

Case Report

Langerhans cells proliferation in ectopic micronodular thymoma with lymphoid stroma: a case report

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Abstract: Ectopic micronodular thymoma (MNT) is a rare tumor. We described a 76-year-old woman, who was referred to our institutional for a mass in the left cervical region. The Magnetic Resonance Imaging (MRI) scan showed a 3.7 cm × 1.7 cm × 2.0 cm mass. The neoplasm was composed of epithelial tumor cells arranged in a micronodular growth pattern set in a stroma showing lymphoid hyperplasia with germinal centers. Immunohistochemical studies showed that the neoplastic epithelial cells were reactive for AE1/AE3, CK5/6, P63, and the lymphoid component to be of mixed B- and immature T-cell lineage. Langerhans cells were confirmed within epithelial nodules for the first time with langerin, S-100, CD1a expression. We report a case of cervical ectopic MNT to emphasize the langerhans cells proliferation and the histopathologic features and differential diagnosis of the rare lesion to promote a better and broader understanding of this less understood subject.

Keywords: Thymoma, micronodular, ectopic, langerhans cell

Introduction

Thymomas are rare thymic epithelial tumors. The World Health Organization (WHO) classification recognizes the following usual subtypes of thymoma: A, AB, B1, B2 and B3 type. Some special or “unusual” variants are also described including micronodular thymoma, metaplastic thymoma, microscopic thymoma, thymoma with anaplasia, and thymic carcinoma [1]. Micronodular thymoma is a rare variant of thymoma. The tumor is characterized by numerous epithelial nodules of spindle morphology, mixed in lymphoid stroma, even with lymphoid follicles and germinal center. Ectopic micronodular thymoma is extremely rare. To our best knowledge, only a single case of ectopic micronodular thymoma has been reported in English literature [2]. In this study, we report an additional case of ectopic micronodular thymoma which is also the first eMNT case with confirmed langerhans cells proliferation. 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.

Materials and methods

Patient and tumor

A 76-year-old woman was referred to our institutional for the consultation of a mass in the left cervical region. According to her medical history, the mass was found on her routine checkup. The magnetic resonance imaging (MRI) scan showed a 3.7 cm × 1.7 cm × 2.0 cm mass in the left cervical region (**Figure 1**). Since the patient once had a subtotal thyroidectomy for a diagnosis of nontoxic nodular goiter (NTNG) seven years ago, the diagnosis of mass was suspected as the residue of the thyroid gland or recurrence of NTNG and surgical resection was performed. The department of pathology in local hospital made a diagnosis of metastatic squamous cell carcinoma of lymph node with uncertain origin. The patient declared no history of myasthenia gravis or other autoimmune disorder.

Histology and immunohistochemistry

The samples were fixed in 4% formalin and embedded in paraffin. Sections were cut and

