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ORIGINAL ARTICLE

Micronodular thymic carcinoma with lymphoid hyperplasia: relevance of immunohistochemistry with a small panel of antibodies for diagnosis—a RYTHMIC study

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Abstract

Micronodular thymic carcinoma with lymphoid hyperplasia (MNTCLH) is a rare form of thymic carcinoma. We present the experience of RYTHMIC, the French national network devoted to the treatment of thymic epithelial tumors through multidisciplinary tumor boards with a review of all tumors by pathologists for classification and staging. Six cases of MNTCLH were diagnosed during a review of 1007 thymic epithelial tumors. Histologically, epithelial cells with atypia and mitoses formed micronodules that were surrounded by an abundant lymphoid background with follicles. There was neither obvious fibro-inflammatory stroma nor necrosis. Spindle cells areas were common. Initial diagnosis was micronodular thymoma in two cases, cellular atypia being overlooked, eclipsed by the micronodular pattern. Immunohistochemistry with a panel of five antibodies showed that cytokeratins (AE1-AE3) and p63-positive epithelial cells also expressed CD5 and that there was no TdT-positive cells within the tumors. CD20 highlighted the lymphoid hyperplasia. Additionally epithelial cells also expressed CD117 and diffusely Glut 1. Twenty-seven micronodular thymomas with lymphoid stroma diagnosed during the same period did not show the CD5 and CD117 positivities seen in MNTCLH and contained TdT-positive lymphocytes. Three of the 6 patients with MNTCLH had adjuvant radiotherapy. Three patients with follow-up information were alive without recurrence at 38, 51, and 95 months. Our study shows that immunohistochemistry, such as that used in the RYTHMIC network with a small panel of antibodies, may easily help to confirm the correct diagnosis of MNTCLH, a rare and low-aggressive form of thymic carcinoma, and avoid the misdiagnosis of micronodular thymoma.

Keywords Micronodular thymic carcinoma with lymphoid hyperplasia · Thymic neoplasm · Immunohistochemistry

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Introduction

Among thymic epithelial tumors (TET), thymic carcinomas are less frequent than thymomas [1, 2]. However, it is important for these carcinomas to be correctly diagnosed since they may require a more aggressive management because of their worse prognosis. Micronodular thymic carcinoma with lymphoid hyperplasia (MNTCLH) is a very rare subtype that can be histologically confused with one of the least aggressive thymomas, micronodular thymoma with lymphoid stroma (for simplicity henceforth called "micronodular thymoma") [3]. We report our experience with 6 cases of MNTCLH that were referred, for a systematic histological review, to the French National Network for TET (RYTHMIC) [4]. We show how systematic immunohistochemistry using a small panel of antibodies could facilitate the correct diagnosis of these carcinomas.

Materials and methods

The RYTHMIC network has been previously described [4]. Shortly, RYTHMIC is supported by the French National Cancer Institute and is devoted to the treatment of TET through regional and national multidisciplinary tumor boards. Clinical data, surgical, and initial pathological reports are collected and discussed during these conferences to determine the adapted treatment for patients. All tumors are secondarily reviewed by a national network of pathologists for classification and staging. Tumors are classified according to the WHO histological classification [1, 5], and according to Masaoka-Koga [6] and TNM [7] staging systems. For each case, all hematoxylin-eosin stained slides and one representative paraffin block are sent by the referring pathologist. The representative paraffin block is used for systematic immunohistochemistry on autostainer (Leica Bond III) using a panel of five antibodies: cytokeratins AE1-AE3 (Agilent Dako M3515), p63 (Roche Ventana 4A4), TdT (Terminal deoxynucleotidyl transferase, Leica PA0339), CD20 (Agilent Dako M0755), and CD5 (Leica 4C7). Additionally, CD117 (Agilent Dako A4502) and Glut 1 (CliniSciences RP128) antibodies are used in cases with initial or secondary diagnosis of carcinoma or B3 thymoma. Specifically for this study, CD117 antibody was also tested on the micronodular thymomas with lymphoid hyperplasia included during the same period. Hematoxylin-eosin stained slides and CD5 and TdT immunohistochemistry of these micronodular thymomas were also reviewed and compared with MNTCLH.

Follow-up data were obtained from the RYTHMIC national register and if necessary from the referring clinician. The duration of follow-up was considered from the date of surgical resection.

Results

There were 6 cases of micronodular thymic carcinoma with lymphoid hyperplasia (MNTCLH) among the 1007 cases reviewed by our network for 8 years (2012 to 2019).

