GMR
The Original

CLINICOPATHOLOGICAL SPECTRUM OF MEDIASTINAL LESIONS WITH IMMUNOHISTOCHEMICAL CHARACTERIZATION OF MEDIASTINAL NEOPLASMS

H. Kamaladevi[1]*, R. Jayapreethy[2], R. Narayana Vadivoo[3]

[1] Assistant Professor, Department of Pathology, Madras Medical College, Chennai, Tamil Nadu, India. Email: kamalaharikrishnan@gmail.com .
[2] Assistant Professor, Department of Pathology, Government Vellore Medical College, Vellore, Tamil Nadu, India. Email: jayaramadass@gmail.com
[3] Assistant Professor, Department of Pathology, Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India.
Email: ramkarthi27@gmail.com
*Corresponding Author: H. Kamaladevi, kamalaharikrishnan@gmail.com

ABSTRACT

Background: Mediastinal lesions comprise a heterogeneous group of congenital, inflammatory, benign, and malignant disorders accounting for approximately 3% of all thoracic tumors and often present significant diagnostic challenges because of their varied histopathological features and anatomical complexity. Histopathological examination remains the diagnostic gold standard, while immunohistochemistry (IHC) serves as an indispensable adjunct in accurately classifying morphologically overlapping lesions and determining their tissue of origin.

Materials and Methods: Prospective observational study conducted over a two-year period at the Institute of Pathology, Madras Medical College, Chennai. Eighty-one patients with mediastinal lesions who underwent CT-guided biopsy, core needle biopsy, or surgical excision were included. Clinical findings, radiological features, histopathological diagnosis, and immunohistochemical profiles were analyzed. Immunohistochemistry was performed selectively in diagnostically challenging cases using lineage-specific antibody panels to establish definitive diagnoses.

Results: The mean age of the study population was 43.8 years, with a male predominance (69.1%). Breathlessness (44.4%) was the most frequent presenting symptom, while the anterior mediastinum was the predominant anatomical compartment (91.4%). Thymic lesions constituted the largest diagnostic category (37.0%), with type B thymoma representing the commonest thymic neoplasm. Metastatic tumors accounted for 18.5% of cases, followed by granulomatous lesions (11.1%), lymphomas (6.2%), cystic lesions (6.2%), germ cell tumors (6.2%), and neurogenic tumors (3.7%). Immunohistochemistry proved particularly useful in differentiating thymic epithelial tumors, lymphomas, germ cell tumors, metastatic carcinomas, mesenchymal tumors, and other poorly differentiated neoplasms through the application of appropriate lineage-specific markers.

Conclusions: Mediastinal lesions demonstrate a wide clinicopathological spectrum with overlapping clinical and radiological manifestations. Histopathological examination remains the cornerstone of diagnosis, while immunohistochemistry significantly enhances diagnostic accuracy in morphologically challenging cases. The integration of clinical, radiological, histopathological, and immunophenotypic findings is essential for precise diagnosis and optimal therapeutic management.

KEYWORDS: Mediastinal lesions; Thymoma; Immunohistochemistry; Histopathology; Mediastinal neoplasms; Thymic tumors.

INTRODUCTION

Mediastinal lesions comprise a heterogeneous group of congenital, inflammatory, benign, and malignant disorders arising from the various anatomical structures within the mediastinum. Although they account for only approximately 3% of all thoracic tumors, they encompass a wide pathological spectrum including thymic epithelial tumors, lymphomas, germ cell tumors, neurogenic tumors, cystic lesions, and metastatic malignancies. Their clinical presentation varies from asymptomatic incidental findings to severe compressive symptoms involving the airway, esophagus, and great vessels, making diagnosis challenging.[1–5] Radiological imaging, particularly contrast-enhanced computed tomography (CT), plays a crucial role in localizing mediastinal masses, assessing compartmental involvement, and guiding tissue biopsy. However, considerable overlap in imaging characteristics among different lesions limits the ability of imaging alone to establish a definitive diagnosis. Histopathological examination therefore remains the gold standard for diagnosis, while immunohistochemistry (IHC) serves as an essential adjunct in differentiating morphologically similar neoplasms and identifying their cell of origin.[3–7] Thymic epithelial tumors represent the most common primary neoplasms of the anterior mediastinum in adults, whereas lymphomas and germ cell tumors constitute important differential diagnoses, particularly in younger individuals. Neurogenic tumors predominantly arise in the posterior mediastinum, while metastatic lesions may involve any mediastinal compartment. Appropriate immunohistochemical markers, including cytokeratins, CD3, CD20, TdT, CD117, OCT3/4, S100, calretinin, and TTF-1, significantly improve diagnostic accuracy in challenging cases.[8–13] Accurate pathological diagnosis is essential because the management and prognosis of mediastinal lesions differ

