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ORIGINAL RESEARCH

Image-guided fine-needle aspiration cytology of mediastinal lesions: A five-year retrospective observational study

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Abstract

Background: Mediastinal lesions are extremely rare and being recognized as notoriously silent, are often considered indolent.

Methods: A five-year retrospective observational study was undertaken on 55 patients with mediastinal lesion who had undergone image-guided fine-needle aspiration cytology (FNAC). Cyto-histopathological correlation was feasible in 31 patients. All clinical, radiological and pathological details were retrieved from institutional records for retrospective analysis.

Results: Of 55 cases, 11% (n=6) smears were non-diagnostic or inadequate/ inconclusive, 4% (n=2) inflammatory, 9% (n=5) benign, 2% (n=1) atypical, 16% (n=9) suspicious for malignancy and 58% (n=32) malignant. Most patients were in 5th-6th decades of life with male: female ratio 2:1 (37 males, 18 females). Maximum 87.3%mediastinal lesions were localized in anterior mediastinum. Non-Hodgkin lymphoma (NHL) (n=11, 22%) followed by metastatic carcinoma (n=9, 18%) constituted most common mediastinal lesions. Commonest malignancy observed during first four decades of life was NHL. Metastatic carcinoma predominated in 6th-7th decades. Sensitivity, specificity and diagnostic accuracy obtained were 93%, 67% and 90.32% respectively.

Conclusions: The study highlights that FNA is a minimally invasive invaluable tool to help characterize mediastinal lesions and further guide clinical management. A changing trend of spectrum of anterior mediastinal lesions is noted, with NHL and metastatic carcinoma being more common as opposed to previously described thymoma. This reaffirms the necessity for a meticulous clinical, radiological and pathological evaluation of mediastinal lesions, to rule out the possibility of malignancy in mediastinum, where malignant lesions now predominate. Knowledge of age-wise distribution facilitates to narrow down differential diagnoses.

Key-words: fine-needle aspiration cytology, mediastinal, metastatic carcinoma, non-Hodgkin lymphoma, thymoma

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Introduction

Mediastinal lesions span a wide histopathological and radiological spectrum. Mediastinum is demarcated by thoracic inlet superiorly, pleural cavities laterally, and diaphragm inferiorly & is divided into anterior, middle & posterior compartments.[1] Location and composition of lesion is critical for narrowing down the differential diagnosis. The clinical spectrum ranges from being asymptomatic to life threatening compressive symptoms. Scrupulous clinical, imaging and pathological evaluation allows correct diagnosis in most cases.

The study was undertaken to determine prevalence, age and compartment-wise distribution of mediastinal lesions and to assess the role of image-guided fine-needle aspiration cytology (FNAC) and biopsy in diagnosis of such lesions.

Materials and methods

Study Design

This was a retrospective observational study undertaken on 55 patients admitted with radiological evidence of mediastinal lesion and who had undergone image-guided fine-needle aspiration cytology (FNAC) and/ or biopsy, over a five-year period, at government medical college and associated tertiary care hospital. All the relevant clinical, radiological and pathological details were retrieved from institutional records for retrospective analysis. As the biopsy records of 31 cases could only be retrieved, the cyto-histopathological correlation was feasible only in 31 of 55 patients (31/55). The need for the ethical approval and informed consent was waived in view of the retrospective nature of the study. The present study involved only the retrospective analysis of our department's archived data that was already de-identified or anonymized due to the implementation of stringent measures to safeguard sensitive data, including patient confidentiality and safety during the routine data collection and archival process and therefore this study poses no risk to the participants' privacy or welfare.

Patient Selection

Inclusion Criteria: Patients of all age groups who presented with radiological evidence of mediastinal lesion and who had undergone image-guided fine-needle aspiration cytology (FNAC) were included in our study.

Exclusion Criteria: Cases with incomplete clinical, radiological and/ or pathological data were excluded from the study. As the patients suffering from bleeding disorders, respiratory distress, sepsis, neurological illness (seizures etc.) or with serious co-morbidities were not subjected for any interventional procedure (FNA/biopsy), their cytological and/ or histopathological data could not be obtained, and hence were excluded from the study.

