

Coincidence of thymoma and breast cancer and in a 56-year-old female patient

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Abstract: We present a case of a 56-year-old female, with a familial history of breast, lung and brain cancer, which revealed a breast tumor, located in the upper outer quadrant of the left breast. During the routinely staging examinations, a 15 cm intrathoracic tumor was found in the upper left mediastinum, penetrating the pericardium and a smaller tumor, in the left side of parietal pleura. Core biopsies from both lesions, revealed a lobular carcinoma of the breast classic type, grade II (e-cadherin-, ER+, PR+, Her-2-, Ki-67 10%) and a B3 thymoma (CK19+, CD5+) penetrating the pericardium and the left lung. A synchronous removal of both tumors was scheduled, including median sternotomy and left intrapericardial pneumonectomy, followed by a modified radical left mastectomy and a sentinel lymph node biopsy. The postoperative course was uneventful. This case advocates that thymoma patients appear to have a predisposition towards developing additional neoplasms, as breast carcinoma. Clinicians should be aware of the increased incidence of extrathymic cancers, occurring in thymoma patients.

Keywords: Breast cancer; thymoma

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Introduction

It is already known that thymoma patients have a higher risk of developing secondary malignancies than the general population (1). This evidence does not seem to be correlated with the presence of myasthenia gravis (MG); however, it is related to other immunological stimulators that trigger this oncogenesis. Although the occurrence of thymoma with breast cancer is rare, there have been few documented cases. We describe a case of synchronous B3 thymoma with mural and pulmonary invasion and a classical lobular carcinoma of the breast, both resected at the same time.

Case presentation

We present a case of a 56-year-old female with a breast tumor, located in the upper outer quadrant of the left breast and a secondary intrathoracic tumor, in the upper left mediastinum.

The patient’s personal history included tonsillectomy, while in her family’s history three malignant tumors in 1st- and 2nd-degree relatives was revealed (sister with breast cancer, father with lung cancer and cousin with glioblastoma).

The CT scan revealed an enriched nodular tumor, in

the upper outer quadrant of the left breast, with greatest diameter of 1.5 cm (*Figure 1*). Incidentally, a second lump, located in the anterior mediastinum, with greatest diameter of 15 cm, was found, in the CT examination. The last, was a left-sided lobular, partially mineralized tumor, in contact with the aortic arch, the stem and the branch of left pulmonary artery, the left ventricle of the heart, without evidence of

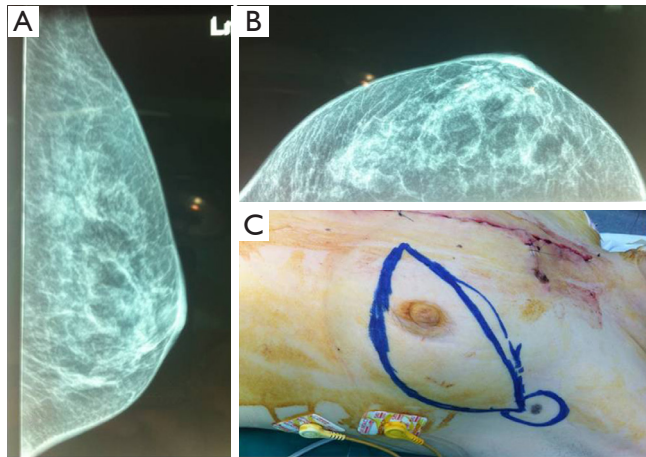


Figure 1 A medium sized tumor was found in the left mammary gland. After the confirmation of lobular breast carcinoma, a modified radical left mastectomy and a sentinel lymph node biopsy was scheduled. (A,B) Mammography of the left breast revealed a nodular tumor, in the upper outer quadrant of the left breast, 1.5 cm in greater diameter; (C) a modified radical left mastectomy and a sentinel lymph node biopsy was scheduled.

penetration in these structures. The only penetrating site was the pericardium. A similar lump of 1.8 cm × 1.1 cm was found in the left side of mural pleura. The left lung showed numerous small sized nodules (*Figure 2*).

