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Micronodular thymic epithelial tumors with lymphoid hyperplasia and mimicking lesions

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Summary. Micronodular arrangement of epithelial cells and lymphoid B-cell hyperplasia with follicles are both peculiar histological features in thymic tissue. Such features may especially occur in thymic epithelial tumors. The most common form is called micronodular thymoma with lymphoid stroma. We have recently described some characteristics of thymic micronodular carcinoma with lymphoid hyperplasia, highlighting how this carcinomatous counterpart should not be misdiagnosed as a thymoma. In this review, we discuss these two entities but also other mimics, which may occur in the anterior mediastinum. These mimics include various types of cellular micronodules and lymphoid backgrounds encompassing a wide range of mediastinal lesions. Non-neoplastic lesions, such as thymic nodular epithelial hyperplasia, thymic lymphoid hyperplasia, or sarcoidosis, as well as tumors of very varying aggressiveness, such as micronodular thymic epithelial tumors, low-grade lymphoma, seminoma, or lympho-epithelial carcinoma, are discussed. We show how these lesions may be misleading and we describe how a correct diagnostic may be obtained in current practice.

Key words: Micronodular thymoma, Thymic carcinoma, Seminoma, Thymic lymphoid hyperplasia, MALT lymphoma, Sarcoidosis

Introduction

Epithelial micronodules with lymphoid hyperplasia have long been recognized as a characteristic feature related to a precise subtype of thymoma (Suster and Moran, 1999). Micronodular thymoma with lymphoid stroma (MNT-LS) is therefore a well-identified entity in the WHO histological classification (Marx et al., 2022). We have recently highlighted that this histological pattern, with subtle but noticeable differences, can also be seen in micronodular thymic carcinoma with lymphoid hyperplasia (Thomas de Montpreville et al., 2021). Focusing on this histological pattern, we have observed that it could also form part of various other histological entities, which occur in the anterior mediastinum, and should therefore be considered in the differential diagnosis of micronodular thymic epithelial tumors. These entities are listed in Table 1 and are the subject of this review in which their main differential characteristics are highlighted.

Micronodular thymoma with lymphoid stroma (MNT-LS).

MNT-LS is histologically characterized by small nodules of spindle or oval bland-looking epithelial cells associated with B-cell lymphoid hyperplasia often containing lymphoid follicles with prominent germinal centers (Suster and Moran, 1999) (Fig. 1). MNT-LS accounts for less than 5% of thymomas and is classified separately from A, AB, and B thymomas (Ghigna and Thomas de Montpreville, 2021; Marx et al., 2022). MNT-LS is a less aggressive tumor, and almost all cases are localized, even if often non-encapsulated, and are cured by surgical resection. Histological diagnosis is usually easy because of the typical pattern of cellular micronodules and lymphoid hyperplasia. However, this pattern is not specific and must not be misdiagnosed. As described in this review, a close morphological examination is mandatory, with immunostaining if

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Abbreviations. LESA-like, LymphoEpithelial SialAdenitis-like; MNT-LS, micronodular thymoma with lymphoid stroma; MALT, mucosa-associated lymphoid tissue

Table 1. Micronodular thymic epithelial tumors and other pathological entities encountered in the anterior mediastinum showing cellular micronodules and/or lymphoid hyperplasia.

Entities	Cellular micronodules	Lymphoid tissue	Main discriminant features
Micronodular thymomas with lymphoid hyperplasia	Bland thymic epithelial cells p63/p40+, CD5-, CD117-	Lymphoid B-cell hyperplasia with lymphoid follicles and TdT-positive thymocytes	
AB thymoma	Bland thymic epithelial cells p63/p40+, CD5-, CD117- CD20+ Inconstant micronodules	TdT-positive thymocytes admixed with epithelial cells. Possible lymphoid B-cells	Epithelial cells admixed within the lymphoid-rich component. Myathenia Gravis (inconstant)
Micronodular thymic carcinoma with lymphoid hyperplasia	Epithelial cells with atypia p63/p40+, CD5+, CD117+	Lymphoid B-cell hyperplasia with lymphoid follicles No TdT-positive thymocytes	
Lymphoepithelial carcinoma	Epithelial cells with atypia p63/p40+, CD5+, CD117+ Inconstant micronodules	Lymphoplasmacytic hyperplasia with lymphoid follicles. No TdT-positive thymocytes	Syncytial appearing tumor cells, positive for Epstein-Barr encoding region (EBER) *in situ* hybridization
Nodular thymic epithelial hyperplasia	Bland thymic epithelial cells	TdT-positive thymocytes Possible B-cell hyperplasia	Microscopic lesion without gross tumor appearance
Seminoma	Atypical cells, CD117+ Inconstant micronodules	Lymphoid hyperplasia with lymphoid follicles	Epithelioid granulomas (inconstant) Faint and focal keratin positivity SALL4+, OCT4+, PLAP+
Sarcoidosis	Follicles of epithelioid cells	Lymph node lymphoid tissue	Keratin negativity, CD68+
Follicular / LESA-like thymic hyperplasia	Lack of epithelial micronodules	Lymphoid B-cell hyperplasia with lymphoid follicles	Normal or hyperplastic thymic epithelium +/- cysts +/- lymphoepithelial lesions
Thymic MALT lymphoma	Lack of epithelial micronodules	Neoplastic lymphoid B-cells with lymphoid follicles	

