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Case Report

Intracaval and intracardiac extension of invasive thymoma complicated by superior and inferior vena cava syndrome

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We present a case of an aged male with invasive thymoma that extended into the right atrium and led to superior and inferior vena cava syndrome. The patient initially presented with edema of the face and bilateral lower extremities. Echocardiography revealed a mass within the right atrium. Imaging studies demonstrated an anterior mediastinal tumor that continuously occupied the bilateral brachiocephalic veins, superior vena cava, and right atrium. Pathological diagnosis of the tumor biopsy was highly suspicious of thymoma. Due to the high risk of wide spread of the tumor, treatments including resection of the tumor were impossible. Several days later he died, and an autopsy was performed. The tumor was type B2 thymoma invading bilateral brachiocephalic veins, superior vena cava and right atrium. Multiple tumor emboli within the pulmonary arteries were identified. Direct cause of death was deemed to be tumor strangulation at the tricuspid orifice. In addition to the superior vena cava syndrome, inferior vena cava syndrome including ectasia of the intrahepatic vessels was confirmed along with pericarditis. To our knowledge, this is the first English report of an autopsy case of intracardiac thymoma extension, and a detailed literature review of similar cases is also presented.

Key words: intracaval, IVC syndrome, right atrial invasion, SVC syndrome, thymoma.

Thymoma is one of the most common tumors in the mediastinum and accounts for 45% of anterior mediastinal tumors in adults, mainly affecting people aged 40–60 years.[1] Thymomas are classified as invasive or noninvasive, depending on the presence or absence of tumor capsular invasion and/or anatomic extension.[1,2] Invasive thymomas, accounting for approximately 30% of thymomas, may invade mediastinal organs such as pleura and pericardium, but they rarely invade the superior vena cava (SVC).[2] Indeed, although SVC syndrome may be associated in 4% of thymomas, the most common cause is extrinsic compression rather than intracaval growth.[3] Furthermore, intracaval growth with extension into the right atrium, called 'transvenous' cardiac metastasis, is extremely rare.[2] We herein report an autopsy case of this rare manifestation of thymoma, and identified complication by inferior vena cava (IVC) syndrome and peculiar pericarditis.

CLINICAL SUMMARY

The case of a 74-year-old Japanese male with SVC syndrome is presented here. His past history includes colon cancer at the age of 65 and cerebral infarction with hypertension at the age of 72. Edema appeared in the face and bilateral lower extremities in mid-December, 2010. Right pleural effusion was pointed out, and a diuretic was prescribed by a local doctor late in December, 2010. A mass within the right atrium was discovered by echocardiography in mid-January, 2011, thus, he was subsequently transferred and admitted to our hospital.

Computerized tomography (CT) of the chest revealed an anterior mediastinal tumor invading the left brachiocephalic vein and SVC (Fig. 1a). Coronal view of a chest magnetic resonance imaging (MRI) scan showed a mediastinal mass occupying the SVC, which extended into the right brachiocephalic vein and right atrium (Fig. 1b). Angiography demonstrated occlusion of the SVC and bilateral brachiocephalic veins as well as meandering dilated thoracoepigastric veins (collaterals), which connect subclavian veins with superficial epigastric veins that inflow into the inferior vena cava (Fig 1c), signs that were compatible with obstruction of the SVC proximal to the inflow portion of the azygos vein.

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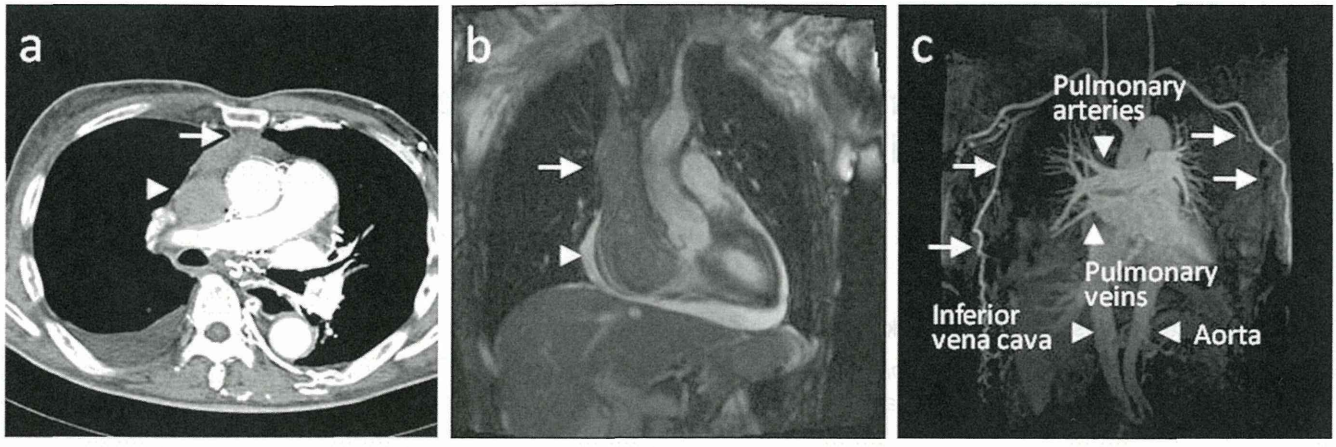

