from leptomeningeal melanocytes that may mimic its malignant counterpart melanoma. Lesions of the spine usually occur in thoracic region in the extramedullary locations and present with spinal cord compression symptoms that usually include lower extremity weakness or numbness. Close follow-up monitoring is important even after gross total surgical resection since these tumors can recur.[22] Since the tumor is aggressive despite being benign, it may not be confined to the spine and an occasional tumor has also been reported as a dumbbell-shaped mass with both intraspinal and intrathoracic components just like the recurrent tumor in the present study.[23] Since population-based incidence is not available, it may be safe to infer that the tumor is rare.

Pachter and Lattes[24] in their study of mesenchymal tumors of the mediastinum encountered two cases of liposarcoma. Both cases presented with severe symptoms of pain and cough. There is usually extensive local invasion. Both the lesions were huge (~15 cm) and total removal of the lesions was not possible. Histologically, both tumors were poorly differentiated and had marked cellular pleomorphism, nuclear atypia, and numerous mitotic figures. One patient died 6 months later and the other was lost to follow-up.

The elderly man with liposarcoma in the current study had a deficient excision since pleural and descending aortic adhesions were discovered intraoperatively. Diagnosis too was not forthcoming because of its rarity in the mediastinum. This patient too died at the 3-month follow-up. There has been a solitary instance in India of a myxoid liposarcoma metastatic to the left lung and posterior mediastinum suggested on aspirate by CT-guided FNA.[25]

The IHC of PS is nonspecific. It is advisable to check for specific markers and if these are negative, only then arrive at this diagnosis. So a definite panel does not exist though CD34 may sometimes be positive. The close congener of this tumor, the atypical fibroxanthoma found in the skin may be positive for CD10, CD68 with focal smooth muscle actin (SMA), and CD34 positivity though they are not definitive but are supportive in the diagnosis.[26]

CONCLUSION

The 12 cases offered in the present study of unusual mediastinal lesions were widely diverse in their clinical appearance, radiologic impression, and morphologic

interpretation. Due to their recondite location, morphologic diagnosis was not easily forthcoming and radiology too was shortcoming. Even knowledge of the compartment in the mediastinum where these lesions arose was of little help. The microscopic appearance of each of these lesions was hardly in harmony with what is expected and generally seen in this location. The cases of primary squamous cell carcinoma and SCC, LCH, melanocytoma, liposarcoma and PS, and GIST are unanticipated and very rarely have paradigms in the mediastinum. A high index of suspicion and immunohistochemical expression played a substantial role in arriving at the final diagnosis. It was, however, unfortunate that most of these unexpected malignant lesions had a bad prognosis; death within a few months of diagnosis was the consequence in many cases.

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