RESEARCH ARTICLE

Relationship Between Computed Tomography Manifestations of Thymic Epithelial Tumors and the WHO Pathological Classification

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Abstract

Objective: To explore the relationship between computed tomography (CT) manifestations of thymoma and its WHO pathological classification. Methods: One hundred and five histopathologically confirmed cases were collected for their pathological and CT characteristics and results were statistically compared between different pathological types of thymoma. Results: Tumor size, shape, necrosis or cystic change, capsule integrity, invasion to the adjacent tissue, lymphadenopathy, and the presence of pleural effusion were significantly different between different pathological types of thymomas (P <0.05). Type B2, B3 tumors and thymic carcinomas were greater in size than other types. More than 50% of type B3 tumors and thymic carcinomas had a tumor size greater than 10 cm. The shape of types A, AB, and B1 tumors were mostly round or oval, whereas 75% of type B3 tumors and 85% of thymic carcinomas were irregular in shape. Necrosis or cystic change occurred in 67% of type B3 thymomas and 57% of thymic carcinomas, respectively. The respective figures for capsule destruction were 83% and 100% . Increases in the degree of malignancy were associated with increases in the incidence of surrounding tissue invasion: 33%, 75%, and 81% in type B2, type B3, and thymic carcinomas, respectively. Pleural effusion occurred in 48% of thymic carcinomas, while calcification was observed mostly in type B thymomas. Conclusions: Different pathological types of thymic epithelial tumors have different CT manifestations. Distinctive CT features of thymomas may reflect their pathological types.

Keywords: CT - thymus - thymic epithelial tumors - thymic carcinomas - pathology

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Introduction

Thymic epithelial tumors account for 15-21.7% of mediastinal tumors and 47% of anterior mediastinal tumors (Chen et al., 2002; Engels and Pfeiffer, 2003). Until 2004, there was a wide range of pathological classifications for thymic tumors (Travis et al., 2004; Okumura et al., 2008). The World Health Organization (WHO) updated the pathological classification in 2004, and thymic tumors are now classified as one of 5 types of thymomas (types A, AB, B1, B2, and B3) or as thymic carcinoma (including neuroendocrine carcinoma) (Travis et al., 2004). Studies have suggested that this WHO classification reflects well the clinical and prognostic features of thymic tumors (Chen et al., 2002; Okumura et al., 2002; Kondo et al., 2004). There have been reports about the CT manifestations of thymic tumors with different WHO pathological classifications, but the number of cases in these reports was limited (Tomiyama et al., 2002; Han et al., 2003; Sadohara et al., 2006). To explore further the relationship between the CT manifestations and the WHO pathological classification, we conducted a retrospective analysis of 105 cases of thymic tumors.

Materials and Methods

Objects

In this study, we analyzed 105 cases of thymic tumors with complete CT data and confirmed surgical pathology between March 1999 and March 2012. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Zhongnan Hospital of Wuhan University. Written informed consent was obtained from all participants.

Methods

Helical CT (PQ6000, PICKER, USA) and 16-slice CT (Somatom Sensation, Siemens, Germany) were used. The scan range was from the thoracic inlet to the diaphragmatic level. The slice thickness and interval were each 5 mm; 80-100 mL (300 mgI/mL) of the contrast agent Ultravist was injected at a rate of 3.0mL/s. Two senior physicians, both specialists in chest CT diagnosis, reviewed the imaging data, according to the recommendation of the Nomenclature Committee of the Fleischner Society (Hansell et al., 2008). They were told before the review

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Table 1. Main Clinical Data and Pathological Classifications

Patient characteristics	A	AB	B1	B2	B3	Thymic carcinoma	χ^2	P-value
Gender								
Male	6	10	10	8	6	12	1.0589	0.9577
Female	6	13	12	7	6	9		
Age								
<40 years	3	2	6	4	5	4	9.1758	0.5155
40-60 years	6	14	13	9	6	10		
>60 years	3	7	3	2	1	7		

