Micronodular thymic carcinoma with lymphoid stroma: a case report

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Case Report

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Abstract

**Background:** Micronodular thymic carcinoma (MTC) with lymphoid hyperplasia is believed to be the malignant counterpart of micronodular thymoma (MT) with lymphoid hyperplasia. Since MT and MTC share a similar morphology, MTC is considered a malignant form of MT; there have been a few cases of malignant transformation from MT to MTC. We report a case of MTC with lymphoid hyperplasia.

**Case presentation:** Our 53-year-old patient presented with an incidental tumor on chest X-ray. The resected tumor consisted of nodular epithelial nests and lymphoid tissue within a surrounding germinal center. Some epithelial nests showed apparent malignant morphology. Atypical epithelial cells with large vesicular nuclei formed nests, some of which showed comedo necrosis. These cells showed transition continuously to benign type B thymoma-like cells, demonstrating cord-like arrangements. Carcinomatous elements, showing a high Ki67 index, expressed Glut1, CD5, CD117, and BCL2; conversely, benign nests displayed attenuated expression of these markers and a low Ki67 labeling index. GTF2I point mutation and Langerhans/dendritic cells, which are indicators of favorable thymoma prognosis, were not detected. Due to pleural metastasis, the patient was treated with lenvatinib 27 months postoperatively.

**Conclusions:** This is the first report of a partially benign, GTF2I-negative MTC. Histological and genetic findings might be predictive of patient prognosis.

Background

Micronodular thymic carcinoma (MTC) with lymphoid hyperplasia is believed to be the malignant counterpart of micronodular thymoma (MT) with lymphoid hyperplasia [1–4]. MT, which was first described in 1999 by Suster et al., is a rare subtype of thymoma, accounting for 5% of thymomas, and comprising neoplastic epithelial nests and surrounding hyperplastic lymphoid tissue containing a germinal center [2]. Since MT and MTC share a similar morphology, MTC is considered a malignant form of MT; there have been a few cases of malignant transformation from MT to MTC [2–9]. Herein, we describe a case of MTC accompanied by a benign histological component of thymoma and review the literature.

Case Presentation

Our patient was a 53-year-old woman who presented with a left pulmonary hilar region mass, discovered incidentally on routine chest radiography 3 months prior to presentation. This mass did not exist on the chest radiograph taken one year previously. Computed tomography (CT) revealed a tumor measuring approximately 3 × 2 cm in the anterior mediastinum, in contact with the main trunk of the pulmonary artery (Fig. 1a). The lesion displayed slight contrast on contrast-enhanced CT (Fig. 1b). As the tumor showed a tendency for rapid growth, it was surgically removed.

Macroscopically, the tumor was not encapsulated but was relatively well-demarcated, 33 mm × 23 mm in size, and with a brownish-yellow cut surface (Fig. 1c). Histologically, the tumor was composed of
epithelial cell nests or micronodules as well as stromal lymphoid tissue with germinal centers (Fig. 2a). Some epithelial cell nests showed comedo necrosis (Fig. 2a). In most parts of the tumor, neoplastic cell nests showed apparent malignant features, such as vesicular, prominent nucleoli, and numerous mitotic figures (Fig. 2b). We also found type B thymoma-like elements within the tumor, which consisted of polygonal epithelial cells and scattered stromal lymphocytes (Fig. 2c). These findings continued to transform along with the geography of the tumor, showing a shift from a malignant appearance into a benign, thymoma-like region. In addition, there was neoplastic epithelium arranged in a cord-like pattern, which appeared to be regressed lymphoid cell infiltration (Fig. 2d).

Immunohistochemically, the malignant tumor cells were positive for AE1/AE3, CEA, EMA, Glut1, CD117, CD5, p63, p40, CK5/6, TdT, and BCL2 (Fig. 2e, g, i). In the benign-looking thymoma-like region, tumor cells were negative for Glut1 and partially positive for CD117, CD5, and TdT (Fig. 2f, h, j). Chromogranin A, synaptophysin, and NCAM were negative in both regions. The Ki67 labeling index was 42% in the malignant region and lower in the thymoma-like region. Stromal lymphoid cells were predominantly composed of CD20- and CD79a-positive B-cells, with scattered CD3-and TdT-positive T cells. The germinal centers were positive for CD10 and negative for BCL2. In some malignant tissues, tumor cells were positive for PD-L1 (Fig. 2k). PD-L1 positive cells composed approximately 5% of the malignant part. In the tumor region, S-100 protein, CD1a, and Langerin-positive cells disappeared. Therefore, we regarded this case as MTC. The tumor was found to have invaded the adjacent adipose tissues but had not reached the phrenic nerve (pT2, Masaoka stageIIb). The patient displayed pleural metastases 10 months after tumor resection and was treated with a gamma knife. Lenvatinib chemotherapy was employed 27 months after the surgery.

We performed Sanger sequencing to detect mutations in GTF2I, which is found in benign thymomas, such as type A and type AB thymomas [10]. The sequences of the primer set are as follows: Primer-F, ATCCCGTACCCTCTTTTCC; Primer-R, AGACAAGAGTTCAAACAGG. The mutations were examined separately in benign and malignant areas using microdissection; however, no mutations were detected.