Figure 1 Imaging studies. (a) Chest computerized tomography showing an anterior mediastinal tumor (arrow) that consecutively extends into the left brachiocephalic vein and superior vena cava (arrowhead). (b) Coronal view of a chest magnetic resonance imaging scan showing a mediastinal mass within the superior vena cava (arrow) that consecutively extends into the right atrium (arrowhead). (c) Angiography of large vessels including the pulmonary arteries and veins, aorta, and inferior vena cava. The superior vena cava is not observed. Instead, meandering dilated thoracoepigastric veins are delineated (arrows).

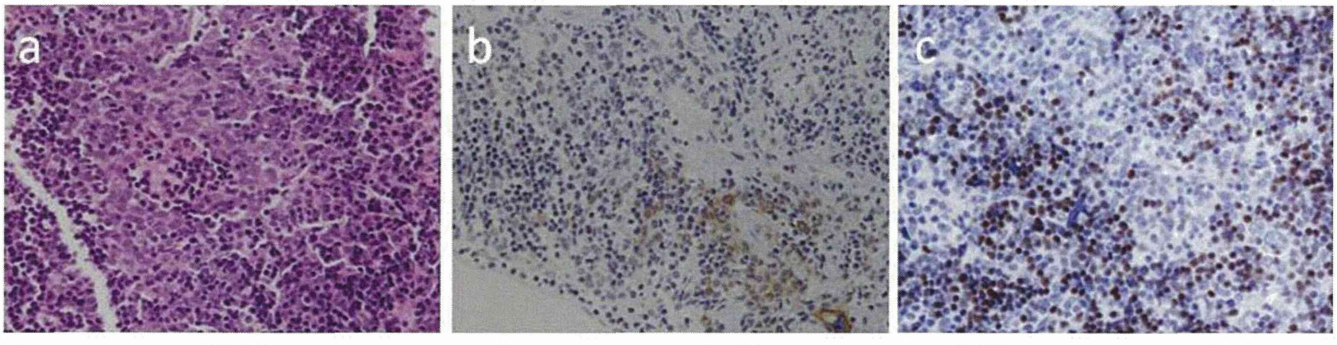

Figure 2 Microscopical features of the tumor. (a) HE staining showing polygonal or rounded epithelial components with an admixture of lymphocytes. (b) Immunohistochemistry of cytokeratin showing focal positive staining for the epithelial cells. (c) Immunohistochemistry of TdT showing diffuse positive staining for the tumor-infiltrating lymphocytes.

Table 1 Antibodies used in immunohistochemistry

Antibody to	Clone	Source	Dilution	Antigen retrieval	Pretreatment
Cytokeratin	AE1/AE3	Dako, Glostrup, Denmark	x400	pH 6CB	Autoclave
CD5	CD5/54/F6	Dako	x50	pH 9EDTA	Autoclave
TdT	SEN28	Nichirei, Tokyo, Japan	x1	pH 6CB	Autoclave
CD99	12E7	Dako	x100	pH 6CB	Autoclave
Fascin	55K-2	Dako	x200	pH 6CB	Autoclave
MMP-2	C-19	Santa Cruz Biotechnology, Santa Cruz, CA	x200	pH 9EDTA	Autoclave
VEGF	A-20	Santa Cruz	x200	pH 9EDTA	Autoclave

MMP, matrix metalloproteinase; pH 6CB, pH 6 Citrate Buffer Solution; pH 9EDTA, pH 9 EDTA buffer; VEGF, vascular endothelial growth factor.

