Histomorphological Spectrum and Diagnostic Challenges in Thymic Epithelial Neoplasms with their Prognostic Significance: A Case Series of 33 Cases at a Regional Cancer Center in Western India

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Abstract

Objective Pathological diagnosis of thymic epithelial neoplasms is challenging due to multiple subtypes, tumor heterogeneity, and variations in inter-observer reproducibility. Very few studies are available on their spectrum in the Indian subcontinent. In this study, we aimed to explore the morphological spectrum and diagnostic difficulties in the classification and subtyping of thymic epithelial neoplasms along with their prognostic significance in the Indian population.

Material and Methods Retrospectively, all surgically resected thymectomy specimens operated at our institute as well as outside review cases during the period were included. Histomorphology and immunohistochemistry (IHC) slides were reviewed and correlated with clinicopathological variables.

Statistical Analysis Microsoft Excel 2019 and SPSS version 20 were used for data analysis.

Results Among the 33 thymic epithelial neoplasms operated during the study period, the commonest subtype was thymoma B2 type followed by AB, B1, A, and B3 types. A single case each of micronodular thymoma, microscopic thymoma, and thymic carcinoma were identified. Six cases of thymomas with more than one pattern (other than ‘A’) were noted. The male:female ratio was 2:1. Stage I in Modified Masaoka staging and pT1a in TNM staging were most common. Seven cases had metastasis, four during initial presentation and three during subsequent follow-up.

Discussion and Conclusion Thymic epithelial neoplasms show morphological overlapping of features. Thorough sampling, morphology, and IHC for exact subtyping of thymoma and diligent search and documenting of lymphovascular invasion (LVI) are vital as both are separate risk factors for metastasis/recurrence and help the clinician in a better follow-up of patients.

Keywords
- thymic epithelial neoplasm
- thymoma
- histomorphology
- immunohistochemistry
- metastasis

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**Introduction**

The thymus plays an important role in the development of self-immunological tolerance. Thymomas and thymic carcinomas are epithelial tumors of the thymus. Even though thymomas are rare tumors with an overall incidence of 0.13 to 0.26 cases per 100,000 population per year, they account for 20 to 30% of tumors in the antero-superior mediastinum. Histologically, thymomas are composed of varying proportions of epithelial cells and lymphocytes. The 2021 World Health Organization (WHO) classification subsequent to the International Thymic Malignancy Interest Group (ITMIG) consensus has revised the diagnostic criteria for thymic epithelial neoplasms. Most studies on thymic epithelial neoplasms are either clinical or have been studies of mixed bag of mediastinal tumors.

The histological spectrum, clinico-pathological features, and metastatic potential of thymic epithelial neoplasms have not been explored in depth in the Indian subcontinent. This study discusses the morphology and describes an approach to subtype thymic epithelial neoplasms and rule out respective differential diagnoses. It also compares lympho-vascular invasion (LVI) status, the Modified–Masaoka staging, and metastatic potential of various thymic epithelial neoplasms and highlights the importance of classifying them for adequate follow-up and prognosis of patients.

**Materials and Methods**

This was a descriptive study, in which we analyzed 33 cases of surgical resection specimens (thymectomies) during a period of 7 years from January 2015 to March 2022, both operated at our institute and review cases operated outside. Small biopsies were not included in the study. The clinical details including age, gender, and associated clinical conditions were obtained from case files and from hospital records. Histology and immunohistochemistry (IHC) slides were retrieved from the archives of our department and were reviewed for histological typing according to the 2021 World Health Organization (WHO) classification of thoracic tumors. Tumor staging was done according to TNM staging and Modified–Masaoka staging system. IHC was done whenever required. The antibodies used were pan CK, CK7, Tdt, PAX8, p63, p40, CD3, CD20, CD1a, CD99, CD5, CD117, EMA, STAT6, TLE1, and CD34. When there was more than one B type thymoma component, according to the ITMIG consensus and WHO classification, the term “combined thymoma” was not used. Instead, all components were listed starting with the predominant component; minor components were reported with 10% increments. Tumors with both A and B components were reported as AB thymoma; the 10% rule was not applied. All these cases were followed up during the study period for recurrence or metastasis.

