

Case Report

Extremely rare case of B3/thymic carcinoma borderline tumor of the middle mediastinum in a myasthenic patient

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Abstract

Thymomas and thymic carcinomas are rare mediastinal tumors. Ectopic middle mediastinal thymomas/thymic carcinomas are even more rare. We report the first case of B3/thymic carcinoma borderline tumor of the middle mediastinum in a 61-year-old myasthenic woman. Preoperative chest tomography and magnetic resonance imaging documented a 4.0 × 3.5 × 2.7 cm mass in the retroinnominate space. A resection of the tumor of the middle mediastinum, associated with an extended thymectomy, was carried out through a median sternotomy. Pathological diagnosis was ectopic B3/thymic carcinoma borderline tumor, stage IIa in the Masaoka clinical staging system; the thymic tissue showed normal fatty involution. Postoperative course was uneventful and, at 1 year follow-up, the patient showed an improvement of Myasthenia Gravis and no sign of tumor recurrence.

Keywords: Ectopic thymoma, Myasthenia Gravis, Middle Mediastinum

Introduction

Thymomas are rare mediastinal neoplasms and thymic carcinomas (TCs) represent only the 1% of all thymic tumors [1].

Embryologically, thymic epithelium arises from the third and probably fourth branchial pouches bilaterally and migrates into the antero-superior mediastinum. A mismigration of thymic gland tissue during embryogenesis is considered the cause of the possible finding of ectopic thymoma in the middle mediastinum [2].

Thymic neoplasms may be associated with a wide range of paraneoplastic disorders; Myasthenia Gravis (MG) can be present in a third of cases.

Case report

A 61-year-old Caucasian female presented with right ptosis, diplopia and dysphagia. Her medical history was positive for Hashimoto thyroiditis and hypercholesterolemia.

She received a diagnosis of MG because of a positive intramuscular prostigmine test, with positive serum acetylcholine receptor (Ach-R) antibodies (11.9 nmol/L; normal range < 0.2 nmol/L) and negative muscle-specific tyrosine kinase antibodies.

Chest contrast-enhanced tomography (CT) revealed a 4.0 × 3.5 × 2.7 cm tumor with heterogeneous enhancement in the right middle mediastinum (Fig.1A and B). The fat plane was not clear between

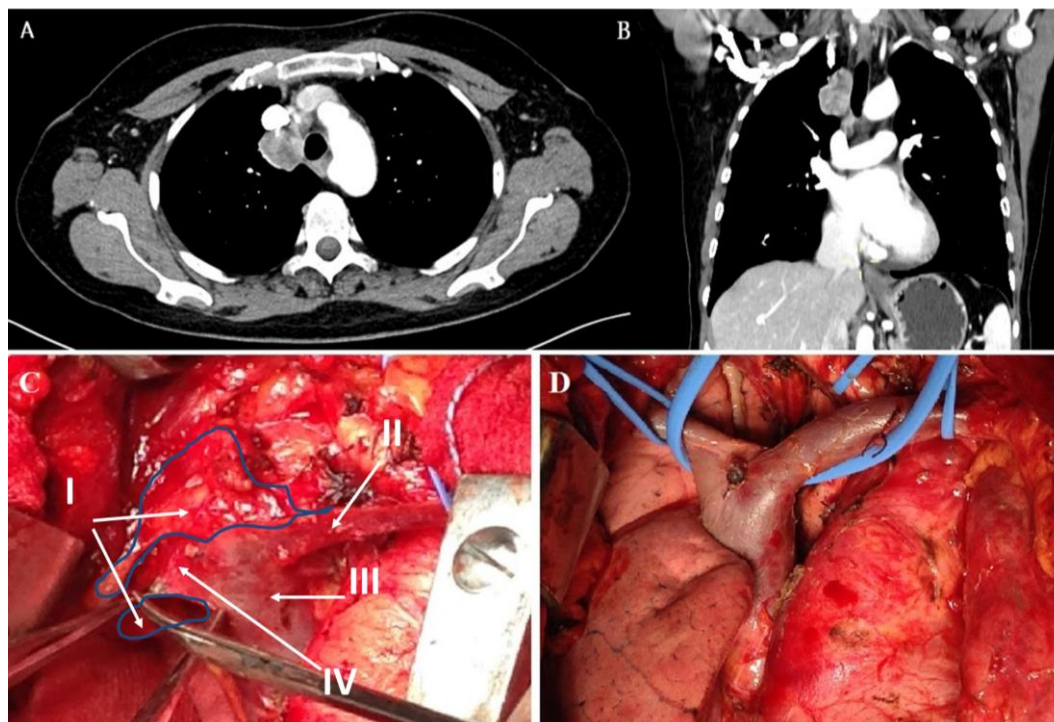


Fig.1: Axial (A) and coronal (B) CT scans of the chest showing the ectopic thymoma in the middle mediastinum. Intraoperative findings: before (C: I: Visible portion of the ectopic thymic tumor partially covered by SVC and right innominate vein; II: Left innominate vein; III: SVC; IV: Right innominate vein) and after (D) dissecting the tumor from surrounding structures.