Clinical and Radiological Evaluation

All the relevant clinical and radiological details of the patients were obtained from our institutional records and were analyzed subsequently. In our institute, it is a protocol that before any interventional procedure, thorough radiological evaluation including a detailed real-time CT scan of the thorax needs to be done so as to plan the route of FNAC and/ or biopsy followed by informed consent from patient or their relatives, along with all the necessary clinical details of patients regarding any co-existent serious ailment, drug history, coagulation profile and platelet count must be reviewed and documented. As per recent literatures, for image-guided FNAC/ biopsy, an international normalized ratio (INR) of < 2.0 and platelet counts as low as >25,000/cu mm can be acceptable, as compared to earlier times, when an INR of 1.5 and platelet count of $\geq$ 50,000/cu mm were preferred.[2]

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Cytological and Histopathological Evaluation

All the necessary cytological and histopathological details of the patients were retrieved from institutional records for retrospective analysis. In our institute, the protocol for doing FNAC in adults involves injecting local anaesthetic, 2% lignocaine, around the puncture site after allergy test; while in children, the procedure is conducted under short general anesthesia (fentanyl and midazolam). 22 Gauge, 90-mm disposable lumbar puncture needles with trocar were used for FNAC. The aspirated material, after evenly smearing on the surface of cleaned glass, were air-dried for May-Grünwald Giemsa (MGG) stain and/ or wet fixed with 90% ethyl alcohol for staining with Papanicolaou's (Pap) andHaematoxylin and Eosin (H&E) stain. For trucut biopsy, under radiological scanning, trucut biopsy gun with 16 gauge co-axial trucut biopsy needle was preferred to create a minimally invasive track, for safest approach. The material thus obtained is fixed in 10% buffered formalin for further histopathological processing and staining with H&E. The patients have to be monitored for at least six hours following the procedure. The stained slides with all the necessary details are subjected for analysis. After the dispatch of final report, the entire patient's data is archived safely for future research purpose.

Ancillary Tests

All the relevant details of special staining, flow cytometry and/ or immunohistochemistry (IHC) were obtained from archives, whenever feasible.

Results

Distribution of mediastinal lesions

Mediastinal lesions were observed to be more common in males with male: female ratio 2:1 (37 males and 18 females). Overall most common mediastinal lesion were non-Hodgkin lymphoma (NHL) (n=11, 22%) and metastatic carcinoma (n=9, 18%). Majority of the mediastinal lesions were localized in anterior mediastinum (87.3%, n= 48), followed by middle (9.1%, n= 5) and posterior mediastinum (3.6%, n= 2). The compartment wise distribution of mediastinal lesions have been summarized in Table 1.

TABLE 1 Compartment wise distribution of various mediastinal lesions

Diagnosis	Anterior mediastinum	Middle mediastinum	Posterior mediastinum	Total
Lymphomas	9	2	-	11
Metastatic carcinomas	7	2	-	9
Sarcomas	6	-	-	6
Round cell tumours	6	-	-	6
Germ cell tumours	4	-	-	4
Neurogenic tumours	-	-	1	1
Anaplastic carcinoma	1	-	-	1
Neuroblastoma	-	-	1	1
Adenocarcinoma	1	-	-	1
Rhabdomyosarcoma	1	-	-	1
Thymomas	4	-	-	4
Cystic lesion	0	1	-	1
Pyogenic lesion	2	-	-	2
Miscellaneous	7	-	-	7
Total	**48**	**5**	**2**	**55**

We observed that NHL (n= 9) comprised 18.7% of all anterior mediastinal lesions and

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constituted most common lesion in anterior mediastinum, as opposed to previously described indolent thymomas, followed by metastatic carcinomas (n= 7) which comprised 14.5% of all anterior mediastinal lesions. In this study, thymomas (n=4) comprised only 8.3% of anterior mediastinal lesions. In posterior mediastinum, one case of neurogenic tumour (n= 1) and one case of neuroblastoma (n=1) were observed whereas in middle mediastinum, one cystic lesion (n=1) and two cases each of NHL (n=2) & metastatic carcinoma (n=2) were observed. Among malignant lesions, NHL (n= 11, 22%)constituted the majority followed by metastatic carcinomas (n= 9, 18%) whereas among benign lesions, thymomas were the predominant ones (n= 4, 80%). Among NHL, total 82% (9/11cases) were located in anterior mediastinum, while among metastatic carcinomas, 78% (7/9 cases) were reported in anterior mediastinum. Maximum cases with mediastinal lesion were identified in 5th-6th decades of life. The most common malignancy of mediastinal region during the first four decades of life was noted to be NHL (8/11 cases, 73%), whereas during 6th-7th decades of life, metastatic carcinoma (8/9 cases, 89%) constituted most common malignant mediastinal lesion, as summarized in Table 2.