Main clinico-pathological data are summarized in Table 1. There were 1 female and 5 male patients aged 54 to 82 years (mean 67.0 ± 9.1). No patient suffered from myasthenia gravis. In patient #1, the thymic tumor was discovered after treatment of a colorectal carcinoma. Other patients had no significant medical history. On positron emission tomography, the mean maximum standard uptake value was 7.9 ± 2.6. Tumor size ranged from 2.5 to 6.8 cm (mean 4.05 ± 1.74; Fig. 1). Follow-up data were not available in three patients who were too recent or lost to follow-up.

Only one patient (#5) had a preoperative needle biopsy with a diagnosis of thymic epithelial tumor showing morphological micronodular features with CD5 and CD117 positivity. The 5 other patients had their tumor resected without preoperative biopsy.

The initial pathological diagnosis on resection specimen was often wrong or uncertain. This diagnosis was micronodular thymoma in 2 cases for which no immunohistochemistry was performed. In two other cases, the initial diagnosis was uncertain with a morphological micronodular appearance and CD5 and CD117 immunohistochemical positivity. Lastly, two cases were referred with a diagnosis of thymic carcinoma: thymic squamous cell carcinoma (n=1) and MNTCLH (n=1).

Histologically (Fig. 1), the six cases showed the same appearance. The tumors were not encapsulated. They were made of irregular epithelial nodules with sharp and round borders. These nodules were surrounded by a dense lymphoid tissue containing lymphoid follicles with germinal centers. There was neither significant fibrosis nor necrosis. Cells were not only polygonal but also sometimes elongated. Atypia with irregular nuclei and prominent nucleoli and mitoses were present, even if they could sometimes seem inconspicuous at first sight. None of the cases showed the bland spindle/oval cells with dispersed chromatin and indistinct nucleoli that are seen in micronodular thymomas. Residual thymic tissue showed normal involution and no follicular lymphoid hyperplasia.

All the six cases showed the same immunohistochemical profile (Figs. 1 and 2). Cytokeratins and p63 expression highlighted the nodular architecture, and no epithelial cells were present in the lymphoid stroma. The lymphoid hyperplasia with follicles was highlighted by CD20 immunohistochemical staining, while epithelial cells were CD20-negative. Cases initially diagnosed as thymomas were immediately identified as possible carcinomas because of CD5 expression by epithelial tumor cells and lack of TdT-positive lymphocytes. All the 6 cases showed epithelial cell positivity for CD5, CD117, and diffuse positivity for Glut1. The immuno-

Table 1 Main clinico-pathological data of the 6 cases of thymic micronodular carcinoma with lymphoid hyperplasia. *PET* positron emission tomography, *maxSUV* maximum standard uptake value, *A and W* alive and well

No.	Age sex	History, symptoms	PET; maxSUV	Tumor size (cm)	Masaoka stage	TNM stage	Adjuvant therapy	Follow-up
1	54 M	Colorectal carcinoma, no	8.5	2.5	IIb	pT1a stage I	No	A and W, 95 months
2	67 M	Smoker (35PY), no	9.2	3.8	IIb	pT1a stage I	Radiotherapy	A and W, 51 months
3	63 M	Pneumonia	10	6.8	IIa	pT1a stage I	Radiotherapy	
4	68 M	Pneumonia	3.5	2.7	IIa	pT1a stage I	No	
5	68 M	Pulmonary embolism	8.5	5.5	III	pT1b stage I	No	
6	82 F	No	Not done	3.0	III	pT1b stage I	Radiotherapy	A and W, 38 months

phenotype was homogeneous, and we did not identify any area with a morphological and phenotypical pattern suggesting an additional component of micronodular thymoma in any of the six MNTCLH.

During the same period, 27 cases were classified as micronodular thymomas (n=20) or WHO type A thymomas with a micronodular component (n=7). These 27 cases showed no cytological atypia that could suggest a carcinomatous nature. A blinded retrospective review of hematoxylin and eosin stained slides of the six cases of MNTCLH and of 14 consecutive cases of micronodular thymomas by the pathologists of the panel showed total concordance. None of the