Tumor biopsy using a right heart catheter was performed late in January. The biopsy material was highly cellular and consisted of polygonal or rounded epithelial cells with an admixture of lymphocytes (Fig. 2a). Immunohistochemistry was performed, using avidin-biotin-peroxidase complex according to standard methods. Table 1 lists all of the antibodies used along with the clone and dilution, the antigenic retrieval method used, and pretreatment methods. Immunohistochemically, cytokeratin was focally positive (Fig. 2b) but CD5 was negative in the epithelial cells, and CD5 and immature lymphocytic markers TdT were diffusely positive for the lymphocytes (Fig. 2c). Therefore, although the quantity of the material was insufficient, the histopathological diagnosis of 'highly suggestive of thymic tumor, in favor of type B1 or B2 thymoma' was made.

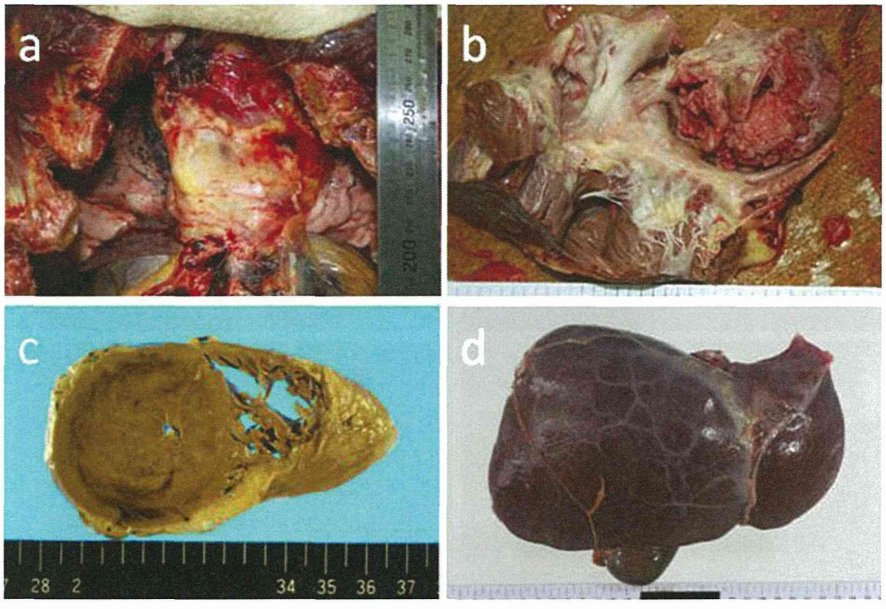

Figure 3 Macroscopical features at autopsy. (a) Poorly demarcated yellowish white anterior mediastinal tumor, 6 × 4 × 1 cm in size, at thoracotomy. (b) Intra-atrial tumor forming a ball-like structure, 6 × 5.5 × 3.5 cm in size. (c) The cut surface of the heart showing hemorrhage in the mid to outer zone of the anterior, lateral, and posterior walls. (d) The liver with dilated lymph vessels.

Considering the patient's age and the wide extension of the tumor, resection of the tumor using cardiopulmonary bypass was deemed too high risk and was thus not performed. Chemotherapy or radiotherapy was also considered impossible based on the results of a clinical conference among thoracic surgeons, cardiovascular surgeons and medical oncologists. He was found fallen and unconscious in a hospital ward early in February, 2011, and without recovering consciousness, he subsequently died.

PATHOLOGICAL FINDINGS

An autopsy was performed 1 hour and 41 minutes after death. The cadaver (61.5 kg, 160 cm) showed edema around the neck. Initial thoracotomy disclosed a poorly demarcated anterior mediastinal tumor, 6 × 4 × 1 cm in size (Fig. 3a), with invasion of the right parietal pleura. Left pleural effusion was yellowish and small (60 ml), while right pleural effusion was bloody and massive (1300 ml). The pericardial effusion was yellowish and increased (300 ml), while the ascites was yellowish and small (100 ml). The tumor extended through the bilateral brachiocephalic veins and SVC into the right atrium (heart: 405 g), forming a ball-like structure, 6 × 5.5 × 3.5 cm in size, with partial adhesion to the endocardium (Fig. 3b). The cut surface of the heart revealed almost whole circumferential hemorrhage in the mid to outer zone of the myocardium (Fig. 3c). The liver (1030 g) showed dilated lymph vessels (Fig. 3d). The lungs (lt. 290; rt. 305 g) showed mild congestion.