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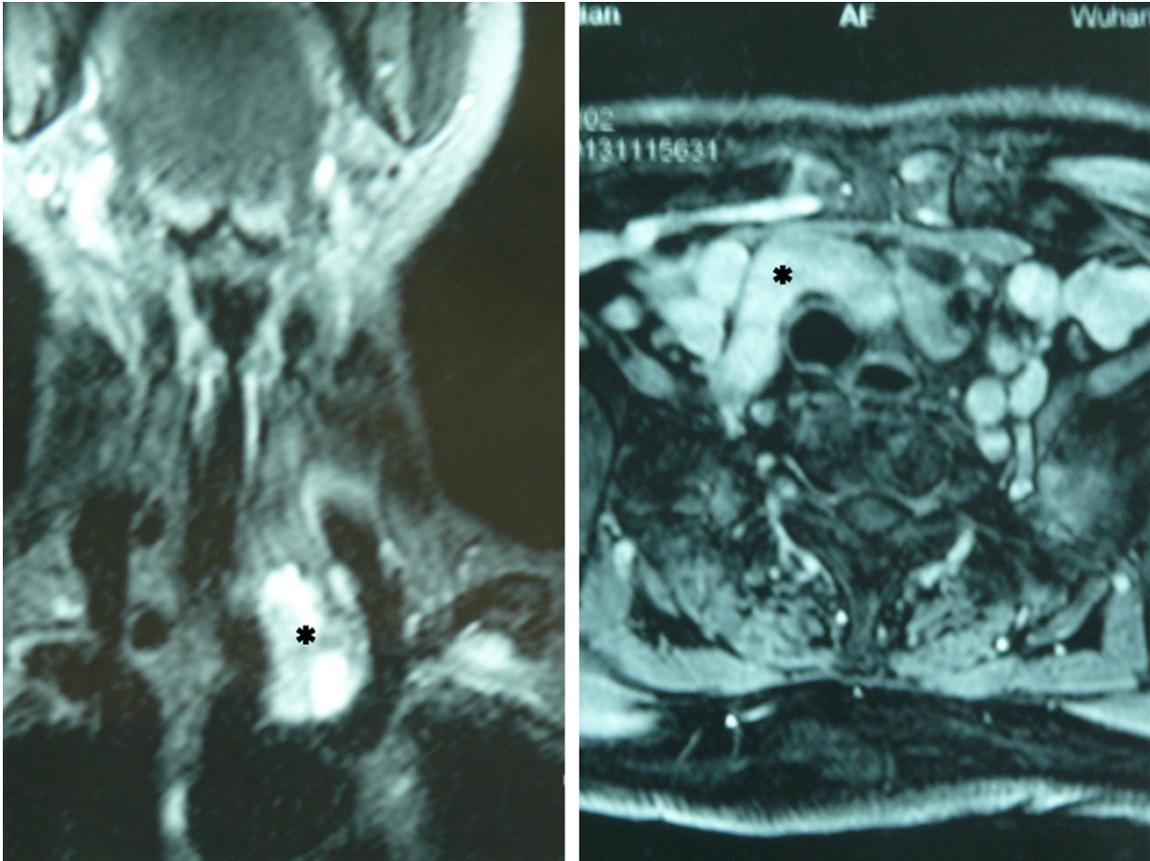


Figure 1. Magnetic Resonance Imaging (MRI) shows a lobular mass (*) at the anterior left cervical region.

Table 1. Antibodies and dilutions used in the evaluation of ectopic micronodular thymoma

Antibody	Dilution	Source
AE1/AE3	1:20	Dako
CK5/6	1:200	ZYMED
P63	1:25	Novocastra
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
CD20	1:2000	Dako
TdT	1:50	Dako
CD99	1:50	Dako
KI67	1:30	Novocastra
SMA	1:400	Dako
Des	1:200	Dako
CD34	1:100	Dako
CD117	1:200	Dako
TTF-1	1:200	Dako

stained with hematoxylin & eosin (H&E). For immunohistochemical staining, sample tissues were sliced with 3-4 μm thickness. After deparaffinization, antigen retrieval with heat and 3% hydrogen peroxide (H_2O_2) methanol solution treatment was done for 30 min to eliminate nonspecific reaction with proteins. The antibodies applied are given in **Table 1**. Immunostaining was performed by an enhancement method based on repetitive microwave heating of slides that were placed into 0.01 M citrate buffer at pH 6.0. Binding of primary antibodies was visualized with an Envision two-step method. Diaminobenzidine was used as chromogen. Nuclei were stained with Mayer's hematoxylin. Appropriate positive controls were included.

Results

Macroscopically, the lobular mass measured 3.7 cm in the largest diameter, exhibited a solid and gray cut surface and was enclosed in a thin fibrous capsule. Microscopically, the mass consisted of two components: one was nodular epi-

