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Type B3 thymoma with marked neuroendocrine differentiation: Report of a case

Kiyoshi Sato, Satoshi Fumimoto, Takayuki Kataoka, Yoshio Ichihashi, Kaoru Ochi, Hidetoshi Satomi, Nobuharu Hanaoka, Yoshikatsu Okada and Takahiro Katsumata

Abstract

Thymomas are tumors originating from the thymus epithelial cells and are the most common tumors of the anterior mediastinum. They have been classified into types A, AB, B1, B2, and B3 by the World Health Organization. Type B3 thymoma is composed of epithelial cell sheets with mild to moderate atypia and scant lymphocytes. An association between thymic carcinoma and neuroendocrine differentiation has been observed by some authors. However, cases of type B3 thymoma with neuroendocrine differentiation are very rarely discussed in the literature. A 68-year-old woman was referred to our hospital with an abnormal shadow on a chest roentgenogram. Chest computed tomography showed that the lesion was located in the anterior mediastinum. She underwent surgery, and the tumor was diagnosed as a type B3 thymoma with neuroendocrine differentiation. An extremely rare case of a type B3 thymoma showing neuroendocrine differentiation is presented herein.

Keywords

Neuroendocrine differentiation, type B3 thymoma, Masaoka staging system, immunohistochemical examination, thymic carcinoid

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Introduction

Type B3 thymoma is predominantly composed of epithelial cells that have a round or polygonal shape.[1,2] The epithelial cells are admixed with a minor component of nonneoplastic lymphocytes, which results in a sheet-like growth of neoplastic epithelial cells, and it is extremely rare to show neuroendocrine differentiation.[3] A case of type B3 thymoma with neuroendocrine differentiation is described.

Case report

A 68-year-old woman who did not exhibit any symptoms, including those of myasthenia gravis or other autoimmune diseases, was found to have an abnormal shadow on her chest roentgenogram at medical check-up (Figure 1(a)) and was referred to our hospital. A chest computed tomography (CT) scan showed a 4.5-cm-diameter tumor with a homogeneous inner component in the anterior mediastinum (Figure 1(b)). The tumor was adjacent to the superior vena cava and the ascending aorta. Blood tests showed all tumor markers within the normal range. Thymoma was suspected, and surgical excision was planned. The patient underwent total thymectomy via a median sternotomy. Grossly, the tumor was widely and firmly attached to the pericardium and right lung and was thought to have invaded the pericardium and lung. Therefore, pericardial resection and right upper lung partial resection were performed. The tumor measured 6 cm × 4.5 cm × 3.5 cm and involved the pericardium and left lung. The cut surface was grayish with lobular formation. Intraoperative histologic examination of a frozen specimen led to a diagnosis of thymoma. No serious complications were observed during the postoperative course, and the patient was discharged on the 17th postoperative day.

Department of Thoracic and Cardiovascular Surgery, Osaka Medical College Hospital, Takatsuki, Japan

Corresponding Author:
Kiyoshi Sato, Department of Thoracic and Cardiovascular Surgery, Osaka Medical College Hospital, 2-7 Daigaku-cho, Takatsuki 569-8686, Japan.
Email: skiyoshi@osaka-med.ac.jp