the tumor and the right wall of the trachea and the posterior wall of right and left innominate veins at their confluence into the superior vena cava (SVC), that presented signs of extrinsic compression. The posterior side of the mass contacted the aberrant right subclavian artery (*arteria lusoria*) and the esophageal wall, however the fat plan between these structures was conserved.

Magnetic resonance imaging (MRI) showed a low intensity lesion both on T1- and on T2-weighted images, as for solid mass.

Several tumor markers were within the normal range.

Postoperative histopathological specimen examination showed a normal fatty involution of thymic tissue, while the middle mediastinal tumor consisted of a multinodular, 4 cm in maximum size, neoplasia, yellowish in color on cut surface with brown necrotic area.

Histologically, it was a neoplasm with a solid growth pattern composed of epithelial cells with minimal atypia, separated by fibrous septa (Fig. 2A and B) and with perivascular spaces. Scattered and isolated

thymic lymphocytes (immunohistochemistry positivity for TdT, CD5 and CD3) at the periphery of the lesion, rare mitosis and necrotic areas were found. Images of neoplastic infiltration of the surrounding adipose tissue were frequently observed. The neoplastic cells were positive for CK19 and negative for CD117 (Fig. 2D) and chromogranin. A focal positivity for CD5 was also reported in the neoplastic cells (Fig. 2C). Therefore, because of the absence of major atypia and intercellular bridges, the lack of TdT+ T cells (Fig. 2E) but the expression of CD5, according to ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma [3], the diagnosis was B3/TC borderline tumor and stage IIa in the Masaoka clinical staging system [4].

The patient was referred to our department for surgical treatment of the mediastinal mass detected by radiological examinations, after a multidisciplinary discussion.

Surgical resection was proposed in order to clarify the pathological diagnosis of the tumor and try to improve the MG by removing thymic tissue.

