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*Case Report*

# Langerhans cell proliferation in micronodular thymic carcinoma with lymphoid stroma: report of a rare case

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**Abstract:** Micronodular thymic carcinoma (MNCA) is an extremely rare variant of thymic carcinoma. We described a 67-year-old woman, who was referred to our institution for a mediastinal mass. The magnetic resonance imaging (MRI) scan showed a 5.0 cm × 4.1 cm × 2.2 cm infiltrative mass invading adjacent tissue with central cystic change. Histologically, the neoplasm was composed of epithelial tumor cells arranged in a micronodular growth pattern set in a stroma showing lymphoid hyperplasia with germinal centers. Contrary to micronodular thymoma-the benign micronodular thymic neoplasm, the epithelial cell component of the present case showed malignancy characterized by cytological atypia, increased mitotic activity and immunoactivity of CD5 and CD117. The lymphoid component was mixed mature B- and T-cells. Langerhans cells proliferation were confirmed within epithelial nodules with langerin, S-100, CD1a expression. We report a case of MNCA to emphasize the histopathologic features and the Langerhans cells proliferation and differential diagnosis of the rare lesion to promote a better and broader understanding of the morphologic spectrum of micronodular thymic neoplasm.

**Keywords:** Thymic carcinoma, micronodular, langerhans cell

## Introduction

Micronodular thymic neoplasm was an uncommon variant of thymic tumors. The majority of cases in literatures are micronodular thymoma (MNT) with lymphoid hyperplasia known for its benign behavior. Malignant micronodular thymic neoplasm, first described by Weissferdt A et al in 2012 [1], were described as micronodular thymic carcinoma (MNCA) with lymphoid hyperplasia or thymic carcinoma with micronodular growth pattern fewer than 10 cases in English literatures [1, 2]. Histologically, the neoplasm was composed of epithelial tumor cells arranged in a micronodular growth pattern set in a stroma showing lymphoid hyperplasia with germinal centers. Contrary to MNT-the benign micronodular thymic neoplasm, the epithelial component of MNCA showed malignancy characterized by cytological atypia, increased mitotic activity and immunoactivity of CD5 and CD117 [1]. Here we presented a case of micronodular thymic carcinoma with lymphoid hyperplasia in stroma, and Langerhans cells proliferation within epithelial components was confirmed in the present case. To our best knowledge, it is the first case of MNCA with Langerhans cells proliferation in epithelial components in the literature. The study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Written informed consent was obtained from the patient.

## Material and methods

### *Patient and tumor*

A 67-year-old, previously healthy Chinese woman underwent a routine physical examination one week ago, and a mass was discovered in her superior mediastinum with ultrasound examination and computed tomography (CT) and MRI. The patient declared no history of myasthenia gravis or other autoimmune disorder, and subsequently surgical resection of the mediastinal mass was performed.

**Table 1.** Antibodies and dilutions used in the evaluation of micronodular thymic carcinoma

| Antibody | Dilution | Source |
|---|---|---|
| P63 | 1:25 | Novocastra |
| CK5/6 | 1:200 | ZYMED |
| AE1/AE3 | 1:20 | Dako |
| EMA | 1:50 | Dako |
| Langerin | 1:100 | Novocastra |
| Cd1a | 1:100 | Dako |
| S-100 | 1:1000 | Dako |
| CD3 | 1:20 | Novocastra |
| CD5 | 1:50 | Novocastra |
| CD117 | 1:200 | Dako |
| CD20 | 1:2000 | Dako |
| TdT | 1:50 | Dako |
| CD99 | 1:50 | Dako |
| KI67 | 1:30 | Novocastra |

*Histology and immunohistochemistry*

The specimens were fixed in 4% formalin and embedded in paraffin. Sections were cut and stained with hematoxylin & eosin (H & E) routinely. Immunohistochemical stains were performed by an enhancement method based on the pressure-cooking-based antigen retrieval of slides that were placed into 0.01 M citrate buffer at pH 6.0 on 5-μm sections cut from paraffin blocks. Binding of primary antibodies was visualized with an Envision two-step method. Diaminobenzidine was used as the chromogen. Nuclei were stained with Mayer's hematoxylin. The antibodies applied are given in **Table 1**.