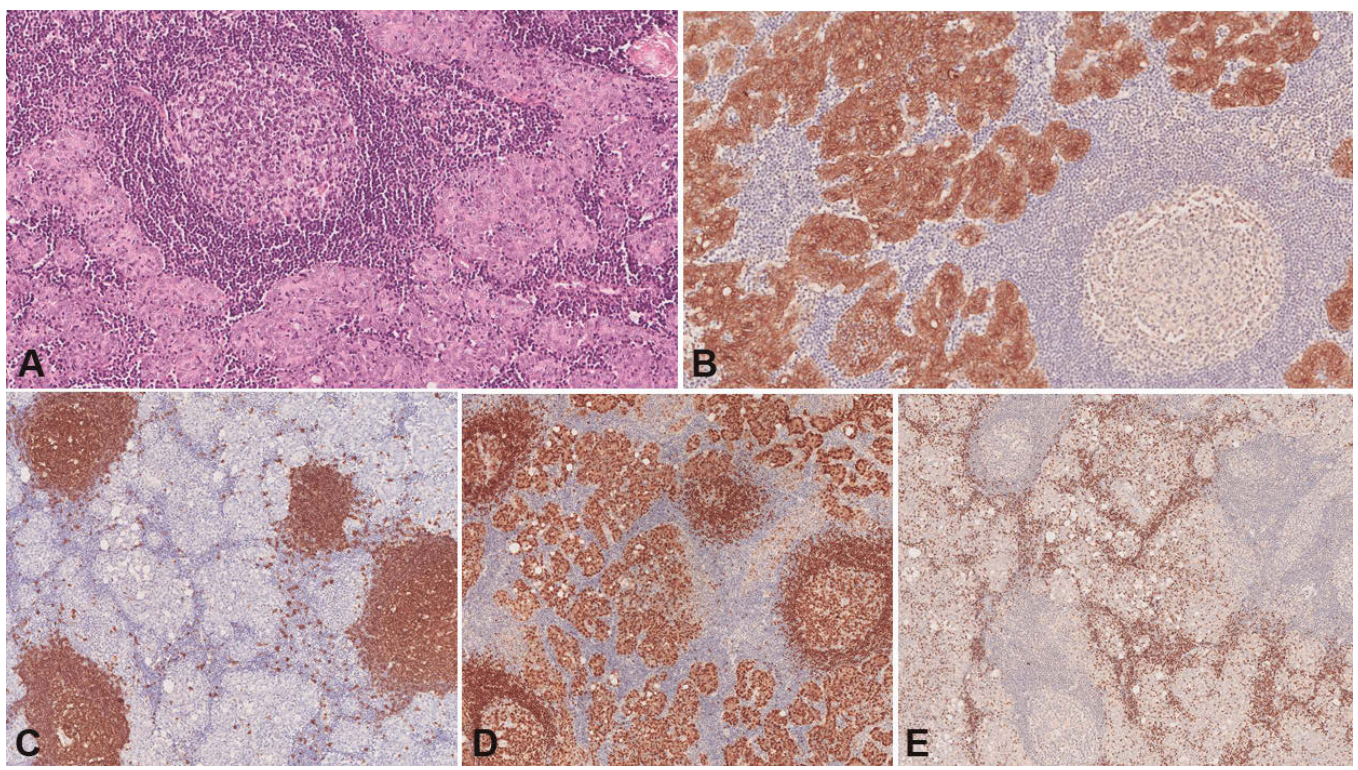

Fig. 1. Typical histological features of micronodular thymomas with lymphoid stroma. **A.** Hematoxylin-eosin stain showing epithelial micronodules in a lymphoid background with a follicle. **B.** Immunohistological staining showing keratin-positive cells (AE1-AE3) restricted to micronodules. **C.** CD20 immunostaining of B-lymphoid cells. **D.** Both epithelial nodules and B-cell lymphoid follicles are Pax8 positive. **E.** TdT-positive lymphocytes surrounding epithelial nodules.

necessary. Otherwise, it may be noteworthy that, on a biopsy sample, a rare ectopic MNT-LS occurring in the cervical region (Yu et al., 2016) may simulate a metastatic squamous cell carcinoma in a lymph node.

Type AB thymoma

MNT-LS and AB thymomas may appear as similar clinicopathological lesions. These two tumors share the same fairly good prognosis. They are associated with the same *GTF2I* mutation (Bille et al., 2024), which is not associated with B-type thymomas. They also share similar histological characteristics: these tumors are both made up of ovoid/spindle bland epithelial cells and present lymphoid-rich and lymphoid-poor areas. So, if the lymphoid-poor areas of an AB thymoma display a micronodular pattern, the AB thymoma could be misdiagnosed as a MNT-LS (Fig. 2). The clue for a correct diagnosis is the presence of epithelial cells in the lymphoid-rich areas of AB thymomas, whereas the lymphoid stroma of MNT-LS is totally devoid of epithelial cells (Marx et al., 2014; Chalabreysse et al., 2021). Additionally, MNT-LS may sometimes co-exist with type A or AB thymomas (Marx et al., 2022), which makes the differential diagnosis even more challenging. Otherwise, AB thymomas may be clinically associated with myasthenia gravis, whereas MNT-LS are usually not (Ghigna and Thomas de Montpreville, 2021).

Micronodular thymic carcinoma with lymphoid hyperplasia

Micronodular thymic carcinoma with lymphoid hyperplasia has been added to the last classification of thymic tumors as a subtype of squamous cell carcinoma (Marx et al., 2022). However, unlike classic squamous