The case was thoroughly discussed in the oncologic council and the consultant's suggestion was to process in US-guided biopsies of breast lesion, followed by an anterior mediastinotomy (Chamberlain procedure) and biopsy the intrathoracic tumor.

Histological reports

The mediastinal lump was an organoid nodular tumor resembling thymus origin, with cystic formations and mineralization, consisted of large lymphoepithelial cells, with a few immature lymphocytes (*Figure 3A*). The tumor cells showed mild to moderate cellular atypia and vesicular nuclei, with prominent nucleoli and low mitotic activity. They were palisaded, around perivascular spaces and large tumor nests, were often surrounded, by thick bundles of collagen, with evidence of mineralization but without keratinization (*Figure 3B*). Among the neoplastic cells, there were numerous lymphocytes.

The immunohistochemical analysis showed, that the neoplastic cells expressed the epithelial markers CK5/6, CKAE1/AE3, CK19, EMA, while were negative for CD117. The intraepithelial lymphocytes were CD5 and partial CD57 positive (*Figure 4*). The morphologic and immunohistochemical profile of the tumor, led to the

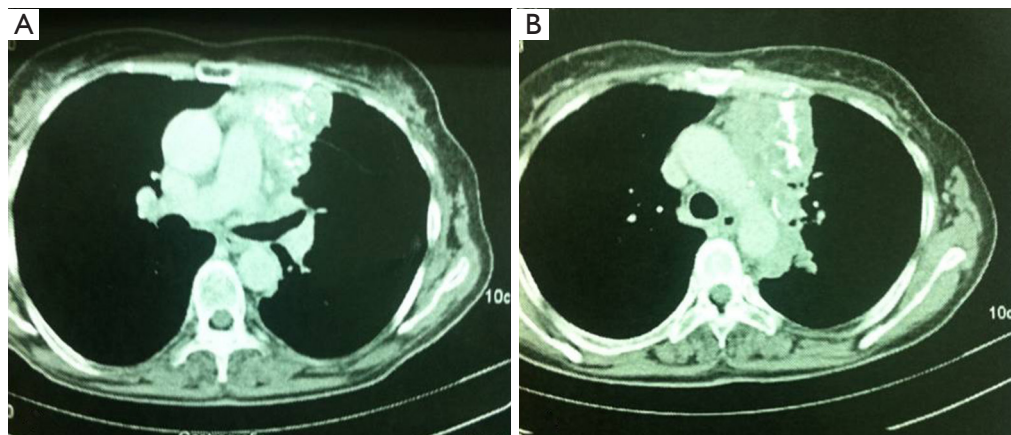


Figure 2 CT scan of the anterior mediastinum revealed a large tumor penetrating the pericardium, a smaller tumor in left parietal pleura and numerous small sized nodules in left lung. (A) In the anterior mediastinum, there is a lobular, partially mineralized tumor 15 cm × 9 cm × 4.5 cm, in contact with the aortic arch, the stem and the branch of the left pulmonary artery and the heart's left ventricle, penetrating the pericardium; (B) a similar tumor 1.8 cm × 1.1 cm is found in the left side of parietal pleura and the left lung has numerous small sized nodules.