Discussion

MTC is a rare subtype of thymic carcinoma, and the histological characteristic of MTC or MT is the formation of tumor nodules accompanied by lymphoid stroma, unlike other common thymomas [1]. To date, 23 cases of MTC have been reported (Table 1) [2–9]. The mean age of the patients was 62.9 years (range 42–82 years) and the mean tumor size was 3.7 cm (range 1.1–10 cm). There was a relative male dominance (male:female = 15:8). MTC shows prominent B-cell infiltration and lymphoid follicles which is suggestive of a good prognosis. However, one patient died due to this disease, and our patient experienced recurrence 10 months after surgery.

The histological differential diagnosis of MTC should include MT. The tumor cells of MT show oval or spindle morphology, similar to that of type A thymoma, and occasionally, atypical cells, such as those of type B thymoma. In addition to atypia, mitotic counts can distinguish between benign and malignant
tumors. The number of mitoses was less than 5/10 high-power fields (HPF) in MT and more than 5/10 HPF in MTC [11]. Our case corresponded to MTC.

Immunostaining is useful in the diagnosis of thymic tumor malignancy [12]. Thymic carcinoma cells, including MTC, are positive for CD5, CD117, and Glut1, for which thymoma and MT cells are negative. Although Langerhans cells and dendritic cells were detected in the MT section, neither was detected in our case [13]. Therefore, CD1a and CD21, which are markers for Langerhans and dendritic cells, respectively, are possible markers for differentiation from MTC to MT.

Lymphocytes infiltrating the thymoma are usually T-cells; however, in MTC, B-cell infiltration is more commonly found [1–4]. The formation of lymphoid stroma occurs due to the host immune response to the tumor [2–4]. In our case, tumor cells in the cord-like structure region with dense lymphocytic infiltration were smaller than those surrounding micronodules or nests. This suggests that the host immune response to the tumor was effective. This hypothesis was supported by the PD-L1 expression by tumor cells.

In some cases, a tumor with the transition between MT and MTC has been observed, suggesting a continuous transformation from MT to MTC [2, 4, 5]. Usually, MT shows type A or AB-like characteristics [1]. Our case had a conventional type B thymoma-like component which showed partial continuity with the MTC component. Tumor cells with type B thymoma-like elements were negative for Glut1, which is a positive marker of thymic carcinoma, but were only partially positive for CD5, CD117, and BCL2, which are markers of thymic carcinoma. These findings suggest that these cells are potentially malignant; therefore, we considered that type B thymoma-like cells transformed to form MTC in our case. Recently, a point mutation in GTF2I was reported in thymic epithelial tumors [10]. Approximately 80% of type A and AB epithelial thymomas carry GTF2I mutation, whereas the majority of type B thymomas and thymic carcinomas do not [10]. In other words, thymic tumors with GTF2I mutation have a favorable prognosis; however, this mutation was not detected in either the type B thymoma or the carcinoma section in our case. Owing to the small number of reported cases, the prognosis cannot be accurately evaluated, but most cases were benign, and the patients are alive. However, MTC with malignant-to-benign transition might provide evidence of tumor progression because the benign portion of the tumor showed either a type A/AB thymoma-like lesion or the presence of GTF2I mutation. Histological findings might be predictive of patient prognosis.

Conclusions

In conclusion, we report a case of MTC arising from MT. This is the first case of genetic analysis of malignant and benign parts present simultaneously, and neither component showed GTF2I mutation. MTC with malignant-to-benign transition might be associated with tumor progression since the tumor displayed findings characteristic of histology or GTF2I mutation.

List Of Abbreviations
MTC; micronodular thymic carcinoma
MT; micronodular thymoma
CT; computed tomography
CEA; carcinoembryonic antigen
EMA; epithelial membrane antigen
CD; cluster of differentiation
BCL; B-cell/CLL lymphoma 2
TdT; Terminal Deoxynucleotidyl Transferase
NCAM; neural cell adhesion molecules
PD-L1; programmed cell death protein 1

Declarations

Informed Consent:
This case report is approved by the institutional ethical committee (approval number 1219). Informed consent was obtained in the form of an opportunity to opt-out on the website.

Data Availability:
The datasets are available from the corresponding author on reasonable request.

Competing Interests and Funding:
The authors have no relevant financial or non-financial interests to disclose and did not receive support from any organization for the submitted work.

Author Contributions:
KZ, HN, and YO diagnosed this case. YK, TK, KK, and TD checked all progress and the manuscript.

Acknowledgments:
Not applicable

References


Table 1 is available in the Supplementary Files section.

Figures

Figure 1
Computed tomography (CT) and macroscopic findings. a) CT shows the tumor (3x2 cm) in contact with the main trunk of the pulmonary artery in the anterior mediastinum. b) Contrast-enhanced CT reveals the mildly contrasted tumor. c) Macroscopically, the tumor is projecting aggressively, with a rough yellow tan-colored cut surface.

Figure 2

Histological and immunohistological findings. a) Histologically, tumor cells form diffuse micronodules or nests. b) Almost all parts of the tumor are suggestive of malignancy; prominent nucleoli, swelling, oval atypical nucleus, and eosinophilic cytoplasm are observed. c) There are regions of small nests which consist of mildly mitotic atypical oval cells, reminiscent of thymoma benign cells. d) Focally, there is a cord-like lesion that appears to be regressing by lymphoid cell infiltration. Immunohistochemically, tumor cells are positive for Glut1 (e), CD117 (g), and CD5 (i) in the malignant region. In thymoma-like regions, tumor cells are negative for Glut1 (f), CD117 (h), and CD5 (j). PD-L1 is positive in 5% of tumor tissue (k).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- casesofMTCver4.xlsx