## Results

Grossly, the mass measured 5.0 cm × 4.1 cm × 2.2 cm in size. The cut surface was grey-white in color with central cystic change, and invasion into adjacent tissue was observed without a clear fibrous capsule. Microscopically, on low power, the histological finding was a micronodular growth pattern characterized by multiple epithelial cell nodules separated by an abundant lymphoid stroma with germinal centers in peripheral zone (**Figure 1A**) and by fibrous to hyaline stroma with few lymphoid cell infiltration in central zone (**Figure 1C**); while on high power, the epithelial cells showed large and oval to polygonal shaped with vesicular nuclei, conspicuous nucleoli and abundant pale cytoplasm. Mitoses varied from 5 to 8 per 10 high power fields, and no necrosis or keratinization was present (**Figure 1B**, **1C**).

Immunohistochemical stains showed the nodular epithelioid component positive for CK5/6, CKpan, CD5 (**Figure 1D**) and CD117 (**Figure 1E**) in peripheral zone, as well as in central zone; the lymphoid stroma in peripheral zone was composed mainly of mature B lymphocytes (CD20+) especially highlighting the follicles and germinal centers. Mature CD3+/TdT- T-lymphocytes were also numerous without immature T cells presence. Some langerin+ (**Figure 1F**), S-100+, CD1a+ cells were scattered within epithelial cell micronodules.

The diagnosis of micronodular thymic carcinoma with lymphoid stroma was made. Follow-up revealed that the patient was alive and well 20 months without recurrence after initial diagnosis.

## Discussion

Micronodular thymoma (MNT) with lymphoid B-cell hyperplasia is a rare variant of thymoma, characterized by numerous epithelial nodules of spindle morphology, mixed in lymphoid stroma, even with lymphoid follicles and germinal center [3, 4]. MNT displays a benign behavior with no cell atypia, increasing mitosis and necrosis. Micronodular thymic carcinoma (MNCA) with lymphoid hyperplasia was more recently described as the malignant counterpart of micronodular thymoma with lymphoid B-cell hyperplasia [1] (**Table 2**). A series of reports gave support to the theory that micronodular thymic tumors with follicular lymphoid hyperplasia had a morphologic spectrum from completely benign micronodular thymoma with lymphoid B-cell hyperplasia to malignant micronodular thymic carcinoma with lymphoid hyperplasia, although there was no an entity of micronodular thymic carcinoma in the newest list of WHO thymic tumors classification [5, 6].

In the present case, on low-power microscopic view, histological findings in the peripheral zone of the lesion showed a typical micronodular growth pattern characterized by multiple small tumor nodules or sheet-like, elongated areas of epithelial components separated by an abundant lymphoid stroma with lymphoid follicles and germinal center. While the abundant lymphoid stroma became less when transitioned