Table 2. Relationship Between CT Manifestations and Pathological Classifications

CT manifestations	A	AB	B1	B2	B3	Thymic carcinoma	χ^2	P-value
Size (cm)								
<5	7(58%)	12(52%)	10(45%)	7(46%)	2(17%)	2(10%)	23.6746	0.0085
5~10	4(33%)	8(35%)	9(41%)	4(27%)	3(25%)	8(38%)		
>10	1(9%)	3(13%)	3(14%)	4(27%)	7(58%)	11(52%)		
Shape								
Round	7(58%)	8(35%)	5(23%)	3(20%)	1(8%)	1(5%)	30.3933	0.0007
Oval	4(33%)	9(39%)	7(32%)	5(34%)	2(17%)	2(10%)		
Irregular	1(9%)	6(26%)	10(45%)	7(46%)	9(75%)	18(85%)		
Calcification								
Yes	2(17%)	3(13%)	6(27%)	5(33%)	3(25%)	4(19%)	2.9315	0.7105
No	10(83%)	20(87%)	16(73%)	10(67%)	9(75%)	17(81%)		
Necrosis or cystic change								
Yes	3(25%)	2(9%)	3(14%)	5(33%)	8(67%)	12(57%)	22.3596	0.0004
No	9(75%)	21(91%)	19(86%)	10(67%)	4(33%)	9(43%)		
Capsular destruction								
Yes	1(8%)	3(13%)	5(23%)	7(47%)	10(83%)	21(100%)	53.2763	<0.001
No	11(92%)	20(87%)	17(77%)	8(53%)	2(17%)	0(0%)		
Invasion of adjacent tissues								
Yes	0(0%)	2(9%)	2(9%)	5(33%)	9(75%)	17(81%)	48.9044	<0.001
No	12(100%)	21(91%)	20(91%)	10(67%)	3(25%)	4(19%)		
lymphadenopathy								
Yes	1(8%)	2(9%)	4(18%)	6(40%)	7(58%)	15(71%)	29.3196	<0.001
No	11(92%)	21(91%)	18(82%)	9(60%)	5(42%)	6(29%)		
Pleural effusion							24.0164	0.0002
Yes	0(0%)	1(4%)	2(9%)	3(20%)	6(50%)	10(48%)		
No	12(100%)	22(96%)	20(91%)	12(80%)	6(50%)	11(52%)		

that the patients had thymic epithelial tumors, but they were blind to the specific pathological classification. They reached a consensus through discussion. Diameters were measured in cross-sectional images. The tumor size was the long-axis diameter. Based on this, tumors were divided into three groups: <5.0 cm, 5.0 ~ 10.0 cm, and >10.0 cm. The tumor shape was evaluated based on the ratio of the long axis diameter to the short axis diameter. The tumor shape was designated round, oval, or irregular if the ratio was <1.5, 1.5-3.0, or ≥3.0, respectively (Tomiyama et al., 2002). Capsule destruction was noted if more than 1/3 of the capsule on the tumor edge was damaged (Tomiyama et al., 2001). The presence of necrosis or cystic change was indicated by lack of enhancement in the intratumor low-density areas. Lymphadenopathy was indicated by a short-axis diameter of the lymph node ≥10 mm. Adjacent tissue invasion included invasion of the blood vessels, pleura, pericardium, and lung tissue. Disappearance of the fat plane between the tumor and vessels, accompanied by focal deformation of blood vessels, tumor thrombus, and vascular obstruction, indicated vascular invasion (Marom, 2010; Marom et al., 2011). Pericardial invasion was noted if the tumor adhered strongly to the pericardium and the pericardium appeared as thickened. Pleural thickening indicated pleural invasion. Pulmonary infiltration was defined as adhesions between the tumor and adjacent lung tissues, poor inflation of the lung under compression, or small patchy consolidation of the adjacent lung tissue (Yang et al., 1997).