Histologically, the tumor formed multiple nodules in a fibrous background (Fig. 4a). Similar to the biopsy material, the tumor nodules consisted of a large number of polygonal or rounded epithelial cells with admixture of lymphocytes; therefore, the tumor was diagnosed as type B2 thymoma. Although the tumor occasionally invaded small veins, direct invasion of the brachiocephalic vein or SVC was not identified. The mass within the right atrium showed the same histology as the primary tumor except for superimposed fibrinous exudates. Multiple tumor emboli were also confirmed in bilateral pulmonary arteries (Fig. 4b). Immunohistochemistry for CD5, CD99, fascin, matrix metalloproteinase (MMP)-2, and vascular endothelial growth factor (VEGF) was performed on the primary and intra-atrial tumors (Table 1). The results were identical between these two tumors; CD5 and CD99 were positive for infiltrating lymphocytes but negative for the tumor epithelium, fascin was weakly positive for the tumor epithelium with an intermix of fascin$^+$ dendritic cells, MMP-2 was negative for the tumor epithelium, and VEGF was diffusely positive for the tumor epithelium (Fig. 4c). Dilatation of subcapsular lymph vessels was confirmed in the liver as well as occasional dilatation of hepatic and portal veins. The hemorrhagic parts of the myocardium showed thinning, disarray and eosinophic change. The external zone of the hemorrhagic parts occasionally showed myocardial necrosis with lymphocytic infiltration beneath the epicardium (Fig. 4d). Detailed investigation of the coronary arteries was performed, and stenosis in up to 90% of the left anterior discending, 40% of the circumflex, and 40% of the right coronary artery was observed along with atherosclerosis, but occlusion was not detected.

DISCUSSION

This aged male patient presented with type B2 thymoma in the anterior mediastinum that extended through the

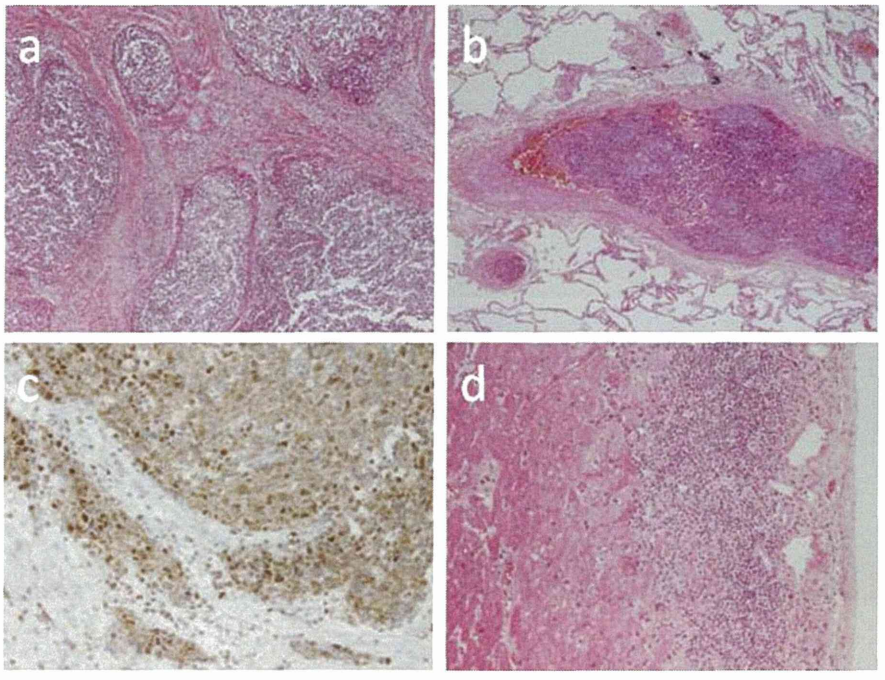

Figure 4 Microscopical features at autopsy. (a) The primary tumor showing multiple nodules with fibrous stroma. (b) Multiple tumor emboli in the pulmonary arteries. (c) The tumor epithelium diffusely immunostained by VEGF (d) Myocardial necrosis with lymphocytic infiltration beneath the epicardium.

brachiocephalic veins and SVC into the right atrium, forming a ball-like structure. Although multiple tumor emboli were discovered in the bilateral pulmonary arteries, and pericarditis was a complication, their extents were not sufficiently indicative of pulmonary and cardiac insufficiencies. Therefore, death of the patient appeared to have been due to tumor strangulation at the tricuspid orifice.