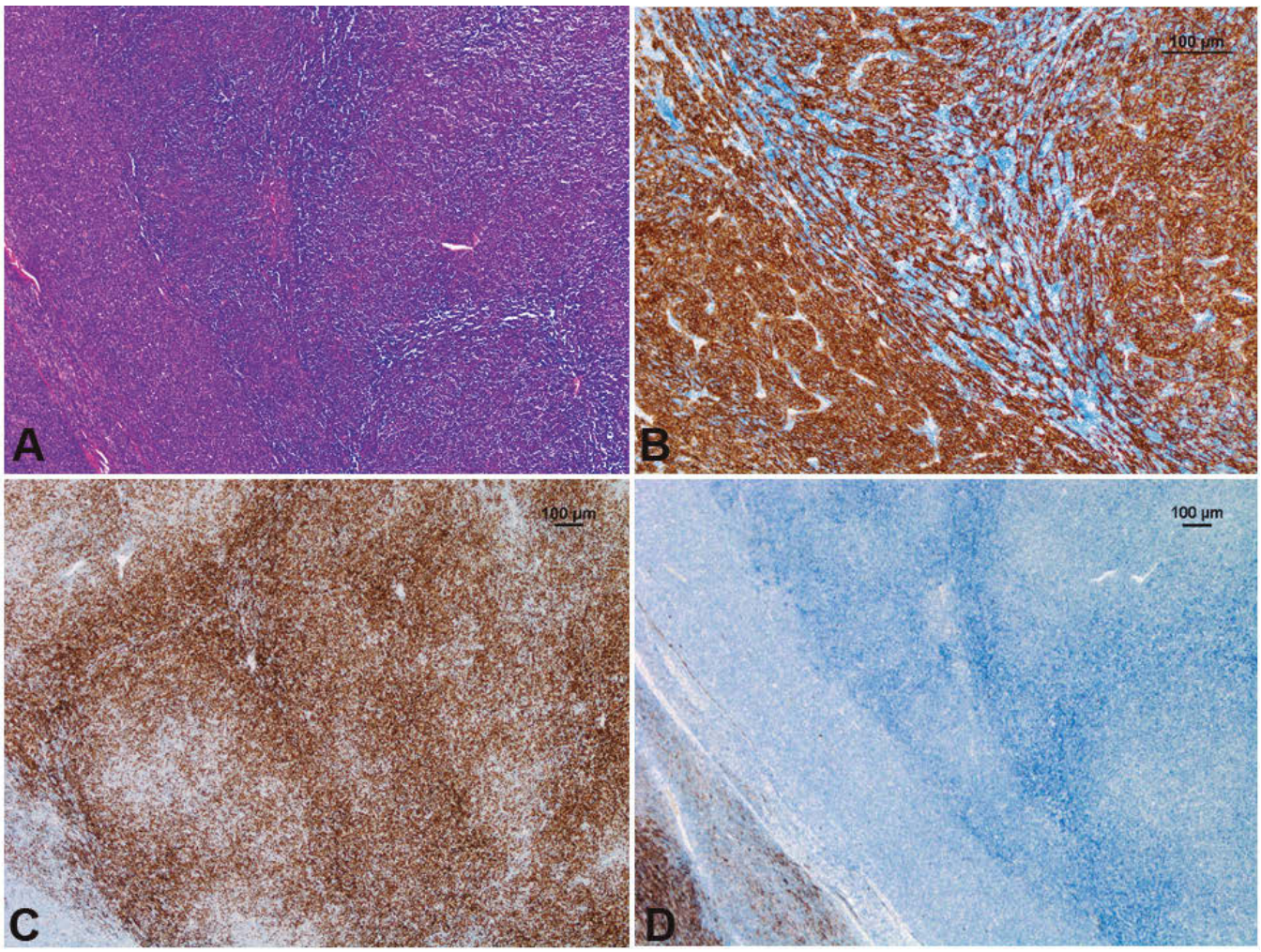

Fig. 2. AB type thymoma with micronodular features. **A.** Hematoxylin and eosin stain showing micronodular areas surrounded by lymphocyte-rich areas. **B.** Immunostaining showing keratin (AE1-AE3)-positive cells in both micronodular and lymphoid areas. **C.** Immunostaining showing TdT-positive lymphocytes in both micronodular and lymphoid areas. **D.** Immunostaining with an anti-CD20 antibody showing positive spindle epithelial cells in the left lower corner and lack of B-cell hyperplasia.

cell carcinoma, the stroma is purely lymphoid and not desmoplastic. Micronodular thymic carcinoma with lymphoid hyperplasia histologically resembles MNT-LS and can be considered its malignant counterpart. This carcinoma displays morphological and immunohistochemical features (Fig. 3) that are distinctive from MNT-LS (Thomas de Montpreville et al., 2021; Yagi et al., 2021; Liu et al., 2022). Carcinomatous epithelial cells display cytological atypia and mitoses; they usually express CD5, CD117, and, diffusely, Glut1. Lastly, TdT-positive immature T cells, which typically surround epithelial nodules in MNT-LS, are absent in micronodular carcinoma with lymphoid hyperplasia. The lymphoid hyperplasia in micronodular thymic carcinoma could be an indicator of anti-tumor immunity and could explain its favorable prognosis when compared with other squamous cell thymic carcinomas. Nevertheless, avoiding misdiagnosis of MNT-LS may have important consequences on the patient's treatment, such as possible post-operative radiotherapy and closer follow-up (Thomas de Montpreville et al., 2021).

Other thymic carcinomas with lymphoid hyperplasia

Lymphoepithelial carcinoma, formerly called lymphoepithelioma-like carcinoma, is a rare subtype of thymic carcinoma (Marx et al., 2022). It is a poorly differentiated squamous carcinoma with prominent reactive lymphoplasmacytic infiltration identical to undifferentiated nasopharyngeal carcinoma (Ose et al., 2021; Zhang et al., 2023). Large syncytial-appearing tumor cells with vesicular nuclei and distinct nucleoli, positive for p63/p40, CD5, and CD117, with lymphoplasmacytic infiltration and germinal centers in the stroma, may simulate a micronodular thymic carcinoma with lymphoid hyperplasia (Thomas de Montpreville et