**Results**

Among the 33 cases studied, the age of patients varied from 24 years to 79 years with the median age being 52 years. There was overall male preponderance; male to female ratio was 2:1 (22/11). Myasthenia gravis (MG) was an associated presentation in 12 cases (36.36%) and pure red cell aplasia (PRCA) in 2 cases (6.06%).

**Gross Examination**

The median largest dimension of tumor was 9.75 cm ranging from 3.5 cm to 16 cm. The subtype of thymoma did not show any correlation with the size of the tumor. Most tumors had homogenous lobulated gray white cut surfaces with a few having variegated cystic, hemorrhagic, and microcystic cut surface (Fig. 1).

**Histomorphological Findings**

Among the histomorphological sub-types, B2 thymoma comprised 8 out of 33 cases (24.24%), while AB and B1 thymomas comprised 7 (21.21%) and 5 cases, respectively (15.15%). Six cases showed mixed histological patterns; one among them was mixed B1 + B2 pattern and five others were mixed B2 + B3 pattern with varying percentages of each component. Two cases each of type A and B3 thymoma were seen. One case each of micronodular thymoma, microscopic thymoma (nodular hyperplasia of thymic epithelium) and thymic carcinoma were identified (Table 1).

Lymphovascular invasion (LVI) was seen in eight cases, which included two cases each of B2, B2 + B3 thymoma, one case each of AB, B1, B3 thymoma and thymic carcinoma (Table 1). Among the eight cases having lympho-vascular invasion (LVI), five cases showed distant metastasis (5/8-62.5%), while only 2 in the remaining 25 cases without LVI showed metastasis (2/25-8%).

One case (Type B1) showed pericardial invasion while four cases (two-Mixed B2 + B3 and one case of B2, B3 each) showed lung infiltration (Fig. 1). Excluding single microscopic thymoma (not staged), most cases were modified Masaoka stage I (13/32-40.6%) followed by stage IIa (12/32–37.5%) (Table 1). Seven out of these 33 cases showed metastasis (21.21%). Metastasis was identified both during initial presentation and during follow-up. Pleura was the commonest metastatic site, while other metastatic sites were liver, lungs, retroperitoneum, and cervical lymph nodes (Table 1).

**Discussion**

The worldwide incidence of thymomas is ~1.3 to 2.5 million per year. Very few studies on thymoma have been conducted in Indian population. Except for a few studies, none of the others have assessed the histomorphology of thymic neoplasms. Among these few Indian studies, Guleria et al had the largest series of thymomas comparing the histomorphological spectrum with other clinico-pathological features.

Sex predilection was not noted for thymoma at global level. Our study showed a male predominance (M:F ratio 2:1) comparable to other Indian studies. Thymomas are frequent in the age group of 40 to 60 years, but a wide range has been reported from <10 years to >80 years. The median age in our study was 52 years (range 24–79 years).
The most common histological type in our study was type B2 thymoma, followed by AB thymoma that was comparable to the studies done in Indian population except the study done by Rathod et al where AB type was the commonest. In our study, commonest stage was stage I followed by stage IIa, similar to the literature on Indian population. Approximately 30 to 44% of the patients with thymoma present with MG, which is more common in type B thymoma and least common in type A. Similarly, in our study 36.36% of cases (12/33) had MG. None of the type A thymomas in our study had MG. The differential diagnosis of B1 thymoma includes T-Lymphoblastic lymphoma (T-LBL) and hyperplastic thymus. B1 thymoma commonly resembles T-Lymphoblastic lymphoma (T-LBL) in small biopsies. Prominent focal starry sky appearance, occasional Hassall's corpuscles, focal perivascular spaces were also noted.