TABLE 2 Age distribution of mediastinal lesions

	0-9y	**10-19y**	**20-29y**	**30-39y**	**40-49y**	**50-59y**	**60-69y**	**>70 y**
Lymphomas	1	3	2	2	3	-	-	-
Metastatic carcinomas	-	-	-	1	-	3	5	-
Sarcomas	-	1	1	-	1	2	-	1
Round cell tumours	-	2	2	-	1	1	-	-
Germ cell tumours	2	2	-	-	-	-	-	-
Neurogenic tumours	-	-	-	-	-	1	-	-
Anaplastic carcinoma	-	-	-	1	-	-	-	-
Neuroblastoma	1	-	-	-	-	-	-	-
Adenocarcinoma	-	-	1	-	-	-	-	-
Rhabdomyosarcoma	-	-	1	-	-	-	-	-
Thymomas	-	-	1	1	2	-	-	-
Miscellaneous	1	1	1	-	1	1	-	-

*The highlighted text in Table 2 depicts predilection of lymphomas in first four decades of life, germ cell tumours in first two decades, metastatic carcinomas in elderly and thymomas in post-adolescence and middle age group.

In our study, most of the metastatic carcinomas had primary in lung; among which 5/9 were metastatic adenocarcinoma while 4/9 was metastatic squamous cell carcinoma. A total of 5/9 metastatic carcinomas presented as anterior mediastinal mass while 4/9 as mediastinal lymphadenopathy.

Cytological evaluation of mediastinal lesions

We have classified the smears into six categories as non-diagnostic (inadequate/ inconclusive), inflammatory, atypical, benign, suspicious for malignancy and malignant, as shown in Table 3.

TABLE 3 Cytological categorization of mediastinal lesions

	Cytological category	**Number of Cases (n)**	**Percentage (%)**
I.	Non-diagnostic -Inadequate/ Inconclusive	6	11%
II.	Inflammatory	2	04%
III.	Benign	5	09%

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IV.	Atypical cells	1	02%
V.	Suspicious for malignancy	9	16%
VI.	Malignant	32	58%

Our department followed a protocol to repeat FNAC in those cases where the smears were classified as non-diagnostic, atypical or suspicious for malignancy. The "non-diagnostic" category included "inadequate" and "inconclusive" smears. The "inadequate" smears were those with the presence of scant or no cellularity, only hemorrhage, and/ or necrosis, while the "inconclusive" smears were those where no conclusive diagnosis could be possible either due to the presence of artifactual changes, the technical difficulty in interpretation or the lack of access to vital clinical/ radiological data. The "atypical" category included those smears which comprised of the cells with cytological features falling beyond the span of reactive changes, but is not unusual enough to warrant a diagnosis of suspicious for malignancy. Thus, 14 such cases with history of repeat aspirations, included 5/14 inadequate, 1/14 inconclusive, 1/14 atypical and 7/14 malignant. Histopathological correlation was feasible in 31 cases. True Positive (TP) were defined as malignant in cytology and histopathology; True Negative (TN) as benign/ inflammatory in cytology and histopathology; False Positive (FP) as malignant in cytology while benign/ inflammatory in histopathology; False negative (FN) as benign/ inflammatory in cytology while malignant in histopathology. The data has been summarized in Table 4.

TABLE 4 Distribution of 31 cases on the basis of cyto-histopathological correlation

	Number of Cases (n)
True Positive (TP)	26
True Negative (TN)	02
False Positive (FP)	01
False Negative (FN)	02

Sensitivity, specificity of image-guide FNAC obtained were 93% and 67% respectively. The diagnostic accuracy obtained was 90.32%. The results of statistical analysis have been summarized in Table 5.

TABLE 5 Accuracy of image-guided FNAC in diagnosing mediastinal lesions

	Overall (%) (n=31)	**95% CI**
Sensitivity (TP/ TP+FN)	93	76.05%-99.1%
Specificity (TN/TN+FP)	67	9.43%- 99.16%
Positive Predictive Value (TP/TP+FP)	96	83.95-99.23%
Negative Predictive Value (TN/TN+FN)	50	17.41-82.59%
Diagnostic accuracy (TP+TN/ TP+TN+FP+FN)	90.32	74.25-98%

Abbreviations: CI, Confidence Interval; TP, True Positive; TN, True Negative; FP, False Positive; FN, False negative

In our study, we encountered a case of mediastinal lymphadenopathy which revealed metastatic squamous cell carcinoma, the classical cytological features of which have been depicted in Figure 1. We also encountered a mediastinal neuroblastoma, which is otherwise one of the most common retroperitoneal tumour in infants and in early childhood.[2] Cytological findings of the same revealed characteristic pseudo-rosettes, as shown in Figure 2. Another rare case of a mediastinal teratoma, displaying classical histopathological features, has been shown in Figure 3.