considerably according to the underlying pathology. Despite advances in imaging and immunohistochemistry, comprehensive clinicopathological studies evaluating the spectrum of mediastinal lesions from Indian tertiary care centers remain limited.[1,3,5,14] Therefore, the present study was undertaken to evaluate the clinicopathological spectrum of mediastinal lesions over the study period and to assess the diagnostic utility of immunohistochemistry in the characterization of these lesions.

MATERIALS AND METHODS

Study Design and Study Population:

This prospective observational study was conducted at the Institute of Pathology, Madras Medical College, Chennai. Consecutive patients presenting with mediastinal masses who underwent image-guided biopsy or surgical excision during the study period were included. The study was approved by the Institutional Ethics Committee and conducted in accordance with institutional ethical guidelines. A total of 81 mediastinal lesions received for histopathological examination during the study period were included. Clinical details, radiological findings, operative notes, and laboratory investigations were retrieved from medical records. Patient demographics, presenting symptoms, anatomical location, histopathological diagnosis, and immunohistochemical findings were analyzed.

Inclusion Criteria and Exclusion Criteria

Patients with mediastinal masses who underwent biopsy or surgical excision and had adequate tissue available for histopathological evaluation were included. Specimens with inadequate tissue for definitive histopathological diagnosis or unsuitable for immunohistochemical evaluation were excluded.

Histopathological Examination and Immunohistochemistry

All tissue specimens were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned at 4 μm thickness, and stained with hematoxylin and eosin. Histopathological diagnosis was established according to the World Health Organization (WHO) classification of mediastinal tumors.[11] Immunohistochemistry (IHC) was performed in diagnostically challenging cases to establish the lineage and origin of the lesion. Antibody selection was based on histomorphological differential diagnosis. The immunohistochemical panel included epithelial markers (pan-cytokeratin, CK5/6, p63, CD117, calretinin), lymphoid markers (CD3, CD20, TdT, CD45), germ cell markers (OCT3/4, β-hCG, alpha-fetoprotein, PLAP), neural markers (S100), neuroendocrine markers (synaptophysin), pulmonary markers (TTF-1 and napsin A), and Ki-67 when required for diagnostic confirmation. Diagnostic interpretation was performed by correlating immunohistochemical findings with histomorphological and clinicoradiological features.[8–13]

Data Collection

The following clinicopathological parameters were evaluated:

- Age
- Sex
- Clinical presentation
- Mediastinal compartment involved
- Radiological findings
- Surgical procedure
- Histopathological diagnosis
- Immunohistochemical profile
- Final diagnosis

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using descriptive statistical methods. Continuous variables are presented as mean values, while categorical variables are expressed as frequencies and percentages.

RESULTS

A total of **81 mediastinal lesions** were evaluated during the study period. The clinicopathological characteristics of the study population are summarized in **Table 1**. The mean patient age was **43.8 years** (range, 10–79 years). The highest proportion of patients belonged to the **40–49-year** age group (24.7%), followed by the **20–29-year** and **60–69-year** age groups (18.5% each). There was a male predominance, with **56 (69.1%)** males and **25 (30.9%)** females.