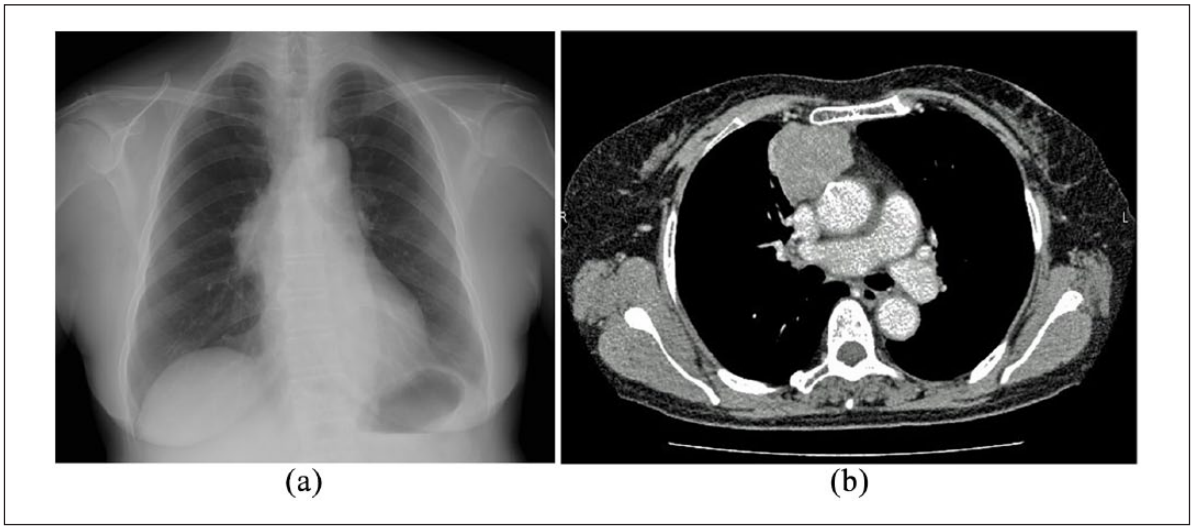

Figure 1. (a) A chest roentgenogram shows a tumor mass of the right pulmonary hilum and (b) a chest computed tomography scan shows the lesion, measuring 45 mm × 45 mm, is adjacent to the superior vena cava and the ascending aortic with a homogeneous inner component in the right anterior mediastinum.

Postoperative microscopic examination showed lobular and alveolar structural growth patterns that were arranged in epidermoid features with prominent nuclear palisading around perivascular spaces, and lacking nuclear atypia and scant lymphocytes, and had invaded the pericardium and S3 segment of the right lung, and these findings were consistent with a Masaoka stage III type B3 thymoma, and stage IIIa according to the 8th edition of the International Association for the Study of Lung Cancer and the International Thymic Malignancy Interest Group TNM staging system (Figure 2(a)). However, rosette-like arrangements were observed in part of the tumor (Figure 2(b)); therefore, immunohistochemical examinations were performed. The tumor cells were diffusely positive for synaptophysin (Figure 2(c)) and chromogranin A (Figure 2(d)), but negative for CD5 and c-Kit. From the aforementioned findings, although there was rosette formation and positive immunohistochemical findings, it was diagnosed as a Masaoka stage III type B3 thymoma with a neuroendocrine differentiation rather than a neuroendocrine tumor due to cellular morphology such as prominent nuclear palisading around perivascular spaces and lacking nuclear atypia.

The patient received 40 Gy radiotherapy for adjuvant therapy and had no recurrences for 3 years postoperatively. Unfortunately, pleural dissemination and multiple lung metastases were found on follow-up CT 3 years and 6 months after thymectomy. She was treated with three courses of chemotherapy, based on a platinum doublet using carboplatin and etoposide, and subsequently with six courses of adriamycin, cisplatin, and cyclophosphamide, and these therapies achieved a partial response. The disease was stable for about 2 years without any treatment and progressed thereafter. Chemotherapy was restarted with four courses of amrubicin and subsequently with four courses of nab-paclitaxel, but the number and size of multiple pulmonary metastases increased, and a pleural effusion appeared. The patient died of the disease 8 years and 3 months after thymectomy.