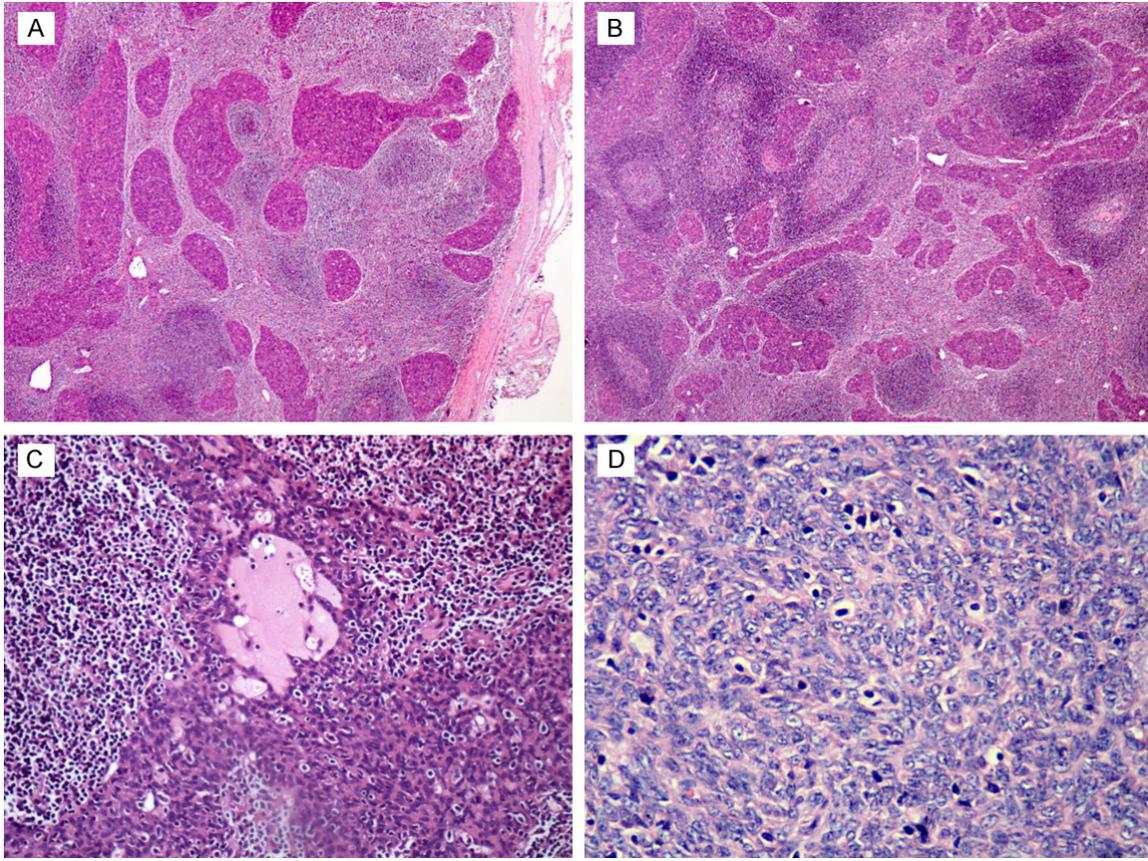


Figure 2. A. Multiple nodules of epithelial cells are scattered in the lymphoid-rich stroma (H&E, $\times 100$). B. Epithelial nodules are scattered in the lymphoid-rich stroma containing prominent germinal centers (H&E, $\times 100$). C. Perivascular space can be seen inside of the epithelial nodule (H&E, $\times 200$). D. High magnification showing nodules of spindle epithelial cells with oval elongated nuclei (H&E, $\times 400$).

thelial component and the other was hyperplastic lymphoid tissue with prominent germinal centers (**Figure 2A, 2B**). The nodules were composed of oval or spindle cells with elongated nuclei and inconspicuous nucleoli without atypia or increased mitotic activity, mixed with few lymphocytes (**Figure 2C, 2D**). The surrounding lymphoid stroma contained a dense proliferation of small lymphocytes with lymphoid follicles formation with prominent germinal centers. The lesion showed no relationship with the residue of thyroid gland; normal ectopic thymus was not observed either.

The epithelial cells were diffusely positive for AE1/AE3, CK5/6, and P63 and focally positive for EMA (**Figure 3A, 3B**). Ki67 labeling index in epithelial cells was low (**Figure 3G**). Lymphoid cells in the stroma were mainly CD20+ B cells. They formed follicles with germinal centers (**Figure 3D**). Immature CD3+, CD5+, TdT+, CD1a+, CD99+ lymphocytes were also numer-

ous with particular perinodular distribution. They were also found scarcely within epithelial cell nodules (**Figure 3C, 3E, 3F**). Ki67 labeling index in immature thymocytes was much higher (**Figure 3G**). Some langerin+, S-100+, CD1a+ cells were scarced within epithelial cell micronodules (**Figure 3H**).

The diagnosis of ectopic micronodular thymoma with lymphoid stroma was made. Follow-up revealed that the patient was alive and well 24 months without recurrence after diagnosis.