Breathlessness was the most common presenting symptom (44.4%), followed by cough (23.5%), myasthenia gravis (14.8%), chest pain (8.6%), and change in voice (6.2%). One patient (1.2%) was asymptomatic. The anterior mediastinum was the most frequently involved compartment (91.4%), while posterior, superior, and middle mediastinal lesions accounted for 4.9%, 2.5%, and 1.2% of cases, respectively. CT-guided biopsy was the predominant diagnostic procedure (90.1%) (**Table 1**).

Table 1. Clinicopathological characteristics of the study population (N = 81)

Characteristic	Category	n (%)
Age (years)	10–19	3 (3.7)
	20–29	15 (18.5)
	30–39	12 (14.8)

	40–49	20 (24.7)
	50–59	14 (17.3)
	60–69	15 (18.5)
	70–79	2 (2.5)
Sex	Male	56 (69.1)
	Female	25 (30.9)
Major symptom	Breathlessness	36 (44.4)
Mediastinal compartment	Anterior	74 (91.4)
Diagnostic procedure	CT-guided biopsy	73 (90.1)

The histopathological spectrum of mediastinal lesions is shown in Table 2. Thymic lesions were the most common diagnosis (37.0%), followed by metastatic lesions (18.5%), granulomatous lesions (11.1%), cystic lesions (6.2%), lymphomas (6.2%), germ cell tumors (6.2%), and neurogenic tumors (3.7%). Representative histopathological features are illustrated in Figures 1–4.

Table 2. Histopathological spectrum of mediastinal lesions

Diagnosis	n (%)
Thymic lesions	30 (37.0)
Metastatic lesions	15 (18.5)
Granulomatous lesions	9 (11.1)
Cystic lesions	5 (6.2)
Germ cell tumours	5 (6.2)
Lymphomas	5 (6.2)
Neurogenic tumours	3 (3.7)
Small cell carcinoma	1 (1.2)
Mesothelioma	1 (1.2)
Ewing sarcoma	1 (1.2)
Descriptive diagnosis	6 (7.4)

Among the **30 thymic lesions**, **Type B thymoma** constituted the predominant subtype (70.0%), followed by thymic hyperplasia (13.3%), Type A thymoma (6.7%), thymic carcinoma (6.7%), and thymic cyst (3.3%) (**Table 3**). Myasthenia gravis was associated with 18 (60.0%) thymic lesions, predominantly Type B thymoma. Representative histopathological and immunohistochemical findings of thymoma are shown in **Figure 1**.

Table 3. Distribution of thymic lesions

Lesion	n (%)
Type B thymoma	21 (70.0)
Thymic hyperplasia	4 (13.3)
Type A thymoma	2 (6.7)
Thymic carcinoma	2 (6.7)
Thymic cyst	1 (3.3)
Associated with myasthenia gravis	18 (60.0)

Immunohistochemistry was performed in diagnostically challenging cases and was useful in confirming tumor lineage and differentiating morphologically similar lesions. In thymomas, epithelial cells showed positivity for pancytokeratin, CK5/6, and p63, while the background immature T lymphocytes expressed CD3 and TdT (Figure 1). Germ cell tumors demonstrated OCT3/4 and β-hCG positivity (Figure 2). Ewing sarcoma exhibited diffuse membranous CD99 positivity (Figure 3). Granulomatous lesions showed characteristic epithelioid granulomas with central caseous necrosis on routine histopathological examination (Figure 4).

Overall, histopathological examination combined with immunohistochemistry enabled accurate classification of the broad spectrum of mediastinal lesions encountered in the present study.

DISCUSSION

Mediastinal lesions comprise a diverse group of benign and malignant entities with overlapping clinical and radiological features, making histopathological examination indispensable for definitive diagnosis. In the present study, histopathology combined with immunohistochemistry facilitated classification of the spectrum of mediastinal lesions encountered during the study period, emphasizing the importance of a multidisciplinary diagnostic approach.[1–7]

The mean age of the study population was 43.8 years, with the highest proportion observed in the 40–49-year age group. A clear male predominance (69.1%) was noted, which is consistent with previous studies by Aroor et al., Dubashi et al., and Takeda et al., who also reported a higher frequency of mediastinal lesions among middle-aged males.[14,15,17]