Discussion

Thymomas are the most common primary tumors of the anterior mediastinum of adults.[1] Disease progression is very slow, the condition remains silent for many years, and the tumor is generally incidentally identified. In the World Health Organization (WHO) classification, thymoma comprises the A, AB, B1, B2, and B3 subtypes[2] that are diagnosed according to the morphology of epithelial cells and the ratio of lymphocytes to epithelial cells. Notably, the proportion of type B3 thymomas has increased from 6% to 34%.[4] Type B3 thymomas comprise round or polygonal epithelial cells that exhibit no or mild atypia and are mixed with a minor component of lymphocytes. The epithelial cells often exhibit a squamoid quality without intercellular bridges, and cellular palisading around perivascular spaces and along fibrous septa is often striking. In most cases, round to oval irregular nuclei are present with inconspicuous nucleoli, and the cytoplasm is eosinophilic to clear, resembling that of koilocytes.[3] Tumor cells occasionally form spindles and fascicles, resembling type A thymomas, or may contain large vesicular nuclei and distinct nucleoli, resembling those of type B2 thymomas.[3]

Type A thymomas may exhibit neuroendocrine differentiation,[3,5,6] which is extremely rare in type B3 thymoma, and to the best of our knowledge, only three cases are reported.[7–9] Immunohistochemical analysis of most type A thymomas with neuroendocrine differentiation does not detect synaptophysin and chromogranin A.[5,10] In contrast, in type B3 thymomas with neuroendocrine differentiation, synaptophysin and chromogranin A were expressed in the three previous cases[3,5,6] and in the present case. Because neuroendocrine