The surgical specimens of thymic tumors were fixed in 10% formalin and stained with conventional H&E staining. The tumor sections were classified by two senior pathologists according to the 2004 WHO pathological classification criteria for thymic epithelial tumors (Travis et al., 2004). Consensus was reached through discussion.

Statistical analysis

SPSS11.0 software was used for statistical analysis. The between-group comparisons of gender, age, and CT manifestations – including tumor size, tumor shape, calcification, necrosis or cystic change, capsular integrity, surrounding organ invasion, lymphadenopathy, and pleural effusion – were compared using the χ^2 test or Fisher exact probability test. $P < 0.05$ indicated a statistically significant difference.

Results

General data

Of the 105 cases in this study, 52 were male and 53 were female. Patient ages ranged from 18 to 75 years and the average age was 47.98 ± 12.54 years. There was no

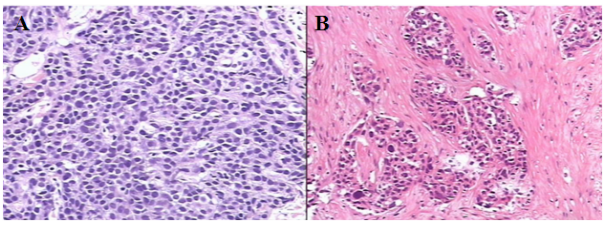

Figure 1. A) Pathological section (hematoxylin and eosin, ×200) of type B3 thymoma shows the tumor tissue is predominantly composed of epithelial cells with a round or polygonal shape, obvious nucleus, unclear nucleolus and mild atypia, admixed with a minor component of lymphocytes (foci of squamous metaplasia and perivascular spaces are common. B) Pathological section (hematoxylin and eosin, ×200) of thymic carcinoma presents tumor cells which have large nuclei, prominent nucleoli, pathological mitosis

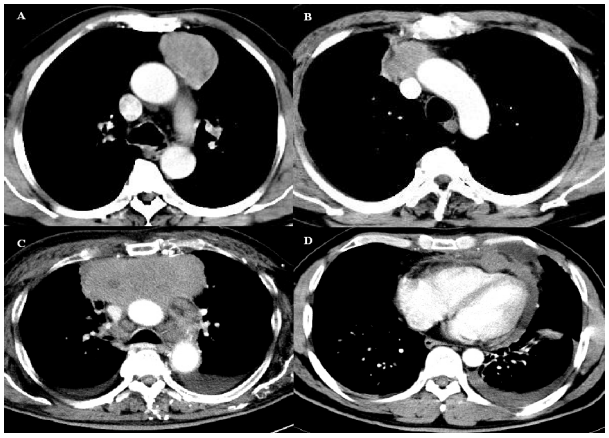

Figure 2. A) Thoracic enhanced CT showed an oval mass with homogeneous enhancement, smooth edges and intact capsule, located in the anterior mediastinum, which was postoperatively diagnosed as type A thymoma, pahtologically. B) Contrast enhanced CT showed an oval mass located in the antero-superior mediastinum with uniform enhancement, damaged capsule and partially disappeared mediastinal fatty space. The patient was diagnosed as thymoma of type AB, pathologically. C) Thymoma of type B2, presented as an oval mass with heterogeneous enhancement, cystic change, mediastinal lymphadenopathy and bilateral pleural effusion. D) Thymoma of type B3 presented with left-side pleural effusion, right-side pleural thickening and obviously thickened-partly nodular-pericardium

significant difference in age or gender between different pathological types of thymic tumors (P> 0.05) (Table 1).