Discussion

MNT is a rare variant of thymoma, first described by Suster *et al* in 1999 [3]. In WHO classification, it was listed as micronodular thymoma with lymphoid stroma with suspected medullar origin [1]. To our knowledge, there were several cases reports of MNTs in English literatures (**Table 2**) [4-7], and only one case of MNTs was located in ectopic site by far [2].

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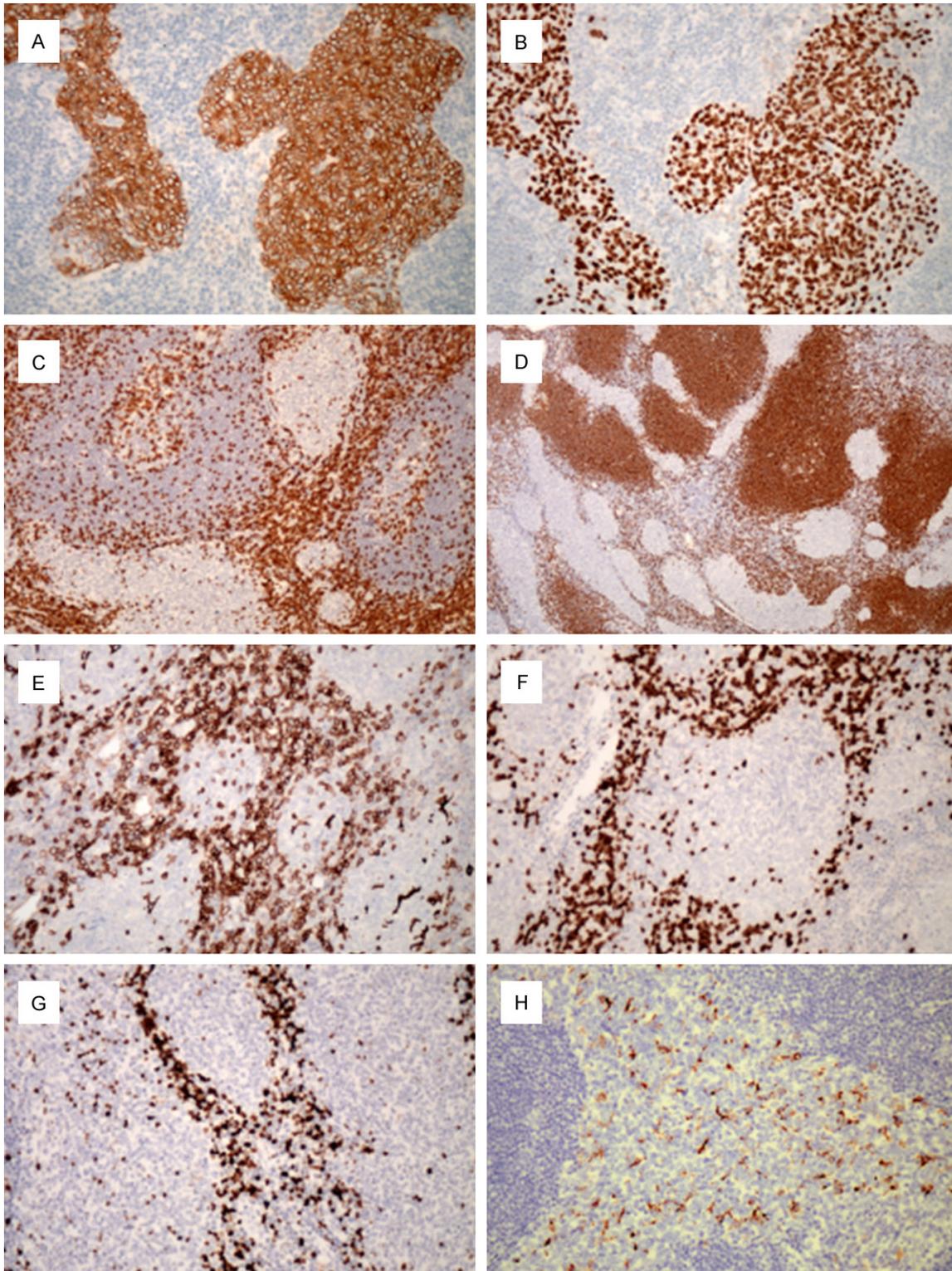


Figure 3. A. CK5/6 staining of epithelial nodules; B. P63 staining of epithelial nodules; C. CD3 staining of lymphoid stroma, scarcely within epithelial cell nodules; D. CD20 staining of lymphoid stroma with germinal centres; E. CD1a staining of lymphoid stroma with perinodular distribution; F. TdT staining of lymphoid stroma with perinodular distribution; G. KI67 staining of MNT showing low proliferation index in epithelial nodules and much higher proliferation index in immature lymphoid stroma with perinodular pattern; H. Langerin staining within epithelial nodules shows scattered pattern.