Thymomas with Predominant Lymphoid Cells

**B1 Thymoma**

These cases showed lobular architecture resembling normal thymus. There were predominantly lymphocytes with scattered round polygonal epithelial cells. Prominent focal starry sky appearance, occasional Hassall's corpuscles, focal perivascular spaces were also noted. The differential diagnosis of B1 thymoma includes T-Lymphoblastic lymphoma (T-LBL) and hyperplastic thymus. B1 thymoma commonly resembles T-Lymphoblastic lymphoma (T-LBL) in small biopsies. However, in specimens, the difference is apparent. B1 thymoma overall shows a lobular architecture with T cells lacking atypia, whereas in T-LBL there is a loss of lobular architecture; neoplastic cells are atypical with high mitosis and necrosis with many tingible body macrophages (starry-sky appearance). The presence of perivascular spaces, medullary islands and identification of...
<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gender</th>
<th>Association</th>
<th>Size of the tumor (cm)</th>
<th>Capsule status</th>
<th>LVI</th>
<th>MM stage</th>
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<th>Metastasis</th>
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<td></td>
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<td>MG</td>
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<tr>
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<td>TNM Stage</td>
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<td>pT1a</td>
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<td>pT1a</td>
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<td>23</td>
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<td>pT1a</td>
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<td>pT1a</td>
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<td>26</td>
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<td>pT3M1a</td>
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<td>pT3</td>
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<td>pT1a</td>
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<td>IVb-1</td>
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(Continued)
epithelial cells by IHC using P63, pan CK, and PAX-8 helps rule out T-LBL and make a diagnosis of B1 thymoma.\textsuperscript{17,18}

B1 thymoma may be impossible to distinguish from thymic hyperplasia (both true thymic and lympho-follicular hyperplasia) on a biopsy,\textsuperscript{19} where sampling is a major limitation. However, on whole specimen, microscopic features of septations, a more pronounced fibrous capsule, strong predominance of cortical over medullary areas and fewer Hassall corpuscles, which are typical features of B1 thymoma, help differentiate it from thymic hyperplasia.\textsuperscript{14,18,19}

**B2 Thymoma**

B2 thymoma was the commonest thymoma in our study. It showed varying proportions of lymphocytes and polygonal epithelial cells. Epithelial cells showed moderate atypia, vesicular chromatin, prominent nucleoli, sparse mitosis, and necrosis with dilated perivascular spaces lined by epithelial cells with lymphocytes within the spaces (\textsuperscript{Fig. 3}).

Both B1 and B3 thymomas come in the differential diagnosis. One case in our study on initial examination appeared to be B1 thymoma. On in-depth examination, increased epithelial cells as compared with B1 thymoma were noted and on IHC, multiple clusters of epithelial cells were highlighted by PAX8. According to the WHO classification, a significant increase in the epithelial cells beyond the density of normal thymic cortex or the presence of three or more contiguous epithelial cells should suggest the

**Table 1**

<table>
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<tr>
<td>Micronodular thymoma</td>
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<td>Median age (years)</td>
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<td></td>
<td>33</td>
<td>70 (3.03%)</td>
<td>24</td>
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**Abbreviations:** MM stage, modified Masaoka stage; LVI, lymphovascular invasion; MG, myasthenia gravis; PRCA, pure red cell aplasia; NA, not applicable; M:F ratio, male:female ratio; TNM, tumor-node-metastasis; cm, centimeters.

**Fig. 2** A case of B1 thymoma with (A) sheets of lymphoid cells and (B) focal Hassal corpuscles and inset showing perivascular spaces; a case of B1 thymoma metastasis to liver (C), highlighted by (D) Tdt-positive lymphoid cells, (E) pan CK-positive delicate epithelial meshwork and (F) scattered PAX8-positive epithelial cells.
Based on this, a diagnosis of B2 thymoma was rendered. IHC played an important role in this case.

Similarly, the distinction between B2 and B3 thymoma is not straightforward. B3 thymomas are lymphocyte poor tumor, which impart them a pink color on hematoxylin and eosin section (H&E), while B2 thymomas are lymphocyte-rich tumors imparting a blue color on H&E section. Sparsity of lymphocytes, presence of epithelial cell nests, and more nuclear atypia in epithelial cells favor a diagnosis of type B3 thymoma over B2 thymoma.