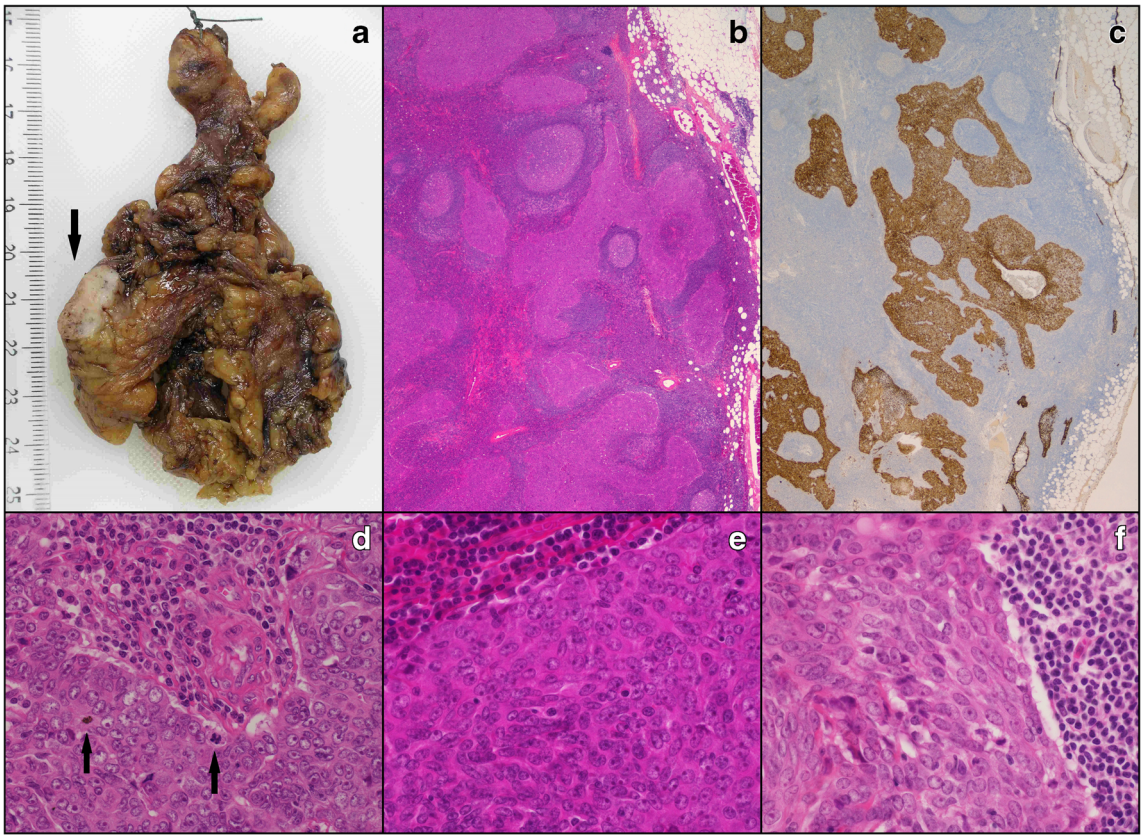

Fig. 1 Pathological features of micronodular carcinomas with lymphoid hyperplasia. Gross appearance of a small intra-thymic tumor (**a**); microscopy showing a non-encapsulated lesion extending into the thymus (**b**; hematoxylin and eosin stain, magnification, low) with epithelial nodules expressing cytokeratins on an adjoining section (**c**; immunohistochemical staining with AE1-AE3 antibody); higher magnification showing mitoses (**d**), epithelial cell with nuclei containing nucleoli (**e**), and spindling of tumor cells (**f**)