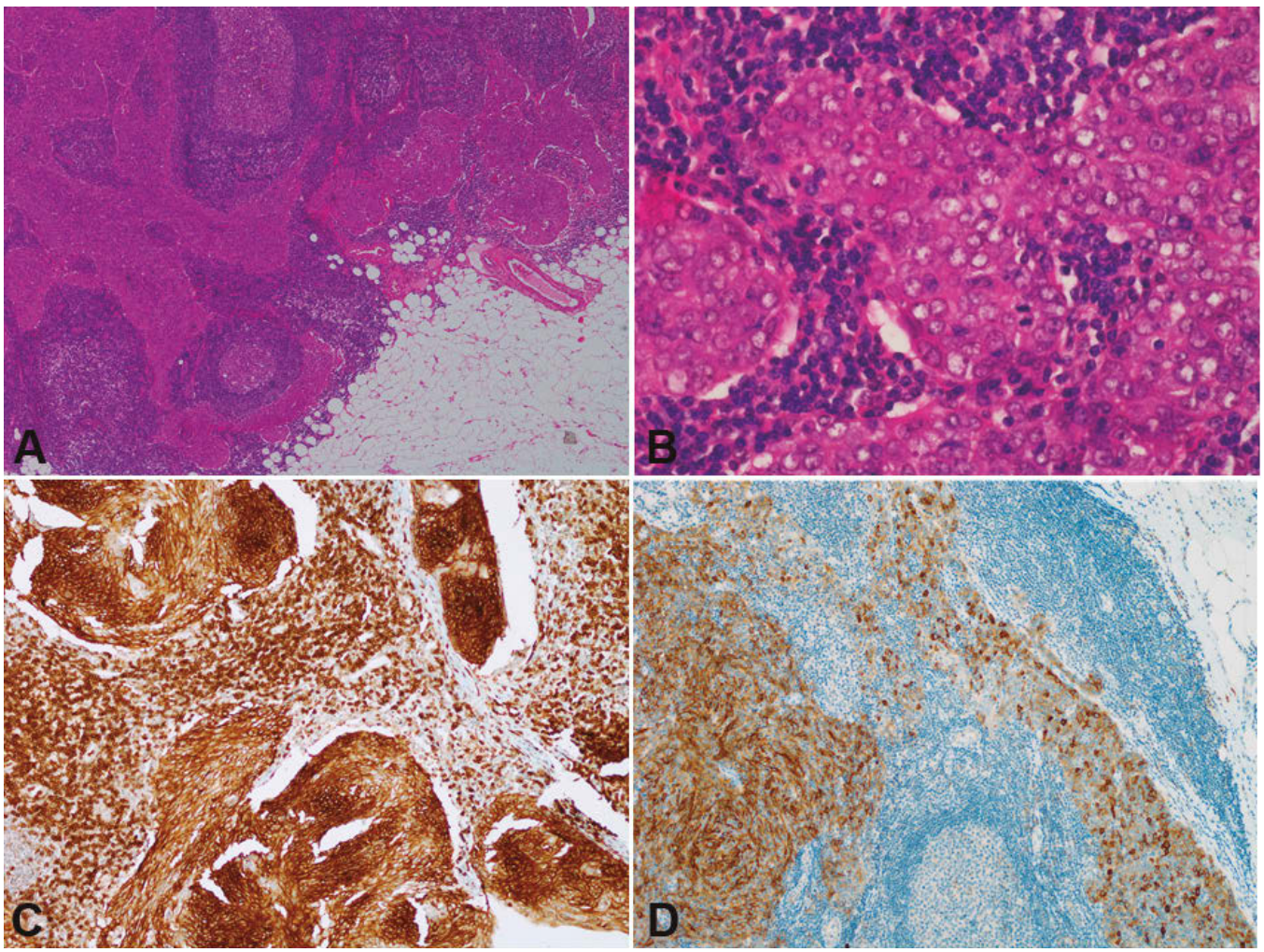

Fig. 3. Micronodular thymic carcinoma with lymphoid hyperplasia. **A.** Low magnification showing a histological aspect very similar to that of a micronodular thymoma with lymphoid stroma. **B.** At higher magnification, epithelial cells are atypical and mitosis is visible. Epithelial nodules are both CD5- **(C)** and CD117-positive **(D)**.

al., 2021). However, thymic lymphoepithelial carcinomas are much more frequently associated with Epstein-Barr Virus infection (Fig. 4) than other thymic epithelial tumors (Ose et al., 2021; Zhang et al., 2023). The differential diagnosis is important since lymphoepithelial carcinoma is a highly malignant tumor with a poor prognosis (Ose et al., 2021).

Undifferentiated large cell carcinoma of the thymus associated with plasma-cell type Castleman disease-like reaction is an extremely rare tumor (Han et al., 2022); tumor cells are reported to be negative for CD5, CD117, and p63/p40 (Han et al., 2022).

Nodular hyperplasia of thymic epithelium

Hyperplastic nodules of thymic epithelium, formerly known as microscopic thymomas, are epithelial proliferations smaller than 1 mm (Fukuhara et al., 2017; Furuya et al., 2018). These micronodules tend to be multifocal and resemble only cytologically type A thymomas (Fig. 5). They characteristically occur in patients with myasthenia gravis and, therefore, may be associated with thymic lymphoid hyperplasia with germinal centers (Chalabreysse et al., 2006). These hyperplastic epithelial nodules should not be considered true thymomas.

Seminomas

The anterior mediastinum is the least rare location of extragonadal germ cell tumors (Napieralska et al., 2018; Szolkowska et al., 2019; El-Zaatari and Ro, 2021; Ghigna and Thomas de Montpreville, 2021). Most of these mediastinal germ cell tumors are benign teratomas.