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Table 2. Micronodular thymoma cases reported in literature

First author	cases	age/sex	sites	Size (diameter)	diagnosis	time
Suster S	18	Mean, 58 ys/7 F, 11 M	thymus	3-10 cm	MNT	1999
Thomas DM	6	NS	thymus	NS	MNT	2002
Mende S	1	45 ys/M	left cervical region	3.5 cm	MNT	2004
Strobel P	18	Mean, 66.3 ys/7 F, 8 M	thymus	NS	MNT	2005
EI MF	2	62 ys, F/64 ys, M	thymus	8 cm/7 cm	MNT	2006
Tahara S	1	56 ys/M	Anterior mediastinum	NS	MNT	2012
Weissferdt A	5	Mean 64 ys/2 F, 3 M	thymus	3.2-10 cm	MNC	2012
Kim NR	1	73 ys/M	thymus	5.1 cm	MNT	2013

MNT: micronodular thymoma; MNC: micronodular carcinoma; Ys: years; F: female; M: male; NS: not stated.

Histologically, MNTs are characterized by proliferation of small tumor nodules focally coalescent, separated by abundant lymphoid stromal component with germinal centers. The nodules are composed of spindle cells containing oval nuclei without atypia or increased mitotic activity. A few scattered lymphocytes can be observed within epithelial nodules. The surrounding lymphoid stroma contains a dense proliferation of small lymphocytes with the formation of lymphoid follicles with germinal centers. Previous studies paid more attention to the stroma lymphoid components [6, 8]. They had been speculated that the striking lymphoid hyperplasia in MNTs is either a host response to tumor antigens or a tissue response to unrelated intrathymic antigens. In our case, immature (CD1a+, TdT+, and CD99+) lymphocytes occurred in an intraepithelial or perinodular distribution. A few mature T cells and very rare single B cells occurred inside micronodules.

Previous reports showed some cells expressing CD1a and S100 occurred mainly among epithelial cells micronodules in MNTs [2, 8]. They believed these cells were interdigitating dendritic cells (IDCs) [8]. We found CD1a+, S-100+ cells scattered within the micronodules too, and we further confirmed some cells expressing langerin. The cells with langerin, CD1a, and S-100 expression should be langerhans cells (LCs). There were few reports emphasizing the proliferation of LCs in different subtypes of thymoma [9, 10]. As antigen-presenting dendritic cells (DCs), Langerhans cell may also play an important role in response to tumor antigen in ectopic MNTs.

Regarding the histological features of our case, there several differential diagnostic consider-

ations: the first is metastatic squamous cell carcinoma, as the initial diagnosis of our case. In metastatic squamous cell carcinoma, there must be primary focal lesion confirmed, and the tumor cells showed histological features including intercellular bridges and cytological atypia. The tumor cells proliferation index (the ki67 labeling index) is much higher in metastatic carcinoma than that in MNTs. The second is myoepithelioma of salivary gland which usually display hyaline cytoplasm, mucoid stroma and myoepithelial markers including SMA, P63, and S-100 expression.

Additional consideration is the biological behavior of MNT. Micronodular thymic carcinoma was described in the literature [11]. Contrary to MNT, the epithelial components of the micronodular thymic carcinoma showed unequivocal signs of malignancy characterized by cytological atypia and increased mitotic activity. Follow-up revealed that the patient was alive and well 24 months without recurrence after diagnosis. There is neither clinical nor morphological evidence of malignancy in our case.

In summary, we present a rare case of ectopic micronodular thymoma with langerhans cells proliferation. Awareness of the existence of ectopic micronodular thymoma is essential for the differential diagnosis of neoplasms in this surgical site in order not to confuse the rare tumor for its histological features to mimics lesions. Accumulation of the rare variant cases and longer follow-up may further obtain more data regarding the prognosis for patients with this tumor.

Disclosure of conflict of interest

None.

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