Intracaval growth of invasive thymoma with extension into the right atrium as shown in the present case is extremely rare,[2] and to our knowledge, only 27 cases have been reported in the English literature or in Japanese literature with English abstract (Table 2). As shown in Table 2, this manifestation of thymoma may occur in any age of adults (25–80 y.o.; mean: 55.1 ± 15.1 y.o.) and in both sexes (M:F = 16:12). In virtually all reported cases, SVC syndrome such as swelling of the face and/or upper extremities was also present. Myasthenia gravis was not an accompaniment in any of the cases, which can be found in 30–50% of patients with thymoma.[1] This may be associated with the advanced extension of thymoma in these reported cases, since complication of myasthenia gravis usually facilitates earlier discovery of thymoma.[10] Histological subtypes may not be contributory to the highly aggressive nature, since those with favorable prognosis such as type A and type AB (mixed-type) thymomas are included in Table 2 as well.[28] Although tumor invasion of mediastinal organs such as the pericardium, pleura, and lungs have been reported, a case with tumor emboli in the pulmonary arteries has never been reported to the best of our knowledge, partly because the present case is a rare autopsy report. Indeed, only two autopsy reports in this category have been published in Japanese,[23,26] but the present case is the first English autopsy report.

In most reported cases with intracardiac extension of thymoma in which tumor resection were performed, cardiopulmonary bypass was required. Cardiopulmonary bypass is an invasive technique with increased mortality and complications such as postoperative bleeding associated with full heparinization are known.[24,27] Cases in which tumor resection was performed without cardiopulmonary bypass included partial resection of the lesion,[4,9] a tumor that only protruded into the right atrium without adhesion,[13] a tumor that was reduced by preoperative radiotherapy,[21] and performance of a transient cava-pulmonary shunt.[2,27] More than half of the cases (17 cases) were alive after follow-up of at least 6 months. Therefore, favorable prognosis is likely to be obtained after successful resection in combination with chemoradiotherapy.

With regard to the pathway of entry into the SVC, the tumor invaded small veins, but direct invasion of the brachiocephalic vein or SVC was not identified in the present case. As pointed out by other authors,[16] although tumors may directly invade the wall of the brachiocephalic vein or SVC, it is more likely for tumors to spread into the brachiocephalic vein through a small vein such as the thymic vein, and then grow along the venous stream into the SVC down to the right atrium in a polyp-like fashion.

As mentioned earlier, histological subtypes do not appear to contribute to the highly aggressive nature of this type of tumor. In order to further investigate the cause for aggressiveness, immunohistochemistry was performed. Although CD5 immunopositivity has been reported to be observed