Breathlessness was the most common presenting symptom, followed by cough and myasthenia gravis. These symptoms largely reflected compression of adjacent mediastinal structures by expanding masses. Similar clinical presentations have

been described in previous clinicopathological series, where respiratory symptoms were the predominant mode of presentation.[1,5,14–16]

The anterior mediastinum was the most frequently involved compartment (91.4%), which agrees with previous reports demonstrating that thymic epithelial tumors, germ cell tumors, and lymphomas predominantly arise within this compartment.[1–5,17] Posterior mediastinal lesions were relatively uncommon and were represented mainly by neurogenic tumors, a distribution consistent with the established anatomical compartmentalization of mediastinal pathology.[1–4]

Thymic lesions constituted the largest diagnostic category in the present study, with Type B thymoma representing the predominant histological subtype. This observation is in agreement with the WHO classification and previous clinicopathological studies, which have consistently identified Type B thymoma as the most frequent thymic epithelial neoplasm.[8,9] Myasthenia gravis was associated with 18 of 30 thymic lesions (60.0%) in our series, further supporting the well-recognized relationship between thymoma and autoimmune disorders.[8,9]

Metastatic tumors represented the second most common group of mediastinal lesions. The majority originated from squamous cell carcinoma and adenocarcinoma, reflecting the mediastinum as a common site for lymphatic spread of thoracic malignancies. Previous studies have similarly demonstrated that metastatic involvement constitutes a significant proportion of mediastinal masses encountered in routine practice.[1,5,14–17]

Granulomatous lesions accounted for approximately 11% of cases and predominantly exhibited caseating granulomatous inflammation. In tuberculosis-endemic regions such as India, granulomatous lymphadenitis remains an important differential diagnosis of mediastinal masses and should always be considered in the appropriate clinical setting.[18,19]

Although germ cell tumors represented a relatively small proportion of cases, immunohistochemistry played a decisive role in confirming the diagnosis. OCT3/4 and β-hCG proved particularly useful in differentiating germ cell tumors from poorly differentiated carcinomas and lymphomas, consistent with current WHO recommendations.[11,13]

Similarly, immunohistochemistry was indispensable for diagnosing uncommon lesions such as Ewing sarcoma. Diffuse membranous CD99 expression, together with characteristic histomorphological findings, facilitated confirmation of the diagnosis while excluding other small round blue cell tumors.

One of the major strengths of the present study was the systematic application of immunohistochemistry in diagnostically challenging cases. Markers including pancytokeratin, CK5/6, p63, CD117, TdT, CD3, CD20, OCT3/4, S100, synaptophysin, calretinin, and TTF-1 significantly improved diagnostic confidence and enabled accurate subclassification of morphologically overlapping lesions. Similar observations have been reported in several contemporary studies evaluating mediastinal pathology.[8–13]

The present study has certain limitations. It represents a single-center experience with a relatively modest sample size, and molecular diagnostic techniques were not routinely available for all tumors. Nevertheless, the study provides a comprehensive overview of the clinicopathological spectrum of mediastinal lesions encountered in a large tertiary care referral center and highlights the complementary role of immunohistochemistry in routine diagnostic pathology.

CONCLUSION

Mediastinal lesions comprise a diverse group of pathological entities with considerable overlap in clinical and radiological presentation, making tissue diagnosis essential for appropriate patient management. In this study, thymic lesions were the most common diagnostic category, followed by metastatic and granulomatous lesions. Histopathological examination remained the cornerstone of diagnosis, while immunohistochemistry was valuable for confirming tumor lineage and differentiating morphologically similar lesions. Integration of clinical, radiological, histomorphological, and immunophenotypic findings supports accurate classification of mediastinal lesions and appropriate therapeutic decision-making.