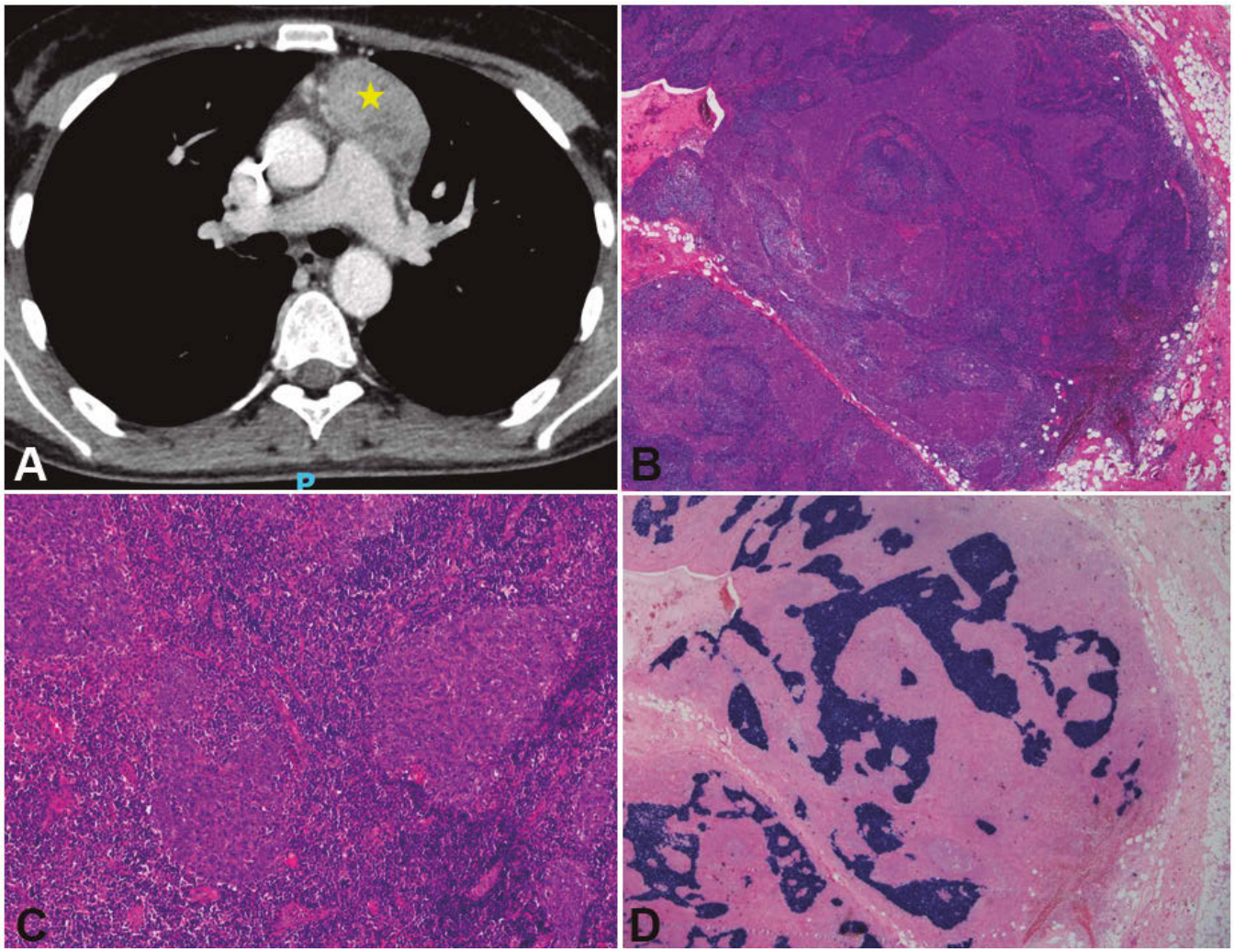

Fig. 4. Thymic Lymphoepithelial carcinoma. **A.** CT scan of the chest showing the thymic mass (star). **B.** Histological appearance of the tumor with epithelial nodules in a lymphoid background at Low-magnification. **C.** Higher magnification of tumor epithelial micronodules. **D.** *In situ* hybridization with an Epstein-Barr encoding region (EBER) probe.

Malignant tumors are rare and classified as either seminomas or non-seminomatous malignant germ cell tumors. Most seminomas that present as large infiltrating lesions are diagnosed by biopsy. Some mediastinal seminomas may also present as straightforwardly resectable thymic tumors. Some clinical data could suggest a mediastinal seminoma rather than the more frequent thymic epithelial tumor: association with Klinefelter syndrome, occurrence almost exclusively in men, mostly at a younger age, and possibly with a slightly increased beta-HCG serum level (Napieralska et al., 2018; Ghigna and Thomas de Montpreville, 2021). Histologically, seminomas may simulate micronodular thymic epithelial tumors with lymphoid hyperplasia: the primitive germ cells often grow in nests associated with lymphoid follicular hyperplasia (Weissferdt and Moran, 2015; Holmes et al., 2021) and fibrous septa. Possible epithelioid granulomas, very unusual in thymic epithelial tumors, may be a diagnostic clue but are inconstant. With immunohistochemistry, seminomas share cytokeratin expression with thymic epithelial tumors (however, more focally and more weakly with dot-like staining) and seminomas also express CD117-like thymic squamous carcinomas (Fig. 6). Of course, when one thinks of the less frequent diagnosis of seminoma, discriminant markers (SALL4, OCT4, or PLAP) and chromosome 12p abnormalities may be used (Fichtner et al., 2022; Ozgun and Nappi, 2023).

Sarcoidosis

Sarcoidosis is a frequent intra-thoracic disease (Tana et al., 2021). Pulmonary sarcoidosis is usually associated with bilateral hilar lymphadenopathy. In mediastinal sarcoidosis, the involvement mainly affects paratracheal lymph nodes in the middle mediastinum (Jeny et al.,