Pan CK also helps in distinguishing different types of type B thymomas. While it highlights a delicate meshwork in type B1, the meshwork is denser in B2 thymoma. In B3 thymoma, pan CK highlights the epithelial cell nests rather than the meshwork (Figs. 2, 3 and 5).

Thymomas with Mixture of Epithelial and Lymphoid Cells

AB Thymoma

The second most common type of thymoma in our study was AB thymoma. These cases showed bland spindled epithelial cells intermixed with type B areas having predominance of lymphocytes (Tdt positive). The spindle cells (type A areas) also showed pseudo glandular, rosette-like, storiform and hemangiopericytoma-like patterns. There was a sharp demarcation between type A and type B areas in some cases, while a few cases showed no clear-cut demarcation between both areas with spindle cells (type A) intermixed with type B areas (Fig. 4).

One of these cases had predominant type A areas with only focal places showing dense lymphoid aggregates; on IHC, Tdt was positive in these lymphoid aggregates, leading to a diagnosis of type AB thymoma (Fig. 4).

Two cases on first look, looked like B1 and B2 thymoma. On thorough examination, both the cases showed focal bland spindle shaped cells; they were in fascicles in first case while in the second, they were arranged in a storiform pattern with no to scant lymphocytes in the background resembling type A thymoma. These spindle cells were pan CK and PAX8 on IHC and the background lymphocytes in these areas were Tdt negative. Both cases were finally reported as type AB thymoma.

Type A and AB thymomas were associated with a more favorable an overall survival than type B Thymomas. Hence, it is on the onus of the reporting pathologist to make a diligent search for the type A component. The above-mentioned two cases showed the importance of thorough histological examination and highlighted the role of IHC in confirmation of type AB thymoma, which has overall better prognosis than type B thymomas.

Micronodular Thymoma with Lymphoid Stroma

It is a rare subtype of thymoma accounting for ~1% of all cases. In our study, there was a single case that showed multiple coalescent nodules of ovoid epithelial cells separated by stroma containing dense lymphoid follicles, some of them showed germinal center. The epithelial cells in the nodules were bland with oval to spindle nuclei with scant to no lymphocytes within the nodule (Fig. 6). There was no atypia or mitosis. With this morphology, the possibilities include type AB thymoma versus micronodular thymoma with lymphoid stroma. The epithelial cells showed strong positivity with AE1 and the lymphoid stroma was completely devoid of pan CK-positive cells. The lymphocytes in the stroma were positive for CD 20 (B cell marker) with negative Tdt and T cell markers. Based on these IHC findings, the diagnosis of micronodular thymoma with lymphoid stroma was made.
Differentiating micronodular thymoma with lymphoid stroma from AB thymoma is challenging. It is vital to recognize micronodular thymoma with lymphoid stroma as it has a very good prognosis with almost nil metastasis/recurrence rate. Points that help to differentiate it from type AB thymoma are enlisted in Table 2.

### Thymomas with Predominant Epithelial Cells

#### Type A Thymoma
There were two cases (6.06%) of pure type A thymoma in our study. Morphologically, type A thymoma showed lobular architecture, composed of bland plump spindles to oval epithelial cells admixed with scant or no lymphocytes. It displayed a variety of architectural patterns consisting of storiform, solid, adenoid, and hemangiopericytoma-like patterns. Focal gland formation, rosette, signet ring cells, and microcysts were also seen. There was no atypia, necrosis, or mitosis. Tumor cells were positive for pan CK, PAX8, P63 and P40 on IHC.