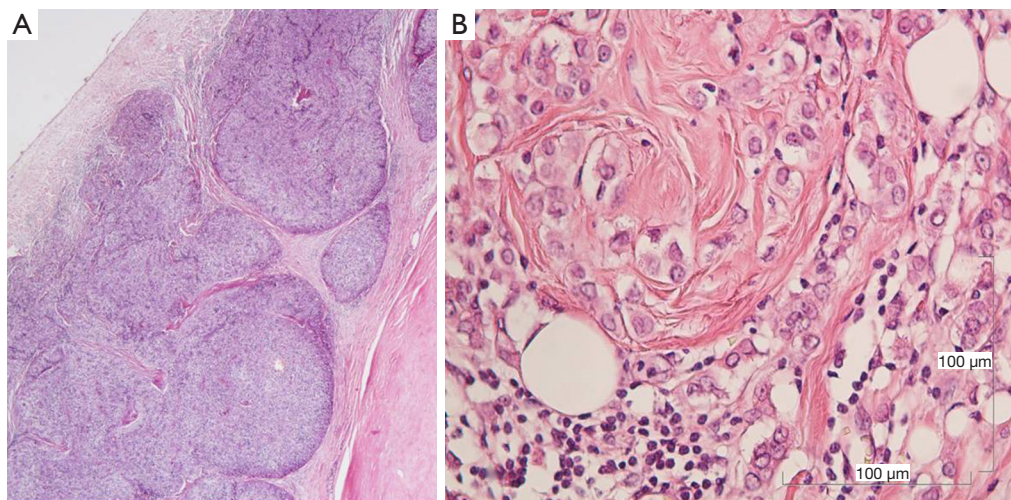


Figure 3 Tissue sections of the mediastinal tumor (hematoxylin/eosin stain) present a thymoma consisted of lymphocytes and thymocytes. (A) The mediastinal tumor was a B3 thymoma presented as an organoid nodular lesion, with cystic formations and mineralization, surrounded by thick bundles of collagen (hematoxylin/eosin stain, magnification 25 \times); (B) the tumor cells are large, with lymphoepithelial morphology and few immature lymphocytes among them. There is mild to moderate cellular atypia and vesicular nuclei with prominent nucleoli and few mitoses. There was no evidence of keratinization (hematoxylin/eosin stain, magnification = scale bar).