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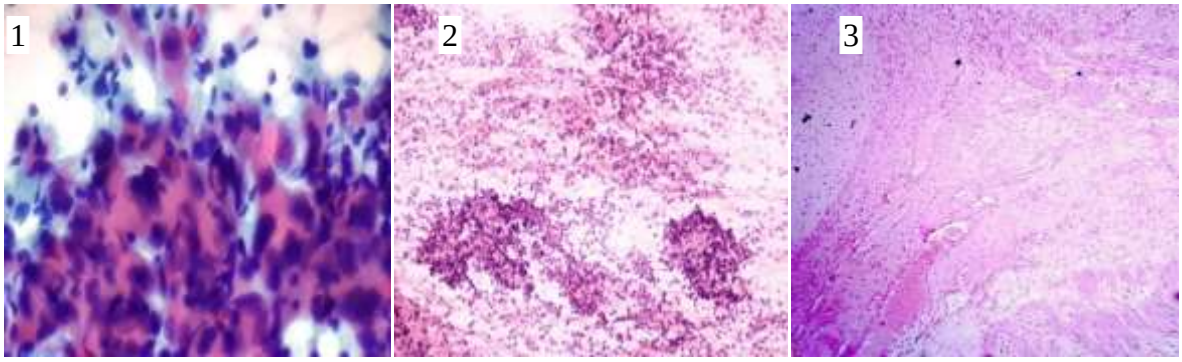
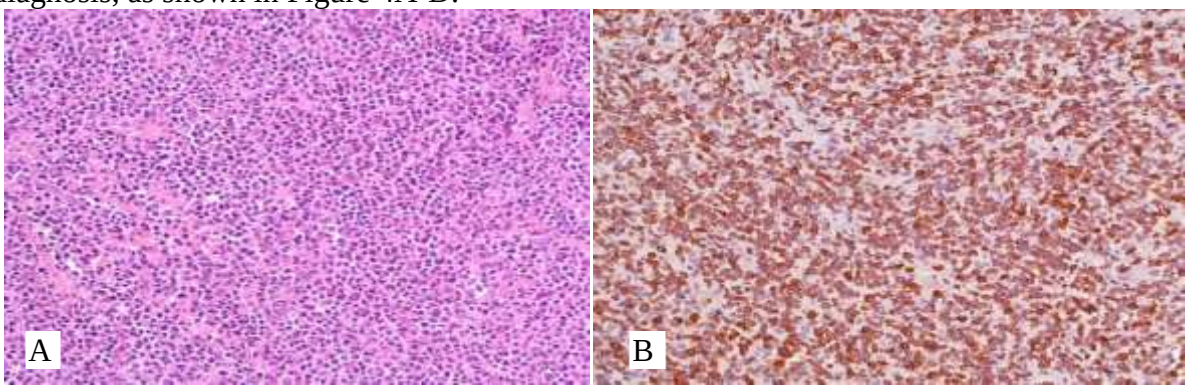


FIGURE 1: Metastatic Squamous Cell Carcinoma (keratinizing): Mediastinal lymph node aspirate displaying loosely cohesive cluster of pleomorphic malignant keratinized squamous cells with classical dense orangeophilic cytoplasm. ***(Papanicolaou; x400)*** **FIGURE 2: Neuroblastoma: Aspiration smear of a posterior mediastinal mass displaying multiple pseudo-rosettes comprising of central zone of fibrillar neural matrix surrounded by small round tumour cells with dark stained nuclei and scant cytoplasm against haemorrhagic background.** ***(H&E; x100)*** **FIGURE 3: Teratoma: Trucut biopsy section of an anterior mediastinal mass displaying foci of cartilaginous, smooth muscle and neural differentiation.** ***(H&E; x100)***