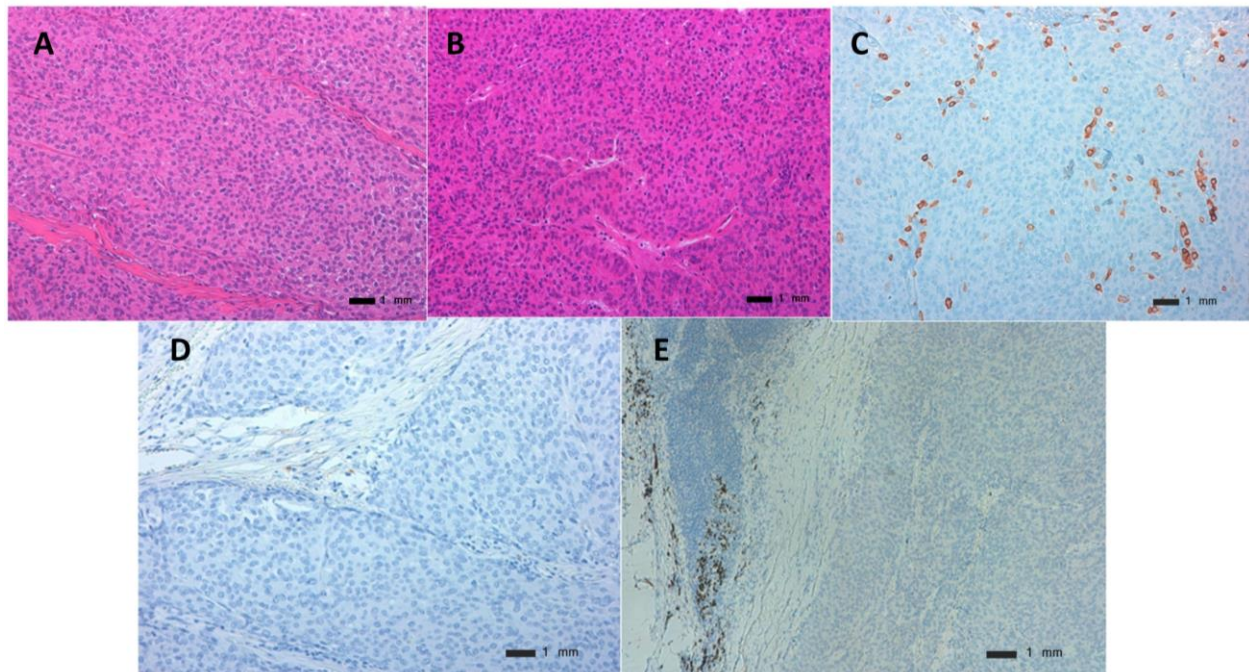


Fig. 2: Solid growth pattern of epithelial cells, perivascular spaces, no major atypia (**A and B**, Hematoxylin and eosin stain, 10X), with an IHC positivity for CD5 (**C**, 10x), negativity for CD117 (**D**, 10x) and lack of TdT+ T cells (**E**, 10x). Scale bars, 1mm.

Therefore, she underwent an extended thymectomy associated with resection of the tumor in the middle mediastinum through a median sternotomy. This surgical access was chosen - instead of a right thoracotomy - in order to better manage the possible radiological suspicion of infiltration of the posterior wall of right and left innominate veins at their confluence into SVC and to perform an extended thymectomy. Intraoperatively, it was possible to dissect the tumor from the trachea, SVC, innominate veins and esophagus, without any sign of invasion of the adjacent mediastinal structures. The middle mediastinal tumor had no connection to the thymic tissue that was also resected together with the surrounding fat tissue (Fig. 1C and D).

The postoperative course was uneventful. The patient was discharged on postoperative day 5 and then was referred to adjuvant radiotherapy. At one-year follow-up, the patient was alive without recurrence and had an improvement of MG. Indeed, her preoperative myasthenic symptoms (ptosis, diplopia and dysphagia) were well controlled by pyridostigmine (90 mg/day), dexamethasone (62.5 mg/day) and azathioprine (100 mg/day). A year after surgery, the immunosuppressive therapy was reduced as follows: pyridostigmine 60mg/day,

dexamethasone 30 mg/every other day and azathioprine 75 mg/day.

Discussion:

Ectopic middle mediastinal thymomas are extremely rare and to date only one case of TC of the middle mediastinum, in subcarinal area, was reported in English literature (Table 1). Our report is the first case of ectopic B3/TC borderline tumor in middle mediastinum (retro-innominate space) in a myasthenic patient. Only three cases of myasthenic patients with a middle mediastinal thymoma were already described in literature but all pathological diagnoses were thymomas AB or B1 according to the WHO histological criteria (Details of these previous cases and the present one are shown in Table 1).

Very few reports have described MG associated with thymic carcinoma [5-7] but never with ectopic borderline tumor. In fact, according to those reports, all such cases involved type B2 or B3 thymoma in thymic carcinoma, that developed from thymoma after a long period, probably in the necrotic tissue of the same thymoma.

Furthermore, the association of an ectopic thymic tumor in the middle mediastinum with no

connection to the normal thymus in a patient with an aberrant right subclavian artery has never been reported previously in the literature.

Differential diagnosis of middle mediastinal masses includes lymphadenopathy (malignant lymphoma, sarcoidosis, Castleman's disease and metastasis), duplication cysts (bronchogenic and esophageal), aortic arch aneurysm, enlarged pulmonary artery, pericardial cyst and tracheal lesions. Neurogenic tumors and mediastinal goiters can also occur in the middle mediastinum.

Although extremely rare, thymomas and TCs should be considered in the differential diagnosis of middle mediastinal tumors and a complete resection should be attempted at the time of the operation, because of their malignant potential and relatively good long-term survival after complete macroscopic resection.

In patients with raised preoperative Ach-R antibody with or without clinically apparent myasthenic symptoms, additional extended thymectomy should be considered for ectopic thymomas, as is usual for MG associated with non-ectopic thymomas.

In patients without raised ACh-R antibody and no myasthenic symptoms, simple resection of ectopic thymomas should be sufficient [2].

Despite TCs have a worse prognosis compared to thymomas, complete surgical excision with negative margins is the treatment of choice when feasible, in order to decrease the risk of local recurrence and improve prognosis [8,9]. Adjuvant treatment - whether or not combined -should also be taken in account, depending on the pathological stage of the tumor. Although the optimal adjuvant therapy after surgical resection has not been well established and remains controversial, because of the rarity of this disease and limited available data, radiotherapy seems to show a better progression-free survival after R0 resection [10].

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Abbreviations:

Ach-R, acetylcholine receptor;
CT, Chest Tomography;
IHC, immunohistochemistry;
MG, Myasthenia Gravis;
MRI, Magnetic resonance imaging;
SVC, Superior Vena Cava;
TCs, Thymic carcinomas.