REFERENCES

1) Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. Chest. 2005;128(4):2893-2909. doi:10.1378/chest.128.4.2893.
2) Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: Tumors of the anterior mediastinum. Chest. 1997;112(2):511-522. doi:10.1378/chest.112.2.511.
3) Juanpere S, Cañete N, Ortuño P, Martínez S, Sánchez G, Bernardo L. A diagnostic approach to the mediastinal masses. Insights Imaging. 2013;4(1):29-52. doi:10.1007/s13244-012-0211-1.
4) Laurent F, Latrabe V, Lecesne R, Zennaro H. Mediastinal masses: diagnostic approach. Eur Radiol. 1998;8(7):1148-1159. doi:10.1007/s003300050524.
5) Davis RD Jr, Oldham HN Jr, Sabiston DC Jr. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. Ann Thorac Surg. 1987;44(3):229-237. doi:10.1016/S0003-4975(10)62059-0.
6) Larsen SS, Krasnik M, Vilmann P, Jacobsen GK, Pedersen JH, Faurschou P, et al. Endoscopic ultrasound-guided biopsy of mediastinal lesions has a major impact on patient management. Thorax. 2002;57(2):98-103. doi:10.1136/thorax.57.2.98.
7) Shabb NS, Fahl M, Shabb B, Haswani P, Zaatari G. Fine-needle aspiration of the mediastinum: a clinical, radiological, cytological and histological study of 42 cases. Diagn Cytopathol. 1998;19(6):428-436. doi:10.1002/(SICI)1097-0339(199812)19:6<428::AID-DC6>3.0.CO;2-M.
8) Thomas CR Jr, Wright CD, Loehrer PJ Sr. Thymoma: state of the art. J Clin Oncol. 1999;17(7):2280-2289. doi:10.1200/JCO.1999.17.7.2280.

9) Nakagawa K, Asamura H, Matsuno Y, Suzuki K, Kondo H, Maeshima A, et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. J Thorac Cardiovasc Surg. 2003;126(4):1134-1140. doi:10.1016/S0022-5223(03)00796-0.
10) Suster S. Thymic carcinoma: update of current diagnostic criteria and histologic types. Semin Diagn Pathol. 2005;22(3):198-212. doi:10.1053/j.semdp.2006.02.007.
11) Wick MR, Perlman EJ, Orazi A, Müller-Hermelink HK, Zettl A, Göbel U, et al. Germ cell tumours of the mediastinum. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, editors. Pathology and genetics of tumours of the lung, pleura, thymus and heart. WHO Classification of Tumours. Lyon: IARC Press; 2004. p. 198-220.
12) Strickler JG, Kurtin PJ. Mediastinal lymphoma. Semin Diagn Pathol. 1991;8(1):2-13.
13) Takeda S, Miyoshi S, Ohta M, Minami M, Masaoka A, Matsuda H. Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. Cancer. 2003;97(2):367-376. doi:10.1002/cncr.11068.
14) 14) Aroor AR, Prakasha SR, Seshadri S, Teerthanath S, Raghuraj U. A study of clinical characteristics of mediastinal masses. J Clin Diagn Res. 2014;8(2):77-80. doi:10.7860/JCDR/2014/7622.4013.
15) Dubashi B, Cyriac S, Tenali SG. Clinicopathological analysis and outcome of primary mediastinal malignancies: a report of 91 cases from a single institute. Ann Thorac Med. 2009;4(3):140-142. doi:10.4103/1817-1737.53348.
16) Vaziri M, Pazooki A, Zahedi-Shoolami L. Mediastinal masses: review of 105 cases. Acta Med Iran. 2009;47(4):297-300.
17) Takeda S, Miyoshi S, Akashi A, Ohta M, Minami M, Okumura M, et al. Clinical spectrum of primary mediastinal tumors: a comparison of adult and pediatric populations at a single Japanese institution. J Surg Oncol. 2003;83(1):24-30. doi:10.1002/jso.10231.
18) Khilnani GC, Jain N, Hadda V, Arava SK. Anterior mediastinal mass: a rare presentation of tuberculosis. J Trop Med. 2011;2011:635385. doi:10.1155/2011/635385.
19) Kumar N, Gera C, Philip N. Isolated mediastinal tuberculosis. J Assoc Physicians India. 2013;61(1):46-47.
20) Paquette M, Truong PT, Hart J, Chang-Stroman LM, Wong M, Gown AM, et al. Primary sarcoma of the mediastinum: a report of 16 cases referred to the British Columbia Cancer Agency. J Thorac Oncol. 2010;5(6):898-906. doi:10.1097/JTO.0b013e3181da16d4.
21) Suster S, Moran CA. Primary synovial sarcomas of the mediastinum: a clinicopathologic, immunohistochemical, and ultrastructural study of 15 cases. Am J Surg Pathol. 2005;29(5):569-578. doi:10.1097/01.pas.0000157934.30155.07