In our study, 11 cases of NHL were sub classified and 5/11 were found to be primary mediastinal B-cell lymphoma (PMBL) which were later confirmed by IHC, 1/11 was found to be grey zone lymphoma (GZL) and 1/11 turned out to be NK-T cell lymphoma. However, remaining 4/11 couldn't be sub classified as these patients were lost to follow up. Morphologically, the tumour cells of PMBL had medium to large cell appearance, round or lobulated nuclei with abundant cytoplasm and classically expressed CD19, CD20, CD22, CD79a, PAX5 and CD45 along with CD30; while in a case of GZL, the smears were hypercellular and demonstrated medium to large, highly pleomorphic tumour cells with binucleated and multinucleated forms against a background that comprised of few inflammatory cells. The histopathological evaluation and subsequent immunophenotyping with expression of CD20, CD30, MUM1, PAX5, and loss of CD79a, revealed the final diagnosis as GZL.

We encountered one rare case of aggressive NK/ T cell lymphoma, which frequently resembles lymphocyte rich thymoma or reactive lymphoid proliferation. On cytological evaluation, the hypercellular smears revealed variable sized lymphoid cells displaying irregular nuclei, and pale blue cytoplasm. Many inflammatory cells along with areas of necrosis were also noted in the background. Trucut biopsy followed by IHC revealed final diagnosis, as shown in Figure 4A-D.



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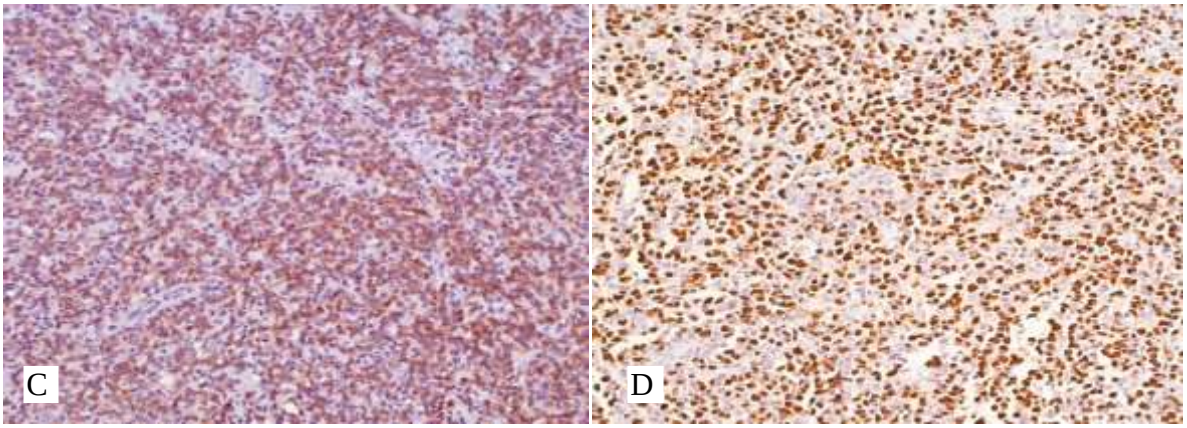

FIGURE 4: A, Trucut biopsy section of an anterior mediastinal mass shows features of NK T-cell lymphoma (H&E)B, CD3 immunostain shows strong positive cytoplasmic staining; C, CD56 immunostain shows positive membranous and cytoplasmic staining; D, In situ hybridization for EBER. (x400, A-D)

Discussion

In the current study, most of the mediastinal lesions were found to be localized in anterior mediastinum and overall malignant lesions were much more common than benign lesions, similar to the results obtained in the studies done by Nasit et al.,[3] Zamboni et al.,[4] Adler et al.[5] and Jereb et al.,[6] as mentioned in Table 6.

TABLE 6 Summary of the concordant results obtained in the current study (italicized)& studies done by various authors

Most common mediastinal lesions are Malignant& Most common location is Anterior mediastinum	Most common lesion in anterior mediastinum is Non Hodgkin Lymphoma (NHL) followed by Metastatic carcinoma	Overall most common mediastinal lesion is NHL followed by Metastatic carcinoma	Most common lesion in first four decades of life is NHL	Most common lesion in 6^{th}- 7^{th} decades of life is Metastatic carcinoma
Nasit et al.[3] (2013)	Nasit et al.[3] (2013)	Nasit et al.[3] (2013) (Metastatic Carcinoma- 38%, NHL- 32%)	Nasit et al.[3] (2013)	Nasit et al.[3] (2013)
Zamboni et al.[4] (2009)	Vaziri et al.[7] (2009)	Shabb et al.[9] (1998)	Vaziri et al.[7] (2009)	Karki et al.[10] (2011)
Adler et al.[5] (1983)	Shrivastava et al.[8] (2006)	Shrivastava et al.[8] (2006)	Karki et al.[10] (2011)	Adler et al.[5] (1983)
Jereb et al.[6] (1977)	Shabbet al.[9] (1998)	Zamboni et al.[4] (2009)	Adler et al.[5] (1983)	-