Table 2 Literature review of thymic tumors with right atrial invasion

No.	Year	First Author	Age	Sex	SVC syn.	Histology	Other organ invasion	Therapy	Follow up	Out come
1	1985	Fujio[4]	53	M	(+)	Mixed-type thymoma	(–)	Resection, radiation, chemotherapy	4 y	Alive
2	1989	Korobkin[5]	80	F	(+)	Malignant thymoma	(–)	Radiation	n.r.	n.r.
3	1990	Airan[6]	38	M	(+)	Thymoma	Right ventricle	Resection (CPB), radiation	n.r.	n.r.
4	1992	Missault[7]	65	F	(+)	Thymoma	(–)	Resection, radiation	1 y	Alive
5	1992	Yokoi[8]	72	M	(+)	Thymoma	Pericardium, lungs	Chemotherapy, resection (CPB), radiation	2 y	Alive
6	1993	Futami[9]	56	M	(+)	Mixed-type thymoma	(–)	Resection, radiation	n.r.	n.r.
7	1994	Okereke[10]	25	M	(+)	Mixed-type thymoma	Pericardium, pleura	Resection (CPB)	1 y	Dead
8	1995	Kohiyama[11]	45	F	(+)	Mixed-type thymoma	Pericardium, lung	Chemotherapy, radiation, resection (CPB)	1 y	Alive
9	1996	Sato[12]	43	F	(+)	Predominantly epithelial thymoma	(–)	Resection (CPB), chemotherapy	3 y	Alive
10	1997	Gleeson[13]	50	F	(+)	Invasive cortical thymoma	Pericardium, lung	Resection	1 y	Alive
11	1997	Filippone[14]	52	F	(+)	Type II malignant thymoma	(–)	Resection (CPB), chemotherapy	1 y	Alive
12	1998	Tsuji[15]	59	M	(+)	Invasive thymoma	(–)	Resection (CPB), radiation, chemotherapy	4 y	Alive
13	1999	Minato[16]	44	M	(+)	Mixed-type thymoma	Pericardium, lungs, pleura	Resection (CPB), chemotherapy	29 mo	Alive
14	2000	Hayashi[17]	72	M	(+)	Mixed-type thymoma	Right ventricle	Resection (CPB), radiation	4 y	Alive
15	2002	Ozer[18]	40	M	(+)	Malignant thymoma (s/o anaplastic carcinoma)	Pericardium	Radiation, chemotherapy	n.r.	n.r.
16	2002	Yamazaki[19]	72	F	(+)	Thymic carcinoma	(–)	Resection (CPB)	10 mo	Alive
17	2003	Funakoshi[20]	77	M	(+)	Type A thymoma	Right ventricle	Resection (CPB), radiation	21 mo	Alive
18	2003	Funakoshi[20]	27	F	(–)?	Consistent with thymoma	(–)	Chemotherapy, radiation, resection (CPB)	<1 mo	Dead
19	2006	Ichimura[21]	56	F	(+)	Type AB thymoma	Lung	Chemotherapy, radiation, resection	23 mo	Alive
20	2007	Shudo[22]	48	M	(+)	Type AB thymoma	Pericardium, lung	Resection (CPB), radiation	6 mo	Alive
21	2007	Noguchi[23]	74	M	(+)	Type B3 thymoma	Pericardium, lung	Warfarin, diuretic	4 y	Dead
22	2008	Dursun[2]	50	F	(+)	Invasive thymoma	(–)	Chemothrapy, resection	2 mo	Dead
23	2008	Pastorino[24]	50	F	(+)	Type B3 thymoma	Pericardium, pleura	Chemotherapy, radiation, resection (CPB)	8.5 y	Alive
24	2009	Amirghofran[25]	53	M	(+)	Type AB thymoma	Pericardium, lung	Resection (CPB), radiation, chemotherapy	5 y	Alive
25	2010	Li[3]	40	M	(+)	Type B3 thymoma	Lung	Resection (CPB), radiation	10 mo	Alive
26	2011	Maekura[26]	76	M	(+)	Thymic carcinoma	Inferior vena cava, pleura, pericardium	Radiation, chemotherapy	7 mo	Dead
27	2012	Toker[27]	53	F	(+)	Invasive thymoma	(–)	Resection, radiation, chemotherapy	n.r.	n.r.
28		Present case	74	M	(+)	Type B2 thymoma	Pleura, pulmonary arteries	(–)	<1 mo	Dead

CPB, cardiopulmonary bypass; n.r., not reported.

frequently (~60%) in the epithelium of thymic carcinomas but not in that of thymomas,[28] the tumor epithelium in the present case was negative for CD5. Although we have recently reported that a lack of fascin immunopositivity in the tumor epithelium and less fascin$^+$ dendritic cells are associated with invasiveness of the thymic neoplasms,[29] the present case demonstrated a typical fascin expression pattern for benign thymoma showing fascin$^+$ tumor epithelium with abundant fascin$^+$ dendritic cells. Although MMP-2 has been reported to be a key enzyme for invasiveness of thymic neoplasms,[30] the tumor in the present case was negative for MMP-2. However, the positivity for VEGF in the present tumor is interesting, since VEGF has been reported to be associated with invasiveness of thymic neoplasms through increased microvessel density.[31] Although more than half of invasive thymomas were reported to be immunopositive for VEGF,[31] VEGF may be associated with intracaval extension.