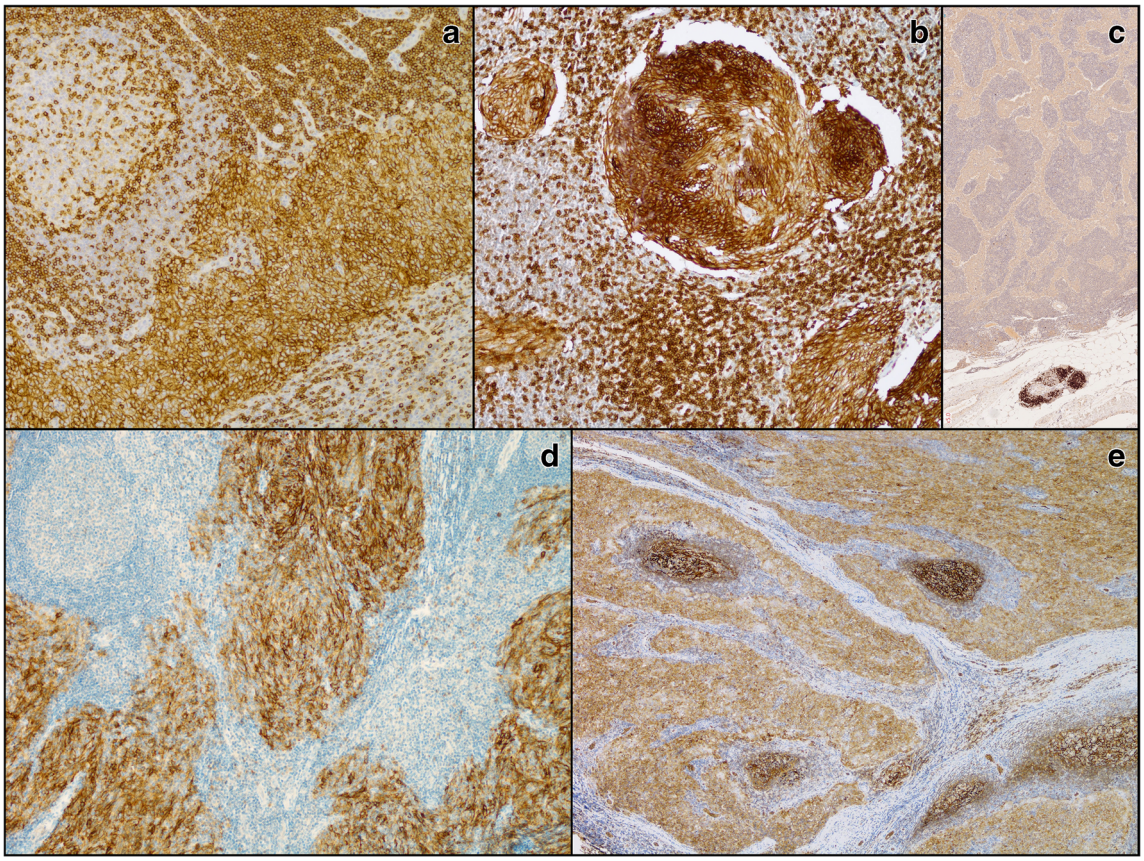

Fig. 2 Immunohistochemical features of micronodular thymic carcinomas with lymphoid hyperplasia. CD 5 expression by epithelial nodules and lymphoid cells (**a, b**), lack of TdT positive lymphocyte within the tumor with positivity of a small thymic lobule (**c**), CD 117 expression (**d**), and diffuse expression of Glut-1 by epithelial nodules and lymphoid follicles (**e**), magnification low

27 cases showed the strong and diffuse CD5 positivity seen in MNTCLH. All micronodular thymomas (25/25 cases) contained TdT-positive lymphocytes, and all were negative for CD117 (26/26 cases).

Discussion

Before our current series, only 17 micronodular thymic carcinomas with lymphoid hyperplasia were reported in the literature. Micronodular thymomas were first reported in 1999 [8]. Two years later, a series of 11 micronodular TET included five cases showing "polygonal epithelial cells with mild to moderate cytological atypia" that were probably MNTCLH [9]. Five similar cases were reported in 2005 under the name of "undifferentiated large cell carcinoma of the thymus with Castleman-like reaction" [10]. The denomination of micronodular thymic carcinoma with lymphoid hyperplasia was coined in 2012 based on a series of 5 cases [3]. These five cases were described as the carcinomatous counterpart of micronodular thymomas. Lastly, a series of ten micronodular TET thymic tumors included one carcinoma [11], and another case of MNTCLH was presented as a case report [12].

As previously underlined the main differential diagnosis of MNTCLH is micronodular thymoma [3]. In our series, all the six cases of MNTCLH presented in a TNM stage I. Histologically, tumor infiltration could not be used as a criterion of malignancy since micronodular thymomas are often unencapsulated as well [13]. Lymphoepithelioma-like carcinoma is also a rare subtype of thymic epithelial tumor with lymphoid hyperplasia [14]. It is usually associated with Epstein-Barr virus [15]. However, in our experience, the differential diagnosis of lymphoepithelioma-like carcinoma may rarely be considered, since MNTCLH show distinctive features such as sharply delineated rounded epithelial nodules almost devoid of lymphocytes, mild or at best moderate cellular atypia, and stroma without fibrosis and with numerous lymphoid follicles. In doubtful cases, EBER hybridization may confirm the lack of association of MNTCLH with Epstein-Barr virus [9, 15].