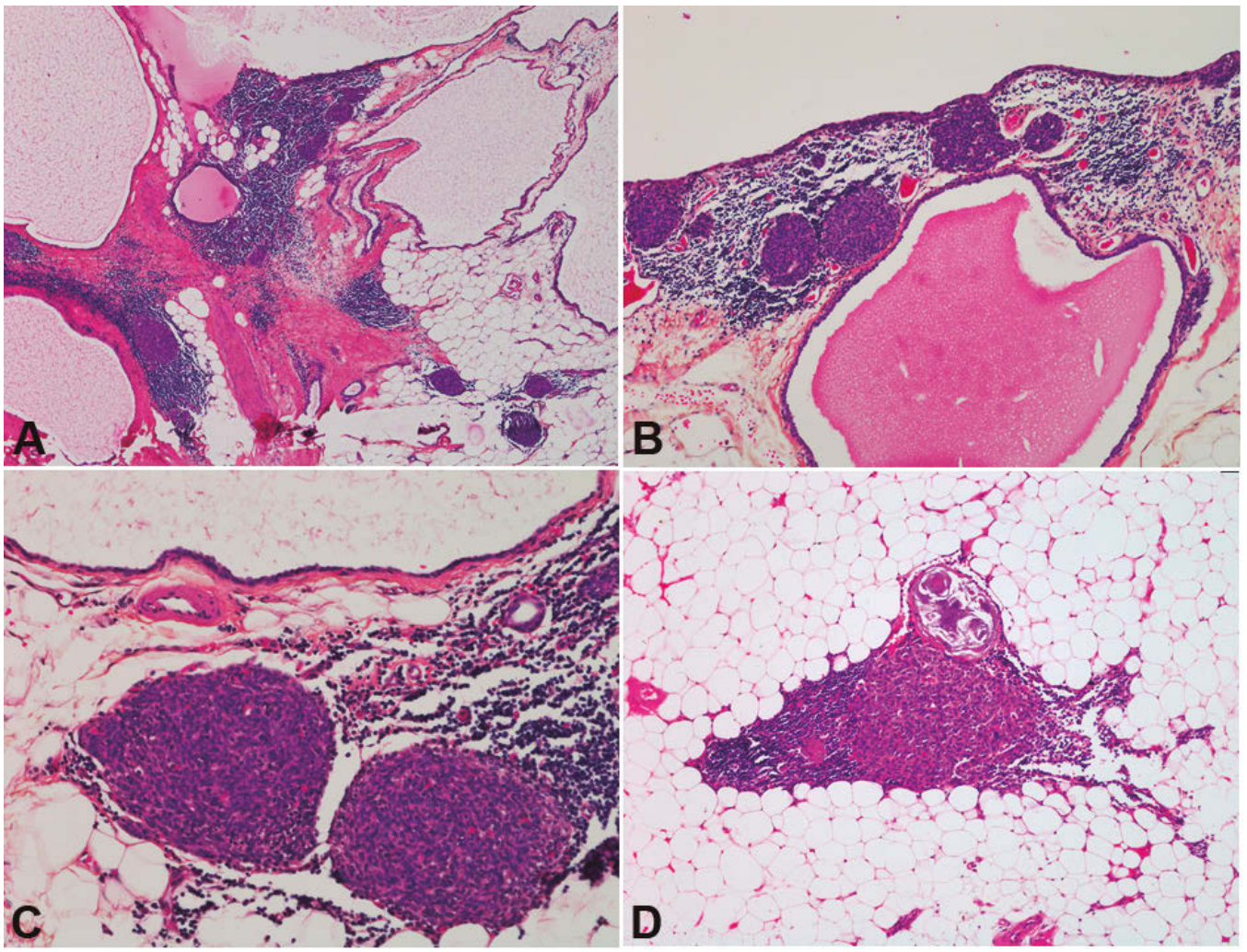

Fig. 5. Nodular hyperplasia of thymic epithelium. **A.** Multifocal epithelial nodular hyperplasia in an involuted thymus with cystic changes. Thymic hyperplastic epithelial micronodules near a thymic cyst **(B, C)** and in an involuted thymic lobule **(D)**.

2020). Even if any mediastinal lymph node station may be involved, less frequent locations-especially the anterior mediastinum (prevascular station)-suggest other diagnoses such as lymphoma or thymoma (Jeny et al., 2020). Nevertheless, in a recent study (Shahana et al., 2023), sarcoidosis accounted for 17% (7/41) of anterior mediastinal masses. Being a non-neoplastic disease, sarcoidosis is not always included in the differential diagnosis of mediastinal tumors. Of course, the histological diagnosis of sarcoidosis is usually easy on any sample from a mediastinal lymph node in a compatible clinical setting (Sève et al., 2021; Tana et al., 2021). However, as shown in Figure 7, the non-necrotizing granulomas with epithelioid cells in the lymph node lymphoid background can morphologically simulate a micronodular thymoma with lymphoid hyperplasia, if a lymph node location is not suspected in the anterior mediastinum.

Thymic B-cell lymphoid hyperplasia and low-grade mucosa-associated lymphoma

Thymic B-cell lymphoid hyperplasia with lymphoid follicles occurs in different benign entities. Follicular thymic hyperplasia is a common condition, which can be associated with any dysimmune disease and is especially seen in Myasthenia Gravis (Lefeuvre et al., 2020). Such follicular thymic hyperplasia is an easy histological diagnosis since the normal thymic architecture is preserved. However, in pseudo-tumorous lesions classified as multilocular thymic cysts (Oda et al., 2019) or thymic hyperplasia with lymphoepithelial sialadenitis-like (LESA-like) features (Porubsky et al., 2021), the lymphoid hyperplasia is associated with cystic and fibrotic changes, and with epithelial hyperplasia.

Low-grade mucosa-associated lymphoid tissue (MALT) lymphoma rarely occurs in the thymus (Zang et al., 2022; Zhou et al., 2022). MALT lymphomas are often associated with chronic inflammation such as thymic lymphoid hyperplasia, especially in Sjögren syndrome (Wang et al., 2022). These MALT lymphomas have a very favorable prognosis (Zang et al., 2022).