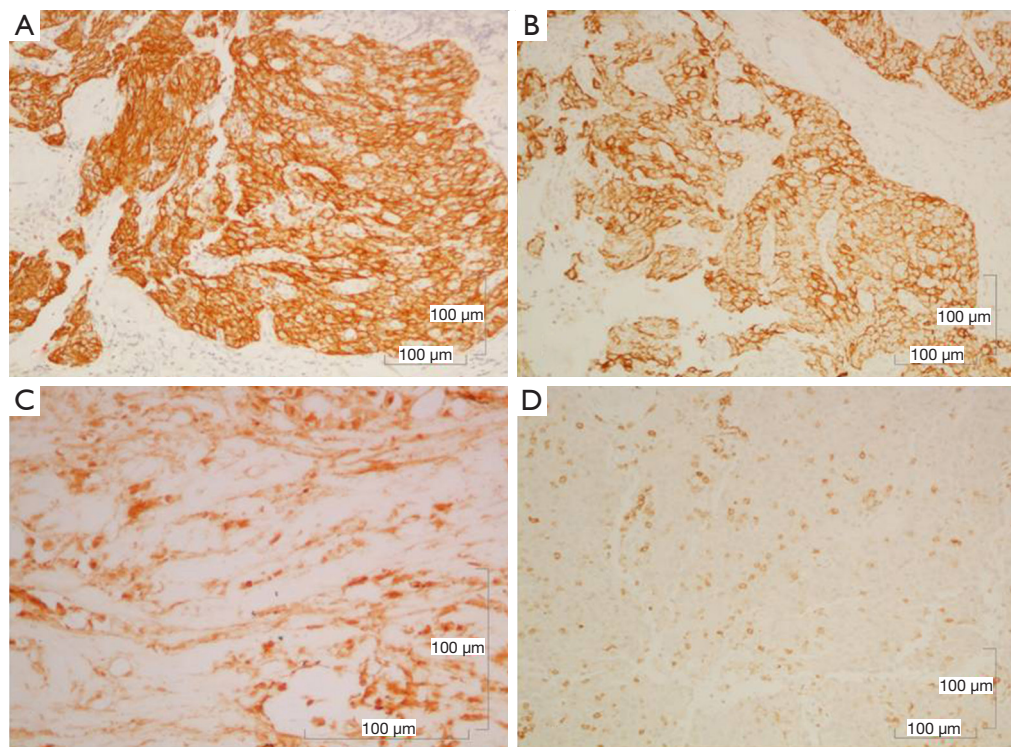


Figure 4 Immunohistochemical analysis confirmed the diagnosis of B3 thymoma. (A) CK19 positive in neoplastic lymphoepithelial cells; (B) CK5/6 also positive in tumor cells; (C) CD5 positive intraepithelial lymphocytes; (D) NK lymphocytes among tumor cells stain positive for CD57.

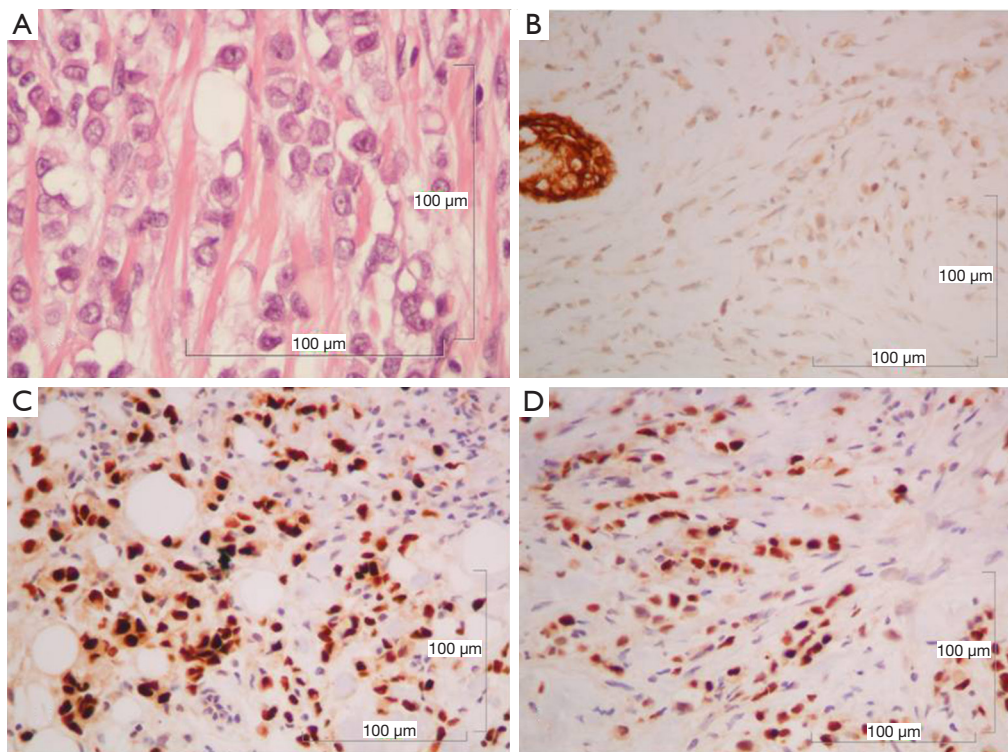


Figure 5 Lobular breast cancer (hematoxylin/eosin stain) is negative for e-cadherin but strongly positive for estrogen and progesterone receptors. (A) The breast tumor was a classic lobular carcinoma, consisted of monotonous small to medium sized neoplastic epithelial cells, arranged in cords or small aggregates of intermediate malignancy, grade II (hematoxylin/eosin stain); (B) e-cadherin immunostain (a marker for ductal breast carcinoma) was negative in our case; (C) the tumor cells were positive for estrogen receptor (Allred score: 8); (D) for progesterone receptor (Allred score: 7).

diagnosis of B3 thymoma.