Most thymomas do not need immunohistochemistry for diagnosis [1, 16], and the feasibility of adding systematic immunohistochemistry, even with few antibodies, depends on the resources of each pathologist. However, our study shows that immunohistochemistry in thymic tumors with a micronodular pattern is of differential diagnostic value in

challenging cases and may represent a "security back-up system." In MNTCLH, the characteristic micronodular pattern is probably misleading, if the pathologist overlooks mitoses and atypia. The obvious micronodular cellular architecture must not eclipse cytological criteria of malignancy. A second look at higher magnification, possibly prompted by an unexpected immunohistochemical result, must lead to a correct diagnosis. In the literature, immunohistochemical data on micronodular thymic carcinomas with lymphoid hyperplasia are very scant. Epithelial cells were reported positive for CD5 in five [9] and one [12] cases, but they were surprisingly negative in five other cases [10]. Five [3] and one [12] cases were reported to be TdT negative. CD117 was investigated and found positive in a single case reported so far [12]. Our series provides a comprehensive overview of the immunohistochemical characteristics of these tumors. Cytokeratin and P63 positivity of epithelial nodules and CD20 positivity of the lymphoid stroma is similar to that observed in micronodular thymomas. However, strong CD5 and CD117 expressions are characteristic of thymic carcinomas [1, 2]. The rim of TdT-positive cells, seen around the micronodules in micronodular thymomas, was absent in all cases. The diffuse expression of Glut-1 that we observed in MNTCLH was similar to that seen in other thymic carcinomas and was different from the focal or zonal expression seen in thymomas and especially in the micronodular type [17]. On positron emission tomography, four cases in our series showed a maximum standard uptake over 8. Such high levels are more suggestive of thymic carcinoma than of thymoma [18, 19] and are possibly related to the high Glut-1 expression. We think that the use of a panel of antibodies (against CD5, CD117, GLUT1, and TdT) is preferable over the use of only one of these antibodies, since none of them is independently totally specific for the differential diagnosis between thymic carcinoma and thymoma [1], and immuno-histological staining may not be entirely reproducible. By contrast, the use of additional markers that support a thymic origin such as Pax8 or CD205 [16] may generally be dispensable, since MNTCLH for clinical and histological reasons are usually undoubtedly of thymic derivation. Furthermore, there have been no reports on molecular and genetic alterations in MNTCLH to underpin the diagnosis, but such studies appear warranted to better understand the heterogeneity of TET and shed light on the pathogenesis of MNTCLH [20, 21].

Despite the few cases reported so far, it seems that the prognosis of MNTCLH is not as poor as that of other types of thymic carcinoma. All reported cases have been treated by resection, and some had adjuvant radiotherapy or chemotherapy [3, 9–12]. Only one previously reported patient with MNTCLH died of disease at 21 months [3]. One case recurred 16 years after surgery [10]. In our series, the three patients with follow-up information were alive with no recurrence at 38, 51, and 95 months after resection. Eleven patients from the literature were also alive and well; five at 1 to 15 years [9], two at 10 and 22 years [10], four at 3 to 26 months [3] and one at 12 months [12] after resection. The three other previously reported cases were lost of follow-up [9–11]. This relatively favorable prognosis is possibly related to the lymphoid hyperplasia, which could be an indicator of anti-tumor immunity. MNTCLHs can be considered low-grade thymic carcinomas. Anyway, even if the prognosis of MNTCLH seems relatively good after resection, the confirmation of the correct diagnosis of carcinoma may have important consequences on the patients' treatment: possible post-operative radiotherapy and closer follow-up.

The frequency of MNTCLH is possibly underestimated. However, the main differential diagnosis, which is micronodular thymoma, is only a rare subtype of thymoma. The frequency in our series is possibly related to the fact that the difficulty for diagnosis makes MNTCLH more likely to be referred for review.

In conclusion, our study shows that MNTCLH may easily be misdiagnosed as micronodular thymoma, especially if the morphologic criteria for malignancy are overlooked and if immunohistochemistry is not performed. This study confirms the relevance of systematic immunohistological staining for the optimal diagnosis of TET. We had previously shown that systematic CD20 immunohistological staining could allow a correct diagnostic of AB thymomas when the A component was not morphologically obvious [22]. Our nationwide review of TET also allows collection of rare subtypes including this largest reported series of MNTCLH.

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Author contributions Vincent Thomas de Montpreville wrote the paper. Audrey Mansuet-Lupo, Cécile Le Naoures, and Lara Chalabreysse contributed to selection of the cases. Anne De Muret, Véronique Hofman, Isabelle Rouquette, Nicolas Piton, and Romain Dubois reviewed histological documents. Jose Carlos Benitez collected clinical data. Vincent Thomas de Montpreville, Nicolas Girard, Benjamin Besse, Alexander Marx, and Thierry Jo Molina designed the research study.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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