NHL was the most common lesion observed in anterior mediastinum as opposed to the previously described thymomas; similar to the findings of Nasit et al.,[3] Vaziri et al.,[7] Shrivastava et al.[8] and Shabb et al.[9] This shift in the spectrum and recent rise in occurrence of lymphomas in mediastinum is alarming and demands meticulous investigation of all patients with mediastinal lesions.

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In our study, NHL was also the overall most common mediastinal lesion followed by metastatic carcinoma, similar to the results obtained in the studies done by Nasit et al.,[3] Shabbet al.,[9] Shrivastava et al.[8] and Zamboni et al.[4] NHL was also the most common malignancy observed in first four decades, supported by the studies done by Nasit et al.,[3] Vaziriet al.,[7] Karkiet al.[10] and Adler et al.[5] Mediastinal lymphomas are predominantly primary but secondary involvement of mediastinum with primary elsewhere, is also not rare. Mediastinal B-cell lymphomas are primarily primary mediastinal B-cell lymphoma (PMBL), is quite aggressive and predominantly affects young females in 3rd-4th decades of life.[11] In children and adolescents, nodular sclerosis-classical Hodgkin lymphoma (NS-CHL) predominates and among NHLs, T-cell lymphoblastic lymphoma[1,12] is common in adolescents and young adults.[13]

PMBL is a subtype of Diffuse Large B-Cell Lymphoma (DLBCL), derived from thymic B-cells. It constitutes 10%[11] of all DLBCL and can be defined as bulky mass (>5 cm in diameter) located exclusively in mediastinum without any evidence of other similar masses at extra mediastinal location.[14] Morphological assessment of lymphoma requires diligent evaluation of architecture, including a comment on partial or complete effacement by diffuse or nodular pattern of cell arrangement, characteristics of tumour cell, background cells, necrosis and extent of fibrosis. The important differential diagnosis of PMBL are Grey zone lymphoma (GZL), NS-CHL, DLBCL-Not Otherwise Specified (NOS) with mediastinal involvement, thymoma and germ cell tumours.[15] As PMBL itself arises in B-cells of thymus, apart from other lymphomas, thymic neoplasm (thymoma and thymic carcinoma) constitute one of its most important differential diagnosis, as discussed earlier. The problem arises when trucut biopsy and/ or FNAC results in inadequate sampling. In such cases, repeat FNAC and/ or biopsy is advisable. For final differentiation, immunohistochemistry (IHC) is required, which reveals pan cytokeratin expression in thymic neoplasms.

GZL have been recently recognized as independent entity in 2005 and were incorporated in WHO classification in 2008.[11] those with morphological features intermediate to classical Hodgkin lymphoma (CHL) and DLBCL are now considered as GZL, a recently recognized variant of B-cell lymphomas. To clarify, GZL can exhibit a wide spectrum both on morphology and on immunophenotyping, i.e. those tumours which resemble CHL morphologically may display DLBCL or PMBL like immunophenotype, and vice-versa. However specific diagnosis is necessary for the initiation of much aggressive management approach in GZL because GZL have dismal prognosis as compared to DLBCL and HL.[16, 17] Not only GZL can involve primarily in mediastinum but can also present as systemic disease.[16] NS-CHL is a common cause of mediastinal mass in children. The histopathological features consist of cellular islands separated by interlacing collagen bands. In addition, other features include presence of fibrosis, lacunar cells, predominant neutrophilic infiltration, and necrosis and 'mummified' Reed Sternberg (RS) cells.[18] Diagnosis of NS-CHL becomes challenging in cases with scant cellularity, massive granulomatous reaction, prominent fibrosis or artifactual cell distortion. The differential diagnosis includes primary mediastinal NHL, mediastinal germ cell tumours, thymoma, and metastatic carcinoma.[19] In mediastinum, especially the syncytial variant of NS-CHL which presents as cohesive aggregates and sheets of neoplastic cells, may be mistaken for metastatic carcinoma,[20] thymoma,[19] large cell lymphoma or melanoma.[20] Lack of monomorphic cell population and abundance of background inflammatory milieu in CHL, particularly demands exhaustive search for RS cells or RS like cells, though RS cells should never be the sole criteria for typing lymphomas. Whenever feasible, IHC evaluation should always be attempted.