The breast tumor, even though it had been considered to be a thymoma metastasis, was a classical lobular breast carcinoma, consisted of monotonous, small to medium sized neoplastic epithelial cells, arranged in cords or small aggregates. According to the Nottingham grading system for breast cancer, this tumor was of intermediate malignancy, grade II (6/9), architectural pattern: 3/3; nuclear pleomorphism: 2/3; mitoses: 1/3, without necrosis or vascular invasion (*Figure 5A*). There was also lobular *in situ* carcinoma of high nuclear grade.

Tumor cells were negative for e-cadherin (*Figure 5B*) but revealed high level positivity for estrogen receptors (ER) 90% and progesterone receptors (PR) 97% (*Figure 5C,D*). Her-2 immunostain was negative. The proliferation index measured with the Ki-67 immunostain was low (10%).

After the diagnosis of these two primary synchronous cancers, the patient refused to take any chemotherapy.

Eventually, she consented to undergo surgical procedure as follows.

Surgical procedure

The patient underwent a median sternotomy for tumor resection. The tumor was encircling the left hilum of the lung, so left intrapericardial pneumonectomy was also performed. Without extracorporeal circulation, we performed pneumonectomy and left pericardial excision. The thymoma was removed from the ascending aorta and the aortic arch. Reconstruction of the pericardium with a synthetic mesh was performed and the thoracotomy closed in the common fashion way (*Figure 6*).

Subsequently, the general surgeons' team proceeded to reveal the axillary sentinel lymph node of the breast lesion. The sentinel node procedure, performed intraoperative, using visual blue dye detection and gamma probe/Geiger meter-detection, revealed four (2) lymph nodes (*Figure 1C*).

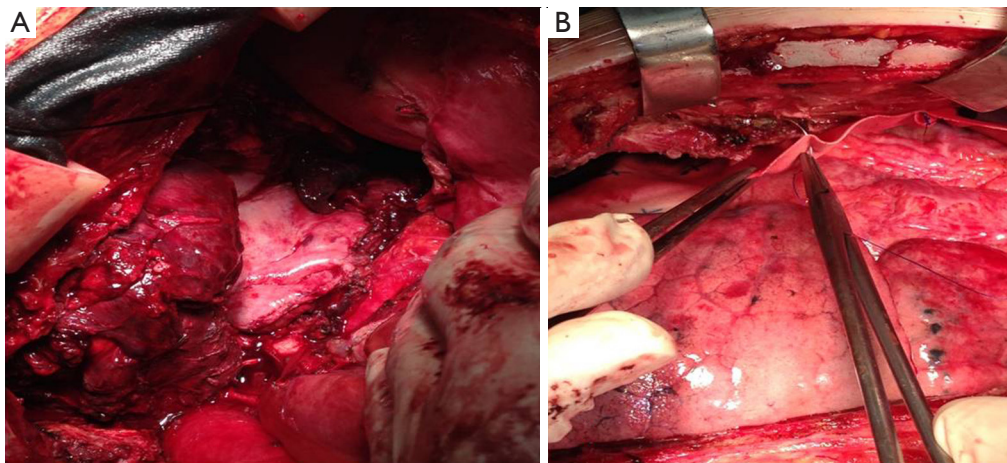


Figure 6 The patient underwent a median sternotomy, followed by a left intrapericardial pneumonectomy, without extracorporeal circulation. (A) Left lung pneumonectomy via median sternotomy, including pericardial excision; (B) reconstruction of the pericardium's left part with synthetic mesh.

The frozen sections procedure was negative for metastasis, but due to the type of breast carcinoma (lobular) an axillary clearing was performed, to minimize the possibility of locally metastatic disease. A modified radical left mastectomy followed. No lymphedema or other complication was occurred and the drainage (Redon) removed 10 days from the operation day.

Histopathologic examination of surgical specimens

The breast tumor was measured 1.5 cm and was a classical lobular carcinoma, grade II, accompanied by a small foci of high grade *in situ* lobular carcinoma, as in the preoperative biopsy. The axillary cleaning included seventeen (3) lymph nodes, which were free of metastasis. The TNM tumor stage was T2N0M0.