Obvious lymphoid follicles with germinal centers occurring in thymic masses related to multilocular thymic cysts, LESA-like thymic hyperplasia, and MALT lymphomas must not be misdiagnosed as micronodular thymic epithelial tumors with lymphoid hyperplasia. Even if the epithelial thymic tissue is hyperplastic or is disrupted by the lymphoid tissue or by fibrosis, there is no epithelial neoplastic proliferation. In doubtful cases,

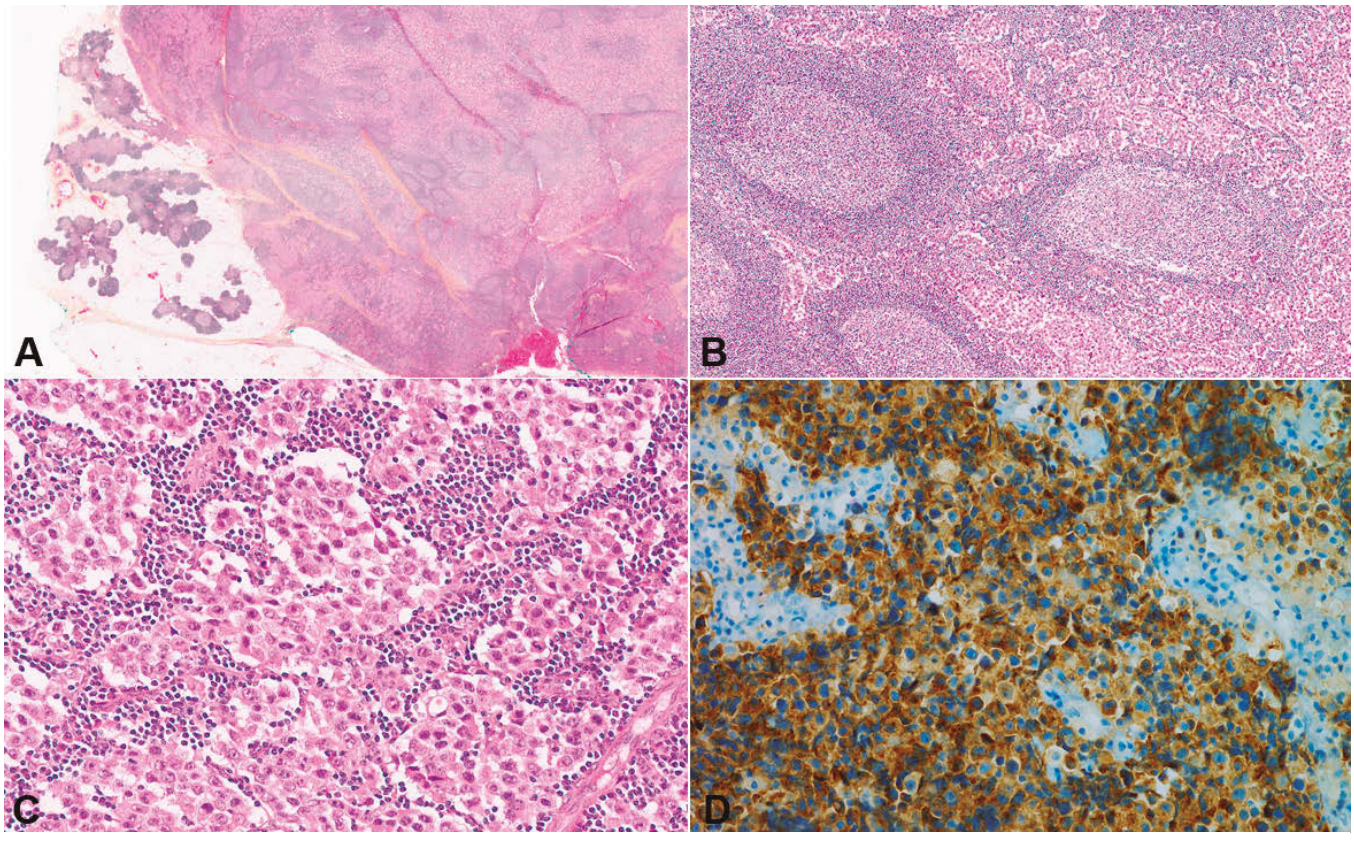

Fig. 6. Thymic seminoma with lymphoid hyperplasia. **A.** Intra-thymic lesion at low magnification. **B.** Lymphoid follicular hyperplasia within the tumor. **C.** Nests of tumor cells surrounded by lymphocytes at higher magnification. **D.** CD117 expression by tumor cells.