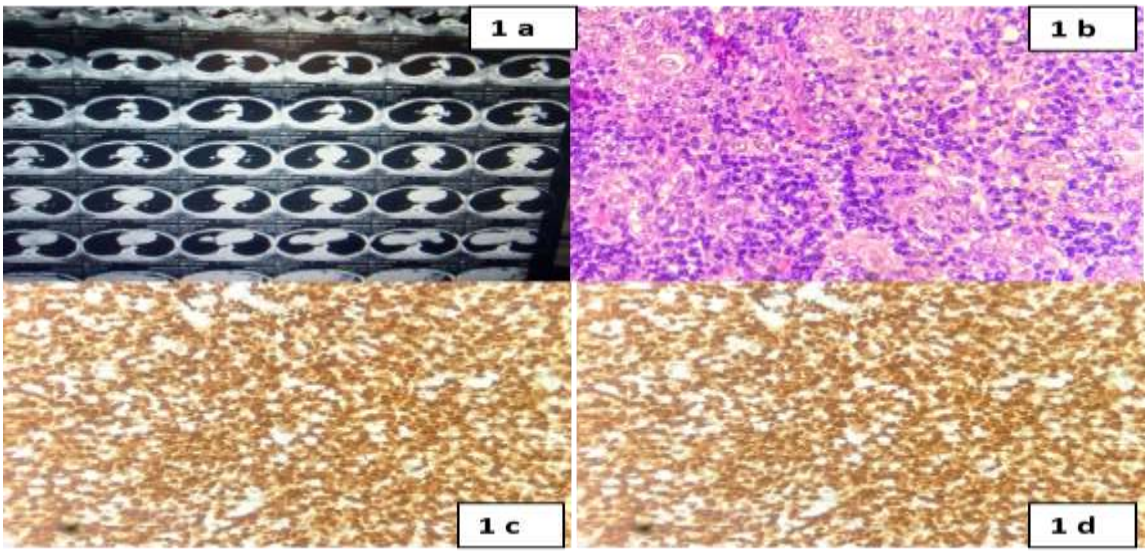

Fig.1a CT showing Anterior mediastinal mass; 1b. Thymoma type B (400X) Dual population: Epithelial and lymphocytes; 1c. IHC CK shows cytoplasmic and membranous positivity in epithelial cells; 1d. 10 IHC Tdt shows nuclear positivity in the background lymphocytes