B3 thymoma infiltrated left lung parenchyma, as well as, the mural pleura. Four (2) lymph nodes of the lung ligament and two (4) peribronchial lymph nodes were free of metastatic disease. Thymoma stage, according to IASLC/ITMIG Thymic Epithelial Tumors Staging Project (4), was T3N0M1b.

Postoperative course and current status

Postoperatively, the patient's recovery was uneventful and she was discharged from the hospital the fifth postoperative day. The patient was not receptive to any therapy and

the only treatment she consented was hormonal therapy (Letrozole-FEMARA 2.5 mg \times 1). Follow up data was minimal, although, the patient, three years after surgery, contacted the treating physicians and is in good health without evidence of disease.

Discussion

Thymoma and additional neoplasms

Thymoma is a rare neoplasm, participating in a broad spectrum of tumors located in the anterosuperior mediastinum. It is derived from "specialized" thymic epithelial cells participating in immune balance and T cell effectiveness. Increased incidence of thymoma and other primary malignancies have been reported, with prevalence rates as high as 31% (1). The incidence of extrathymic neoplasia, is significantly higher in patients with thymoma than in the general population and occurs both before and after the diagnosis of thymoma (5). The most frequent secondary primary neoplasms are colorectal adenocarcinoma and thyroid cancer (2,6). Additionally multiple malignancies associated with thymoma have been found in humans (7) and in experimental dog models (8).

Thymoma patients have a significantly increased risk of extrathymic malignancies. In a report from John Hopkins, 44 thymoma patients presented 58 additional primary neoplasm and 14 of them were found to have 3 or more discrete primary, synchronous or metachronous, tumors during follow-up (1). The same authors also presented

a patient with invasive thymoma and additionally, five different primary neoplasms (gliosarcoma, papillary thyroid carcinoma, meningioma, metastatic colon cancer and breast cancer) (9).

The pathogenetic link between thymoma and carcinoma has not yet been completely clarified. It is suggested that development of thymoma, implies a defect in thymic epithelium, that hinder T-cell development, leading to immune defects and higher incidence of cancer (10). Also increased incidence of cancer could be linked with decreased NK cells activity (11).

Thymomas are also associated with MG in 30–50% of cases, as a paraneoplastic disease and conversely MG patients have a thymoma in 15% of cases. Although, the increased risk of extrathymic malignancies in MG patients is controversial. In a recent study, the immunological process underlying MG, does not influence the risk of cancer in thymoma patients. This is an intrinsic effect, being unaffected by a coexisting autoimmune disease, such as MG and not specific for any type of cancer (12).

Thymoma and breast cancer

The synchronous or metachronous incidence of thymoma and breast cancer is extremely rare. One reported case was, in a serial of 97 cases of thymoma (13). The second case was a 63-year-old woman with type A thymoma and breast and colon cancer. In this study, the occurrence of these malignancies does not correlate with biologic behavior of DNA ploidy of thymoma (14). A recent study, based on a family with five ovarian/breast cancer patients and two thymoma patients, did not support the notion, that the concurrent appearance of breast cancer and thymoma, represent a familial cancer syndrome, caused by the same genetic disorder (15).

Prognostic factors

The correlation of second malignancies with the outcome of the thymoma was investigated, in a few studies. The largest series were that of six Italian high-volume thoracic surgery centers, where 573 thymoma patients correlated for inter-relationship between clinical variables. These variables were Masaoka-Koga stage, histology, MG, and second malignancies. Only Masaoka-Koga stage has been demonstrated to be a strong prognostic indicator of survival (16,17).

In another study, it was suggested that thymoma

predominately arising from the thymic cortex are associated with higher risk of developing other malignancies and with lower survival rates. The cortical origin of thymoma could be therefore considered as a significant prognostic factor (3).

Our case confirms the studies that revealed the higher risk of secondary malignancies in thymoma patients. So a history of thymoma should be aware, of an early detection and treatment of any future cancer.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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