This subtype needs to be differentiated from mesenchymal tumors, type AB thymoma, B3 thymoma - spindle cell variant and thymic spindle cell carcinoma. Mesenchymal tumors such as solitary fibrous tumor and synovial sarcoma resemble type A thymoma. An immunohistochemical panel...
consisting of CD34, STAT6, CD56, TLE, p63 and pan CK can help resolve the diagnosis. Type A and type AB thymomas are difficult to differentiate when the tumor shows predominantly spindle cells; however, if the tumor has any Tdt-positive lymphocyte dense area (impossible to count) or >10% of the tumor area has a moderate infiltrate of Tdt-positive T cells (difficult to count), then it has to be classified as type AB thymoma. Differentiating type A thymoma with atypia from type B3 thymoma-spindle cell variant is also challenging as both cases can show nuclear atypia and spindle cells. Typical morphological and IHC features help to distinguish them. The presence of architectural features characteristic of type A thymoma (gland/rosette/cyst/pericytomatous pattern), absence of perivascular spaces, and Tdt-positive lymphocytes in the stroma favors a diagnosis of atypical type A thymoma rather than type B3 thymoma.

Thymic spindle cell carcinoma may lead to confusion with type A thymoma but it will have more cytological atypia, brisk mitosis along with variable expression of CD5 and CD117 in epithelial cells.

**B3 Thymoma**

There were two cases of B3 thymoma; one among them was a rare variant: B3 thymoma with anaplasia (Fig. 5). On biopsy, the case was diagnosed as spindle cell thymoma. Histology of the resection specimen showed cells arranged in a lobular pattern, highly pleomorphic, oval to spindle cells with focal storiform pattern intermixed with Tdt-positive lymphocytes showing focal perivascular spaces (Fig. 5). Cells showed moderate cytoplasm, vesicular nuclei, and prominent nucleoli. Focal necrosis and mitosis (4–6/10 high power field (hpf) mitosis) noted. Based on these findings, atypical type A thymoma was ruled out (Table 2). Other differential diagnoses for this case include B3 thymoma-spindle cell type and thymic carcinoma. Anaplasia occurring in a thymic epithelial neoplasm alone should not entail a diagnosis of thymic carcinoma. Thymic carcinoma shows loss of organotypical features, more pronounced atypia, presence of mature lymphocytes compared with immature lymphocytes in thymoma and the epithelial cells show CD5 and CD117 positivity (Table 2). As our case morphologically retained organotypical features, showed the presence of Tdt-positive lymphocytes and CD5, CD117-negative epithelial cells, a final diagnosis of B3 thymoma with anaplasia was made.

**Thymic Carcinoma**

There was a single case showing sheets of neoplastic epithelial cells with focal squamoid differentiation. It showed moderate nuclear atypia with no lymphocytes. It showed keratination and intercellular bridging along with necrosis and more than 10 mitosis/10 hpf. On IHC, these epithelial cells were CD5 and CD117 positive. In addition, biopsy from the cervical lymph node also showed metastasis. All these features confirmed the diagnosis of thymic carcinoma. Thymic carcinoma must be differentiated from type B3 and atypical type A thymoma (discussed above and in Table 2).
Microscopic Thymoma (Nodular Hyperplasia of Thymic Epithelium)

We had a single case of microscopic thymoma. The patient was a young female (24 years) who presented with myasthenia gravis. Thymectomy was done as a treatment protocol. Gross and microscopy were unremarkable except for focal areas (0.2–0.3 mm in the maximum dimension) showing proliferation of spindled to ovoid epithelial cells (type A like) without lymphocytes. These epithelial islands were highlighted by PAX8 (Fig. 6). There was no expansile growth or organotypic features. Based on the above findings, a diagnosis of microscopic thymoma (nodular hyperplasia of thymic epithelium) was rendered.