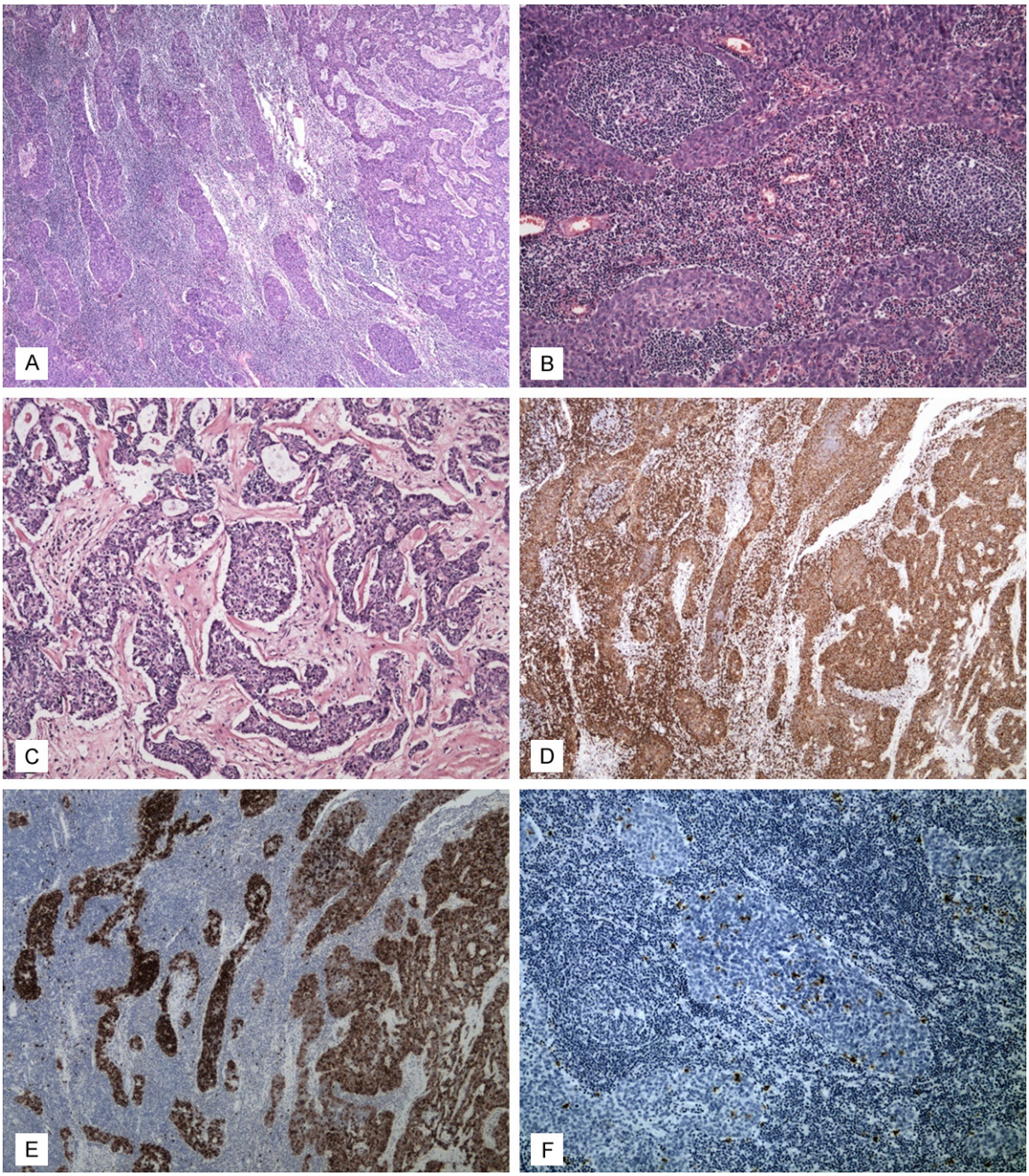


**Figure 1.** A. The tumor showed a micronodular growth pattern characterized by multiple epithelial cell nodules separated by an abundant lymphoid stroma with germinal centers in peripheral zone (left) and by fibrous to hyaline stroma with few lymphoid cell infiltration in central zone (right) (H & E, × 100); B. The tumor showed micronodular growth pattern characterized by multiple epithelial cell nodules separated by an abundant lymphoid stroma with germinal centers: epithelial cells showed large and oval to polygonal shaped with vesicular nuclei, conspicuous nucleoli and abundant pale cytoplasm. Mitoses varied from 5 to 8 per 10 high power fields (H & E, × 200); C. The epithelial components showed trabecular growth pattern with less micronodular structures in the central zone and the lymphoid stroma replaced by fibrous to hyaline one (H & E, × 200); D. The epithelial component was positive for CD5 in peripheral zone (left), as well as in central zone (right) (× 200); E. The epithelial component was positive for CD 117 in peripheral zone (left), as well as in central zone (right) (× 200); F. Langerhans cells were scattered in the epithelial nodules with langerin positivity (× 200).

to the central zone and replaced by fibrous and hyaline stroma with little lymphoid tissue. The epithelial components showed trabecular growth pattern with less micronodular structures

**Table 2.** Micronodular thymic carcinoma with micronodular growth pattern cases reported in literature

| First author | Cases | Age/sex | Sites | Size (diameter) | Diagnosis | Time |
|---|---|---|---|---|---|---|
| Weissferdt A | 5 | Mean 64 ys/2 F, 3 M | thymus | 3.2-10 cm | MNC | 2012 |
| WS Mneimneh | 1 | 75 ys/F | thymus | NS | MNC | 2015 |

MNC: micronodular carcinoma; ys: years; F: female; M: male; NS: not stated.

in the central zone of the lesion. These histological findings were different to the previous reports of MNCA with solely micronodular pattern. On high power examination, the epithelial cells of the micronodules showed spindle to round or oval shaped with vesicular nuclei and abundant pale eosinophilic cytoplasm with atypia and increasing mitotic activity (5-8/10 HPFs) compared with bland appearance of epithelial cells in classical MNT [7]. There was no necrosis or keratinization presence in this case.