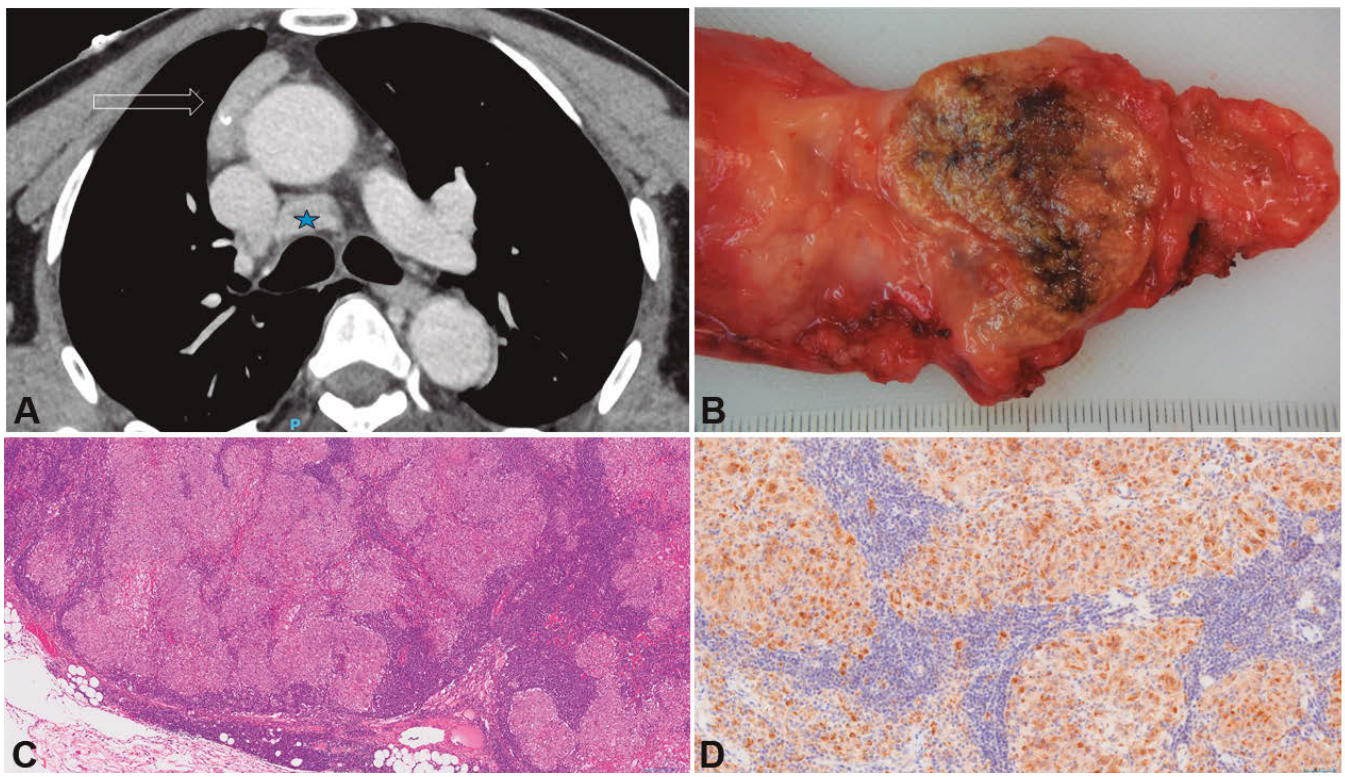

Fig. 7. Sarcoidosis mimicking a micronodular lesion in the anterior mediastinum. **A.** CT scan of the chest showing a large lesion in the anterior mediastinum (arrow). A lymphadenopathy is also present in front of the left main bronchus (star). **B.** Gross appearance of the lesion with anthracosis. **C.** Histological appearance of epithelioid granulomas forming nodules in the lymph node (hematoxylin-eosin stain, low magnification). **D.** Immunohistochemical expression of CD68 by epithelioid cells.

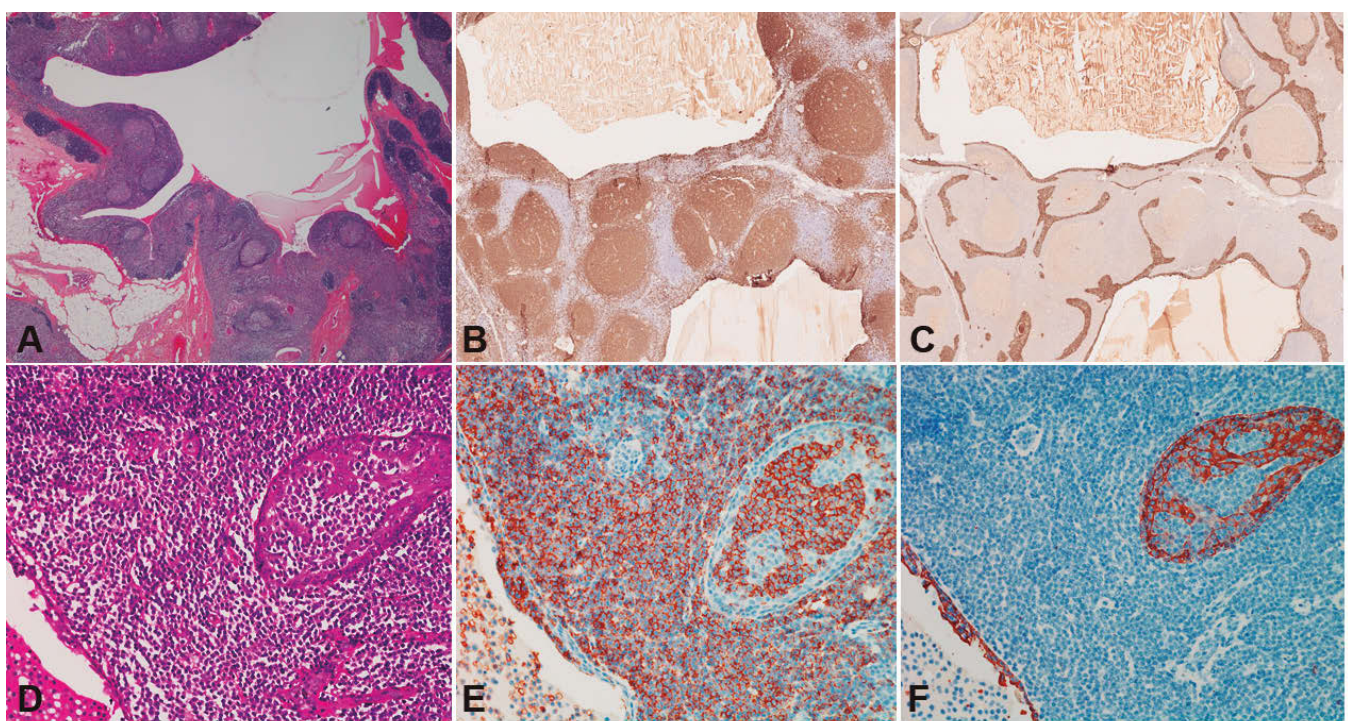

Fig. 8. Thymic lymphoid hyperplasia and MALT lymphoma: lymphoid hyperplasia with cystic changes (**A-C)** and lymphoepithelial lesion in MALT lymphoma **(D-F)**. Hematoxylin-eosin stain **(A, D)**, CD20 **(B, E)**, and keratin **(C, F)** immunostainings.

this can be confirmed by immunostaining for cytokeratin, which only shows possible lymphoepithelial lesions (Fig. 8).

Conclusion

In the mediastinum, micronodular cellular nodules and lymphoid hyperplasia first evoke micronodular thymoma with lymphoid stroma and micronodular carcinoma with lymphoid hyperplasia. However, pathologists should be aware of mimicking lesions, which can be rather easily diagnosed mainly by keeping them in mind.

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Conflicts of Interest. The authors declare no competing interest.

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