With regard to the cause for dilatation of the intrahepatic vessels, IVC syndrome associated with obstruction of the right atrium may be concerned. To the best of our knowledge, this is the second case of IVC syndrome associated with thymic neoplasms extending into the right atrium. The first case was a 76-year-old Japanese man with thymic carcinoma that invaded the region surrounding the IVC through the diaphragm, compressing the IVC.[26] Furthermore, myocardial necrosis with lymphocytic infiltration beneath the epicardium was observed in the present case. Pericarditis associated with myocardial infarction may be reminiscent of post-acute myocardial infarction syndrome, also known as Dressler syndrome.[32] However, the occurrence of Dressler syndrome has greatly diminished in the modern era due to advancements in therapy.[33] Further, subacute or chronic myocardial infarction that is associated with Dressler syndrome was not observed in the present case. Although coronary arterial stenosis of up to 90% was observed, no arterial occlusion was detected. Usually, myocardial infarction occurs from the inner myocardium since the blood supply starts from the outer myocardium. Interestingly, it has been reported from canine experiments that myocardial infarction induced by coronary venous or coronary sinus thrombosis is localized on the epicardial side.[34,35] Therefore, we postulate that obstruction of the right atrium may have brought about venous infarction of the myocardium through obstruction of the coronary sinus in the present case.

In conclusion, we report a rare case with invasive thymoma extending into the right atrium. To our knowledge, this is the first documentation of tumor emboli in the pulmonary arteries and the first English report of an autopsy case and a case with IVC syndrome in this category.

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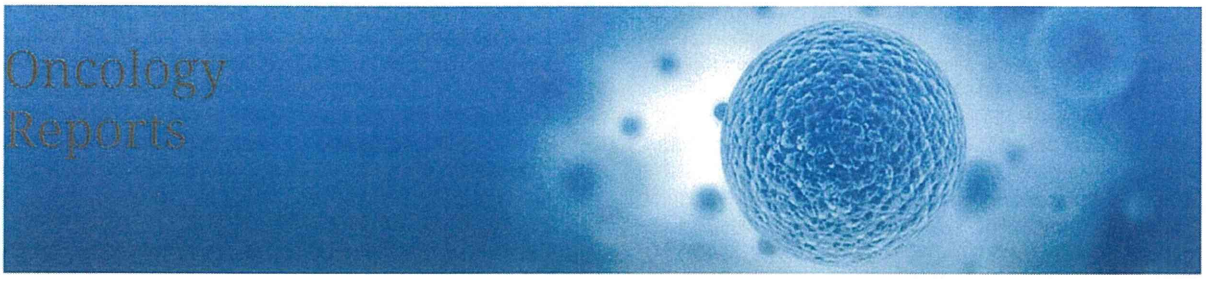

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Gene expression profiling and molecular pathway analysis for the identification of early-stage lung adenocarcinoma patients at risk for early recurrence

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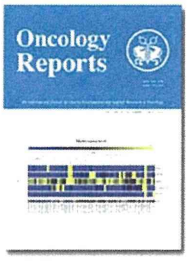
Abstract

Clinicohistopathological staging is insufficient to predict disease progression and clinical outcome in lung carcinoma. Based on the results of the principal component analysis of 24 samples of early-stage lung adenocarcinoma, two subgroups were identified within the early-relapse group. The histological classification of all samples of group A was poorly differentiated, whereas one out of three in group B was poorly differentiated. DAVID functional annotation analysis revealed that the molecular pathways enriched in group A included those associated with cell adhesion molecules (CAMs), cell cycle and antigen processing and presentation, whereas those in group B included CAMs, T cell receptor signaling, cytokine-cytokine receptor interaction, toll-like receptor signaling, chemokine signaling, primary immunodeficiency and natural killer cell-mediated cytotoxicity. The CAM pathway was enriched in both groups. This comprehensive gene expression and functional pathway analysis identified a distinct molecular pathway, CAMs, that correlated with the early relapse of patients with early-stage lung adenocarcinoma.

Introduction

Lung cancer is the leading cause of cancer-related deaths in Japan and also worldwide in most developed countries. Every year, ~60,000 individuals succumb to lung cancer in Japan, and the number is increasing rapidly. Even in early-stage lung cancer, ~40% of patients with stage I and II non-small cell lung cancer (NSCLC) die from recurrent disease within 5 years despite complete resection (1,2). The precise diagnosis and classification of cancers are critical for the selection of appropriate therapies. However, since no reliable clinical or molecular predictors are currently available, it is difficult to select high-risk patients who require more aggressive therapies such as adjuvant chemotherapy.