Immunohistochemical stain showed positivity of CD5 and CD117 and higher proliferation index of the epithelial components in both peripheral and central zone also gave support to the diagnosis of MNCA other than MNT. We were interested in whether there were Langlerhans cells proliferation or not in the epithelial components of this case since we had confirmed the phenomenon in a rare ectopic MNT [8], and the Langerhans cells proliferation was observed in six MNT cases from other group at the mean time [9]. The immunohistochemical stain of langerin in the present case showed that Langerhans cells proliferation could be observed in the epithelial components not only in the micronodules in peripheral zone but also in the epithelial trabecula in the central zone, and the density of Langerhans cells in peripheral zone is relatively higher than in the central zone. It was known that the Langerhans cells originated from the bone marrow and then migrated into different parts of the body to perform the function of antigen recognition and presentation. It was hypothesized that the Langerhans cells proliferation reflects a host immune reaction against epithelial tumoralantigens [9]. We had no idea about the clinical importance of the Langerhans cells proliferation in micronodular thymic neoplasms by far. Further study would be carried out to detect the Langerhans cells proliferation in the thymic neoplasms including not only more cases of MNCA and MNT but also other subtypes of thymic neoplasms. The role of Langerhans cells in the thymic neoplasm could be clarified then.

Lymphoid hyperplasia with germinal centers of the stroma in the present case reflected the host immune response in reaction to tumor epithelial antigens, which is believed to be beneficial, leading to the improved survival [10, 11]. It was reported that the malignant transformation may also occur in the lymphoid component of micronodular thymic neoplasms, the extranodal marginal cell lymphoma and follicular lymphoma were two common subtype of the malignant transformation of the lymphoid stroma of the micronodular thymic neoplasms [3]. In the present case, there was no morphological and immunohistochemical evidences of the malignant transformation of the lymphoid stroma but mixed mature B cells with germinal center formation and some mature T cells without TdT expression in peripheral zone, and the lymphoid stroma was replaced by the fibrous and hyaline stroma in the central zone of the tumor.

Since MNCA was an extremely rare tumor, awareness of potential diagnostic pitfalls is important for the correct diagnosis. MNT should be the first differential diagnostic consideration for MNCA. As a benign one of micronodular thymic neoplasm, MNT showed no cellular atypia and low mitotic activity without CD5 and CD117 expression in epithelial components [12], and necrosis was not seen in the MNT. The other subtypes of thymoma including type B3 thymoma and type A thymoma could be the diagnostic pitfalls for their epithelial components proliferation mimicking the micronodules in MNCA. Both two subtypes of thymoma could be ruled out easily in the present case for its distinct micronodular structure with lymphoid stroma [5]. The lymphoepithelioma-like thymic carcinoma or spindle cell 'sarcomatoid' carcinoma should be also considered as differential diagnosis [13, 14]. The lymphoepithelioma-like thymic carcinoma had histologic features similar to lymphoepithelioma-like carcinoma of the nasopharynx with sheets of large cells with vesicular nuclei and prominent eosinophilic nucleoli with a scant and indistinct rim of cytoplasm and lymphocytes in the stroma may be

dense or may not be present [15]. Spindle cell 'sarcomatoid' carcinoma of thymus showed spindle and pleomorphic cells with hyperchromatic nuclei, prominent nucleoli, and numerous mitoses and few lymphocytes in the stroma [16].

In summary, we present a very rare case of micronodular thymic carcinoma with lymphoid stroma and confirmed Langerhans cells proliferation in the epithelial nodules. Awareness of the existence of micronodular thymic carcinoma is important for the differential diagnosis of thymic neoplasms in order not to confuse the rare tumor for its histological features to mimics lesions. Accumulation of the MNCA cases and longer follow-up may further obtain more data regarding the prognosis for patients with this lesion.

## Disclosure of conflict of interest

None.

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