Non-invasive imaging is generally the first investigation to evaluate mediastinal masses. Earlier literatures have described thymomas to be the predominant anterior mediastinal neoplasm.[1, 12] The reasons for diagnostic errors, while interpreting thymic lesions on imaging,

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includes misinterpreting normal thymus, ectopic thymus, thymic rebound hyperplasia and the inability to differentiate between lymphomas of primary thymic origin and thymomas. The histological features of a normal thymus in a child resemble lymphocyte rich thymoma. On histopathology, appearance of regressed (involuted) thymus of elderly population, comprising spindle to oval cells, sparse lymphocytes and glandular and cystic spaces with rosette-like structures, simulates features observed in thymomas of spindle cell type.[21, 22] Normal thymus undergoes different physiologic variations like expected age related involution or its response to stress. It rapidly atrophies in response to systemic stress associated with surgery, infection, neoplasia and chemotherapy, however after cessation of stressful episode, thymus returns to its normal size or may enlarge significantly beyond normal, which is termed 'thymic rebound hyperplasia'.[23] Incomplete assessment of such scenarios often lead to serious diagnostic errors. Fortunately, this rebound phenomenon is reversible and is noted to be resolved on subsequent imaging studies. Due to high inter-individual variation, it is impossible to define the size thresholds of normal thymus and tumours, hence it is always prudent to perform image guided FNAC/ biopsy of mediastinal lesions for better evaluation rather than relying only on imaging findings. Various locations and extension of thymus can also lead to diagnostic error, like ectopic thymus is often labelled as pathologic masses by inexperienced hands. Differentiation between thymomas and lymphomas of primary thymic origin is extremely difficult, only on basis of imaging.[23] Thymic enlargements ignorantly misinterpreted as indolent thymomas/ thymic neoplasm on imaging, are now better diagnosed as lymphomas on pathological evaluation. Thymomas and lymphomas also resemble each other on pathological evaluation as round cell tumours. Thus, it is extremely important to be cautious while reporting such tumours.

Thymoma poses a challenge even with small biopsy and the sub classification is often not possible with FNA. The role of FNA in diagnosing thymoma is thus quite challenging and FNA has never been the primary diagnostic modality for diagnosing mediastinal thymomas. Moreover, the WHO classification of thymomas is not possible, and only broad diagnosis could be rendered on cytology. Hence, it is even recommended that the sub classification of thymoma should never be attempted only on the basis of cytological findings. As the diagnosis of thymoma depends on the presence of dual population of cells and the ratio of epithelial cells and lymphocytes, it is very difficult to render a definitive diagnosis, especially on a limited cytological sample and/ or due to suboptimal cytological sampling. It is a possibility that only a single population of cells is sampled resulting in erroneous diagnosis. For example, the presence of only lymphoid component could be misinterpreted as benign/ reactive lymph node or malignant lymphoma while the presence of only epithelial component may be misinterpreted as a carcinoma, sarcoma, germinal centers or even as a granuloma. The spindle cell thymomas (WHO type A or AB) can also be misinterpreted as a spindle cell lesion, such as carcinoid, low-grade sarcoma, or as the sclerosis seen in a large cell lymphoma. [24]

Current WHO classification of thymomas (including rare variants- sclerosing thymoma, micronodular thymoma and lipofibroadenoma)[25]takes into account, the type of tumour cell as spindle/oval (A, AB) or round/ epithelioid (B1-3), degree of epithelial atypia and relative proportion of epithelial cell (E) and lymphoid cell (L) population.[25] Among these, Type B1 frequently mimics lymphoma[14] due to the presence of round epithelioid thymic epithelial cells; Type B2 consist of dual population of epithelial cells (E) and lymphoid cells (L), where the lymphoid cells are generally mature small lymphocytes, however, often the lymphoid population comprises large transformed cells, hence the main diagnostic challenge is to rule out lymphoma. Thymomas with high L: E ratio thus resembles lymphomas, while those with predominant epithelial component resemble metastatic tumours; hence, there exist fair chances of misdiagnosis where lymphomas could be reported as high L: E ratio thymomas