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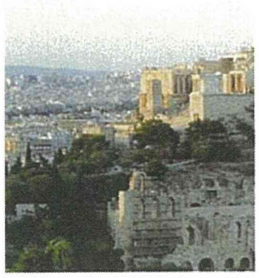

Genetic abnormalities that exist in a certain population of early-stage lung cancer patients possibly induce aggressive phenotypes that demonstrate rapid tumor growth, persistent invasiveness and a high potential for distant metastasis. The expression of a number of genes is altered in cancer cells due to mutations, deletions, amplifications, and either the upregulation or downregulation of mRNA transcription. Comprehensive DNA microarray analysis of gene expression patterns is a powerful tool that permits the simultaneous evaluation of a large number of genes in cancer cells [3,4]. Microarray gene expression profiling has recently been used to define prognostic signatures in patients with NSCLC [5–11]. However, information concerning gene expression profiling and molecular pathways relating to the outcomes of patients with early-stage lung cancer has yet to be well characterized.

Adenocarcinoma is currently the predominant histological subtype of NSCLC. The results of several expression profiling studies have demonstrated that the expression profiles are distinctive and recapitulate the known histological subtypes [5–7]. As a significant proportion of patients relapse within 2 years, identification of early-stage patients with a poor prognosis could delineate the appropriate candidates for adjuvant therapy. The present study aimed to identify a novel prognostic signature in early-stage lung adenocarcinoma using cDNA microarray and bioinformatics analysis.

Materials and methods

Patient samples

Intraoperatively, immediately upon removal of a lung lobe in which a primary lung carcinoma was located, a 500-mg sample of tumor tissue was cut and immediately immersed in liquid nitrogen and stored at -80°C until use, as previously reported [12]. We studied frozen specimens of lung cancer tissue from 64 randomly selected patients who underwent complete resection of stage I or II NSCLC lesions at Tokyo Medical University, Tokyo, Japan from May 2003 to December 2006. Tumor tissues were processed by the Human Tissue Bank section at our department according to standard operating procedures and protocols. Briefly, frozen tissue samples at -80°C were pulverized, and total cellular RNA was collected from each flash-frozen sample using TRIzol RNA isolation reagent (Invitrogen). Total RNA was processed with an RNeasy Mini kit (Qiagen). *In vitro* transcription-based RNA amplification was then performed on at least 8 µg of total RNA from each sample. The RNA quality was assessed using a bioanalyzer (model 2100, Agilent). According to the results from the RNA quality assay, 24 lung adenocarcinoma samples were selected as our dataset.

Microarray analysis

Complementary DNA was synthesized using the T7-(dT)24 primer: 59-GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGCGG-(dT)24-39. The cDNA was processed using phase-lock gel phenol/chloroform extraction (#E0032005101, Fisher). Next, *in vitro* transcriptional labeling with biotin was performed using the Enzo BioArray kit (#900182, Affymetrix). The resulting cRNA was processed again using the RNeasy Mini kit. Labeled cRNA was hybridized to an Affymetrix GeneChip (Human Genome-133 Plus 2.0 Array) according to the manufacturer's instructions. The raw fluorescence intensity data within the CEL files were preprocessed with the robust multichip average algorithm, as implemented with the R packages from Bioconductor. This algorithm analyzes the microarray data in three steps: a background adjustment, quantile normalization, and finally summation of the probe intensities for each probe set using a log scale linear additive model for the log transform of (background corrected, normalized) PM intensities.

Data analysis

Affymetrix Human Genome-U133 Plus 2.0 GeneChip data, quantified with MAS5, were imported into the Subio Platform (Subio Inc., Tokyo, Japan). Signals <1 were replaced with 1, log2 transformed, and then mean-subtracted by each probe set to obtain the log ratio against the average of the expression patterns. No normalization was applied.

Samples were classified into two groups, recurrence-positive and recurrence-negative. Probe sets in both groups whose detection values were absent in half of the samples were removed. At this point, 28674 out of 54682 probe sets remained. Finally, unvarying probe sets, whose log ratios were between −1 and +1 in all samples, were filtered out to obtain the final quality controlled probe sets (24420).

Principal component analysis (PCA) was applied to the log ratio data of quality controlled genes. We recognized that the samples in the recurrence-positive group might be distinguishable as PC1 score negative (A) and positive (B) subgroups.

We extracted the differentially expressed genes (DEGs) for both A and B subgroups. We defined DEGs for A as being> 4-fold upregulated or downregulated compared with the