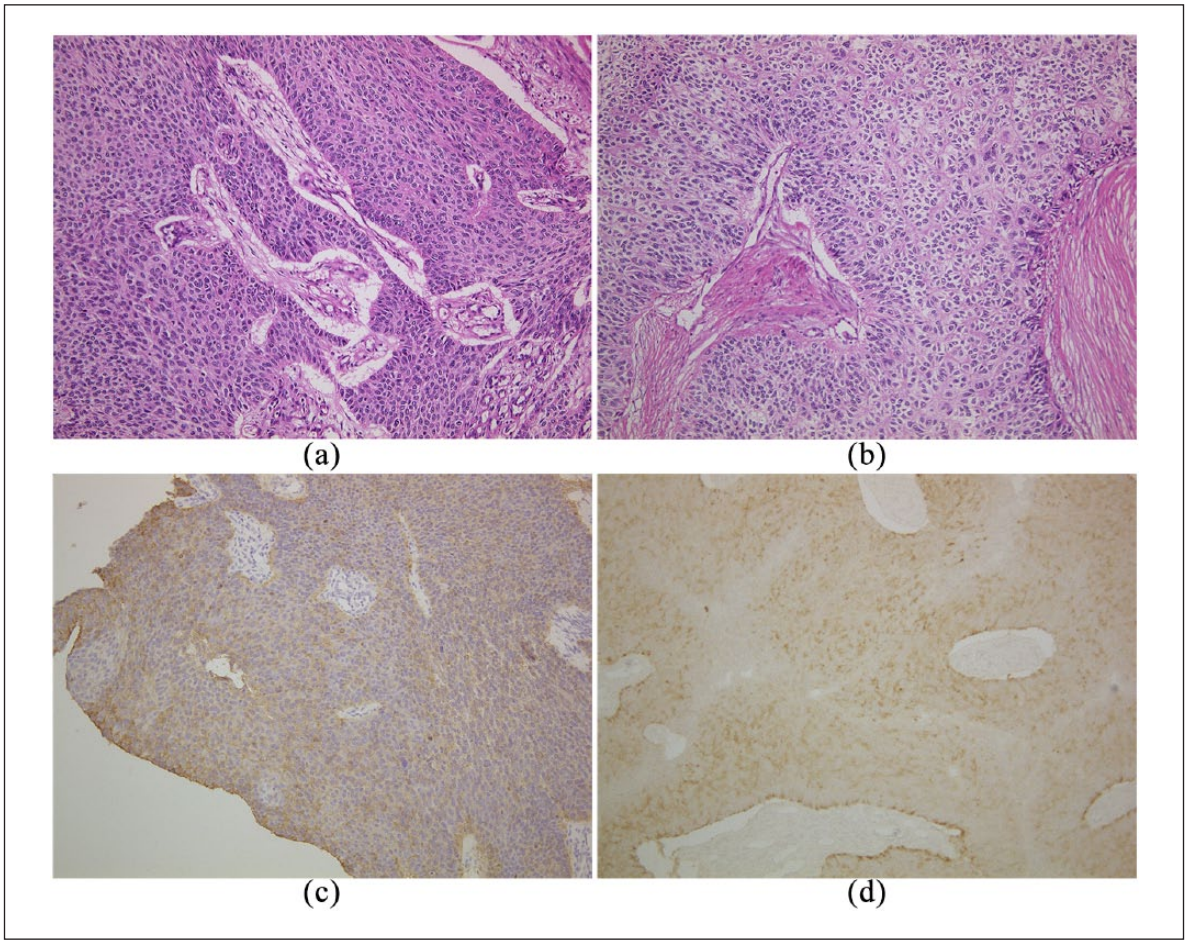

Figure 2. Microscopic examination shows lobular and alveolar structural growth pattern, arranged in epidermoid features with prominent nuclear palisading around perivascular spaces and scant lymphocytes (a), and rosette-like arrangements were observed in part of the tumor (b) (hematoxylin and eosin stain, original magnification ×100). Immunohistochemical staining shows that the tumor cells were diffusely positive for synaptophysin (c) and chromogranin (d) (immunohistochemical stain: synaptophysin, ×100 and chromogranin, ×200).

tumors such as carcinoids typically express synaptophysin and chromogranin A,[11–13] neuroendocrine differentiation associated with type B3 thymoma may be similar to that of neuroendocrine tumors.

Although consensus guidelines are not available for the treatment of type B3 thymoma, it is generally accepted that complete resection is an important independent prognostic factor. For example, the 5- and 10-year overall survival rates of patients with type B3 thymoma, who were treated with curative intent, are 84% and 65%, respectively (100%, 89%, 86%, 60%, and 89%, 86%, 61%, 42% in Masaoka stages 1, 2, 3, and 4, respectively).[4] These results are consistent with several recent reports[14–17] indicating that patients with type B3 thymoma have the worst prognosis among the other subtypes of thymoma.[4] This finding may be explained by the lower resectability of these patients' tumors compared with patients with the other types. Furthermore, such low resectability is associated with the high percentage of invasive tumors. For example, the invasiveness of type B3 tumors such as Masaoka stage 3 or 4 ranges from 41.7% to 100%.[4,14–17]

Other than complete resection, the Masaoka staging system is the most definitive independent prognostic factor.[4,14–17] Tumor size and adjuvant radiotherapy are controversial prognostic factors.[4,18–22] There are no reports, to our knowledge, showing that neuroendocrine differentiation affects the prognosis of thymomas. Two of the three patients with type B3 thymoma with neuroendocrine differentiation mentioned above were followed for 6 months after surgery without recurrence, and there was no mention of follow-up for one case. Disease recurred in our patient 3 years and 6 months after surgery, and she died of the disease 8 years and 3 months after surgery. To our knowledge, the present patient was followed for longer than any other patient with type B3 thymoma with neuroendocrine differentiation. The 5-year freedom-from-recurrence (FFR) rate of Masaoka stage 3 type B3 thymoma is 84%,[4] indicating that our patient experienced a relatively poor clinical course. Therefore, neuroendocrine differentiation may influence the prognosis of type B3 thymoma. Studies of more patients are required to support this conclusion.

Conclusion

Here, we describe a rare case of a type B3 thymoma with neuroendocrine differentiation. The patient lived for 8 years and 3 months after thymectomy. Her clinical course was shorter compared with the FFR of conventional Masaoka stage III type B3 thymoma. Therefore, analysis of more patients is required to determine whether neuroendocrine differentiation predicts worse prognosis.

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Ethical approval

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Informed consent

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ORCID iD

Kiyoshi Sato https://orcid.org/0000-0001-6130-0494

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