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Table 1: Report of ectopic thymomas/thymic carcinomas in the middle mediastinum

Age/ gender	M.G.	Size (cm)	Type/ Stage	Surgical Access	Imaging	Clinical course	Reference
60/F	No	5.5×3.5×2.8	AB/ II	Right thoracotomy	CT: Heterogeneously enhanced mass MR: T1 low, T2 high	Adjuvant treatment: 50 Gy RT	Kojima K et al. 2002
60/F	No	6.0×5.5×4.1	AB/ I	Sternotomy	CT: Heterogeneously enhanced mass and calcification MR: T1 low, T2 slightly high mass	Postoperative course: uncomplicated Adjuvant treatment: none	Kanzaki M et al. 2004
53/M	Yes	7	AB/ Unknown	N.A.	CT: Soft tissue mass MR: T1 intermediate	N.A.	Minniti S et al. 2004
47/M	No	10×7.5×7	AB/ II	Left thoracotomy	CT	Adjuvant treatment: RT	Venavaga K et al. 2005
69/F	No	10×10×7	Metastatic thymoma/ Unknown	N.A.	CT	N.A.	Kuzdzal J et al. 2006
69/F	No	7.5×4.8×3.2	A/ I	V.A.T.S.	CT MR: Heterogeneous mass	Adjuvant treatment: none	Nakamura H et al. 2007
71/F	No	7×6×4	A/ I	N.A.	CT: Soft tissue density mass	Adjuvant treatment: none	Huang TW et al. 2007
61/M	No	3.5	AB/ I	V.A.T.S. from the right side	CT: Soft tissue density mass MR: T1 iso and T2 low mass, and septal enhancement (18)F-FDG PET: Slightly positive mass (11)C-acetate PET: Highly positive mass	Adjuvant treatment: none	Sakurai H et al. 2009
69/F	Yes	N.A.	Thymoma	N.A.	N.A.	N.A.	Takizawa M. et al. 2012
56/M	No	6.5×4.5×3.5	AB/ II	Anterolateral minithoracotomy in 4 th right intercostals space assisted by thoracoscopy in 7 th intercostals spaces	CT: Solid and uniform mass, and slight enhancement MR: T1 iso and T2 heterogenous mass, and slight enhancement	Adjuvant treatment: 50 Gy RT	Shikada Y et al. 2012

Table 1. (Continued)

50/F	No	4.0×3.5×1.8	B3/ II	V.A.T.S. from the right side	CT: Soft tissue density and heterogeneously enhanced mass MR: T1 low, T2 relatively high and heterogeneously enhanced mass (18)F-FDG PET: Moderately positive mass	Postoperative course: No recurrence 12 months after surgery Adjuvant treatment: 50 Gy RT	Sato M. et al. 2012
51/M	Yes	2	B1/I	V.A.T.S. from the right side with the sternum lifted, through subxiphoid incision	CT: well-defined nodule	Postoperative course: necessity of noninvasive ventilation after anesthesia. Worsening of ptosis and neck muscle weakness on postoperative day 3. Adjuvant treatment: none MG outcome: pharmacologic remission 14 months after surgery; patient's condition well controlled with tacrolimus.	Koezuka S. et al. 2013
42/ F	No; Ach-R antibodies +	4.9	AB/I	V.A.T.S. from the right side+ sternotomy	CT: heterogeneous tumor MR: low intensity on both T1- and T2-weighted Images (18)F-FDG PET: no significant increased accumulation of FDG (SUV max 2.2–2.7)	Postoperative course: uneventful. Neither tumor recurrence at 12-months FUP, nor MG symptoms	Tokuno J. et al. 2014
55/ F	No	5.5×5.0×4.5	Thymic carcinoma/I	V.A.T.S: from the right side with five-port approach	CT: Tumor on subcarinal area (18)F-FDG PET: large hypermetabolic subcarinal lesion with a standard uptake value of 14.3	Adjuvant treatment: RT. No evidence of recurrence on CT scan 9 months after surgery.	Vernon J. et al. 2015
61/F	Yes	4.0×3.5×2.7	B3/thymic carcinoma borderline tumor/ IIa	Sternotomy	CT: Tumor with heterogeneous enhancement MR: low intensity on both T1- and T2-weighted images as in solid mass	Postoperative course: uncomplicated. No tumor recurrence at 1 year FUP Adjuvant treatment: RT MG outcome: Improvement of myasthenic symptoms, with reduction of immunosuppressive therapy.	Present case 2015