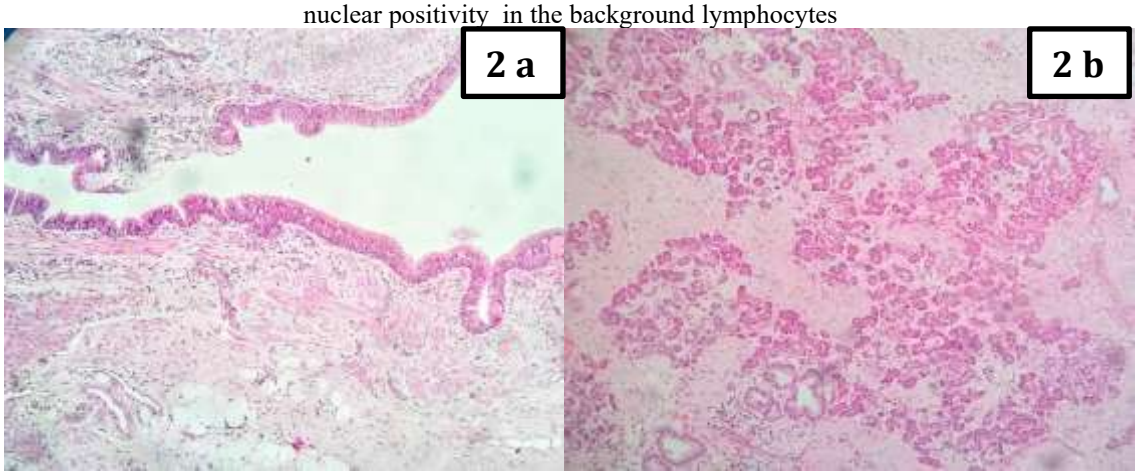

Figure 2. Mature teratoma. (a) Cyst lined by pseudostratified ciliated columnar epithelium (H&E, ×100). (b) Pancreatic acini within the teratoma (H&E, ×100).

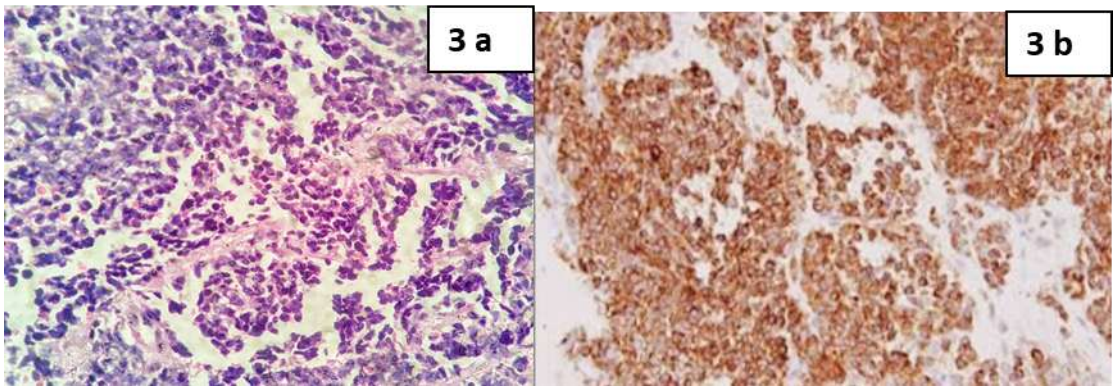

Figure 3. Ewing sarcoma. (a) Histopathology showing a small round cell tumor (H&E, ×100). (b) CD99 immunohistochemistry showing membranous positivity.

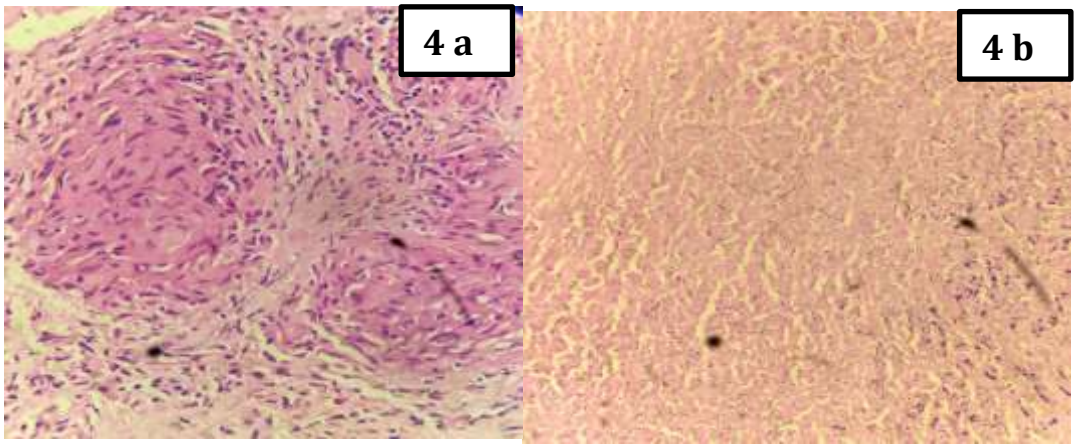

Figure 4. Granulomatous lesion. (a) Multiple epithelioid cell granulomas. (b) Central caseous necrosis.