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and metastatic tumours as epithelial cell predominant thymomas, and vice a versa. Type B3 consists predominantly of epithelial component with rare immature T lymphocytes, mild to moderate nuclear atypia and foci of squamous metaplasia. Notoriously, it mimics thymic squamous cell carcinoma; as both can present as invasive growth, thus the distinction on histopathology is quite impossible.[25]

The FNA is a useful tool for sub classifying lymphomas. Image-guided FNA being the least invasive modality is the best first line investigation to evaluate mediastinal lesions. It is not only cost-effective, but also very safe, and the results can be obtained rapidly, given the lesion is accessible and the material is adequate. However, certain limitations are noteworthy which includes the absolute dependency on operator's skill to identify and sample correct area; to obtain an adequate sample so as to minimize the sampling error; and the inability to ensure that whether the aspirated material is a true representative of the pathology. Another concern is the inability to assess the actual architecture or the pattern of arrangement of tumour cells. This becomes a hurdle particularly in diagnosing NS-HL, when the aspirate lacks the adequate sample comprising RS cells and rather mimics a reactive pathology.[19] Hence, it is always better to take a collaborative approach for diagnosing mediastinal lesions rather than depending solely on cytology for a conclusive diagnosis. Especially, if the clinical picture is suggestive of lymphoma with negative or atypical cytological features, it is recommended to perform either repeat aspiration and/ or biopsy. Particularly the notorious ones including HL, GZL, large cell lymphoma, and reactive lesions require a meticulous multidisciplinary approach for a definitive diagnosis. And hence, a careful approach should be undertaken so as to avoid both under and over-diagnosis.

In our study, the sensitivity and specificity of image-guide FNAC obtained were 93% and 67%, respectively. We obtained the diagnostic accuracy of 90.32% which was similar to that obtained in the studies done by Güllüoglu *et al.*[26] and Shaheen *et al.*[27] Pérez Dueñas V et al.[28] who have reported comparable sensitivity 95.2 % and accuracy 93.5%, but higher specificity 84.2% while Desai *et al*.[29]have reported lower sensitivity 88% and higher specificity 82%, respectively. Nasit*et al*.[3] have recorded comparatively low sensitivity of FNAC as 71.42%. Diagnostic accuracy study done by Assaad MW *et al.*[30] recorded that histologic diagnoses were concordant with FNAB diagnoses in 78% cases which was comparable to our study. Dixit et al.[31] have revealed that in their study the accurate tissue diagnosis was made in 89.9% cases by FNAC or core biopsy of mediastinal lesions, which was similar to our study. However, Nasit *et al.*[3] (97%) and Annessi *et al.*[32] (100%) have recorded exceptionally higher diagnostic accuracy in their studies. The diagnostic accuracy obtained in our study was higher as compared to the studies by Shabb et al.[9] (86%), Rosenberger and Adler et al.[33] (83%), Assaad MW *et al.*[30] (82%), Pedersen *et al.*[34] (81%), Adler *et al.*[5] (79%), Morrissey *et al.*[35] (77%), Neyaz *et al.*[36] (74%) and Dubashi *et al.*[37] (50%). The reason could be the improvement in technique and better understanding of morphology of such lesions with time.

Conclusion

Hence, in the patients presenting with a mediastinal lesion, the prime responsibility of a clinician, radiologist and pathologist is to differentiate among lymphomas, thymic masses and metastases. A 'paradigm shift' noted in the spectrum of mediastinal lesions, with obvious rise in malignant ones, is a cause of serious concern, and demands a meticulous approach to avoid erroneous diagnosis. An attempt to categorize mediastinal lesions on imaging and small biopsies, particularly with limited tissue sample and with insufficient knowledge regarding normal physiological changes and biological behavior of thymic mass, is perilous. Given the rarity of mediastinal lesions, it is imperative to undertake a comprehensive research study involving a large and diverse patient population, preferably on a global scale, to further enrich our knowledge and gain a more comprehensive understanding of the momentous

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paradigm shift, allowing us to accurately gauge its gravity. On global level, this research will pave the way for establishing the proposed cytological categorization system for better diagnosis of mediastinal lesions on cytology; and thus, in a way, will surely contribute to reduce the mortality, provided that such lesions are meticulously investigated, at the earliest.

Conflict of interest

The Authors have no conflict of interest to declare

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