While the previous WHO classification categorizes microscopic thymoma under thymoma subtype, it was removed from the recent WHO classification (fifth edition) as multiple studies done failed to show any evidence of their progressive potential, and the recently recommended term for this entity is nodular hyperplasia of thymic epithelium.2,17

Lymphovascular invasion in Thymic Epithelial Neoplasms

As proven by Alkaai et al in their study,20 the presence of LVI is a standalone risk factor for metastasis/recurrence. This is again highlighted by our findings that show significantly higher proportion of cases with LVI showed metastasis (5/8, 62.5%) compared with cases without LVI (2/25, 8%). This underscores the importance of a diligent search for LVI by pathologists and including LVI status in their reports so that the patient can be followed up and treated accordingly.21

Importance of Differentiating Specific Subtypes in Thymomas

While the modified Masaoka staging system is the most important prognostic factor in thymomas, histologic types of thymoma correlate with the stage; most type A thymomas (60%, 31%), type AB thymomas (67%, 26%), and type B1 thymomas (50%, 31%) present as stage I or stage II disease and are resectable; stage III and IV are rare in type A, AB and type B1 thymomas. Similar to the published literature, none of our type A, AB, and B1 thymomas had stage higher than II. Type B2 (28%, 11%) and type B3 (27%, 18%) present more frequently as stage III or stage IV disease. Likewise in our study, 40% of mixed B2 + B3 thymomas (2/5) and 50% of B3 thymomas (1/2) had stage higher than II. However, none of our B2 thymomas had stage higher than stage II. Also, almost all micronodular thymoma with lymphoid stroma (62%, 36%) analogous to the single case seen in our study (stage I), present as stage I or II disease.17,18

Overall survival and metastasis/recurrence rate also varied between different subtypes of thymomas. Overall the survival of type A, type AB, and type B1 thymoma at 5 and 10 years are almost 100%, while for B2 thymoma, the overall survival at 5 years is around 70% and is around 50% for B3 thymoma.17

The most common location for metastasis in thymic epithelial neoplasms was the pleura as seen in our study. Other
metastatic sites include lungs, thoracic nodes, liver, peritoneum, abdomen-pelvic lymph nodes, and bones with lymph node metastasis being more common in carcinomas.\(^1\,17\,20\,22\,23\) Recurrence and metastasis are extremely rare in type A, while it may be seen in type AB thymoma in 3% of cases and in 11–14% of cases in type B1 thymoma. Similarly, none of our type A and AB thymomas had recurrence or metastasis while one out of five B1 thymomas showed lung metastasis on 2-year follow-up (~Fig. 2). The rate of recurrence was significantly higher in B2 thymoma (14–32%) and B3 thymomas (44%). Proportion of cases with pleural metastasis for B2 and B3 thymoma were 8–10 and 14–15%, respectively, while it was similar between both for distant metastasis (3–5%).\(^17\) In our study, while two mixed B2 + B3 thymomas (2/5, 20%) and one B3 thymoma (1/2, 50%) showed metastasis during initial presentation, two B2 thymoma presented with metastasis (2/8, 25%) 3 years and 4 years post-surgery (~Fig. 3). Micronodular thymoma with lymphoid stroma has very good prognosis with no reports of recurrence/metastasis until date.\(^17\,18\) All these highlight the significance of histologic subtyping of thymomas, which guide the clinicians in further follow-up of the patient.

### Conclusion

Most common thymic epithelial neoplasms were B2 and AB type followed by type B1. Stage I was the predominant stage. This study underscores the importance of thorough sampling, detailed histological evaluation, and role of IHC in the final diagnosis of thymoma. The salient points to be remembered are:

- Pathologist should be aware of rare entities of thymomas such as micronodular thymoma with lymphoid stroma as they closely resemble AB thymomas and have comparatively very good prognosis.
- Focal areas of spindle cells in lymphocyte poor background seen along with lymphocyte predominant B1 or B2 thymoma should alert toward the diagnosis of AB thymoma, which has an overall better prognosis.
- The presence of anaplasia in thymic lesion does not always indicate thymic carcinoma. B2 or B3 thymoma with anaplasia and atypical type A thymoma can present with atypia similar to thymic carcinoma.
- Diligent search and documenting of LVI and exact categorization of the thymoma are vital as both are individual risk factors for metastasis/recurrence and help the clinician in a better follow-up of patients.

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### References


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Histomorphological Spectrum and Diagnostic Challenges in Thymic Epithelial Neoplasms

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