Relationship between CT manifestations and pathological classifications

All 105 cases underwent plain CT scan and enhanced CT scan. Surgeries were completed within one week of the CT examination. Sixty-five cases underwent complete resection while 40 received partial resection. Tumor size, tumor shape, necrosis or cystic change, capsule integrity, invasion of the adjacent tissue, lymphadenopathy, and the presence of pleural effusion were significantly different between different pathological types of thymic tumors (Table 2). The tumor size ranged from 2.0 to 18.5 cm with an average of 8.65 ± 3.86 cm. The sizes of types A, AB, B1, B2, and B3 thymic tumors and thymic carcinoma were 6.33 ± 3.41, 6.00 ± 3.30, 6.38 ± 3.79, 7.32 ± 4.60, 12.40 ± 4.98, and 11.00 ± 3.74 cm, respectively. There was no significant difference in size between types A, AB, and B1,

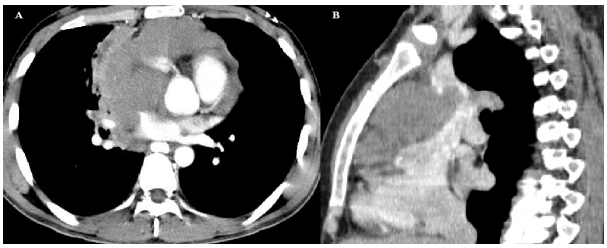

Figure 3. Axial Contrast Enhanced CT (A) and its sagittal MPR (B) showed a mediastinal mass with a cast-like growth along the mediastinal vascular space, invading the blood vessels and the pericardium. A pedicle-like filling defect in the superior vena cava was obviously observed on the sagittal reconstruction. The patient was pahologically diagnosed as thymic carcinoma, post-operatively

but the sizes of types B2 and B3 and thymic carcinoma were significantly different from those of other types of thymic tumors. More than half of the type B3 thymic tumors (58%) and thymic carcinomas (52%) had a tumor size greater than 10 cm. The percentage of tumors with an irregular shape increased in various types of thymic tumors, from low to high in the following sequence: types A, AB, B1, B2, B3, and thymic carcinoma. The shapes of types A, AB, and B1 thymic tumors were mostly round or oval; 75% of type B3 thymic tumors and 85% of thymic carcinomas were irregular in shape. Necrosis or cystic change occurred in 67% of type B3 thymomas and 57% of thymic carcinomas, respectively. Capsule destruction occurred in 47% of type B2 thymomas, 83% of type B3 thymomas and 100% of thymic carcinomas. The incidence of surrounding tissue invasion increased with increases in the degree of malignancy. The incidenc of surrounding tissue invasion was 33%, 75%, and 81% in type B2, type B3, and thymic carcinomas, respectively. Pleural effusion occurred in 50% of type B3 thymomas and 48% of thymic carcinomas. There was no significant difference in calcification between the different pathological classifications. Calcification occurred in 29% of type B thymomas.

Discussion

Before 2004, the pathological classification of thymic epithelial tumors was confusing and considerably different from that of today (Rosai and Sobin, 1999). The current WHO classification is as follows (Travis et al., 2004; Okumura et al., 2008): type A tumor, composed of a homogeneous population of neoplastic epithelial cells having spindle-like and oval shapes, lacking nuclear atypia, and accompanied by few or no non-neoplastic lymphocytes; type AB tumor, foci with the features of type A thymoma are admixed with foci rich in lymphocytes, with sharp or indistinct segregation of the two patterns; type B1 tumor, resembles the normal functional thymus in that it combines large expanses with an appearance practically indistinguishable from that of normal thymic cortex with areas resembling thymic medulla; type B2 tumor, the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a predominant population of lymphocytes (perivascular spaces are common); type B3 tumor,

predominantly composed of epithelial cells with a round or polygonal shape and exhibiting mild atypia admixed with a minor component of lymphocytes (foci of squamous metaplasia and perivascular spaces are common) (Figure 1A); thymic carcinoma (Figure 1B). The classification of types A, AB, B1, and B2 tumors does not specify which tumor types are encapsulated thymomas and invasive thymomas, but the classification of type B3 corresponds to atypical thymoma and thymic carcinoma. The WHO classification reflects the clinical and functional characteristics of thymic epithelial tumors, and thus is helpful for clinical assessment and treatment (Chen et al., 2002; Okumura et al., 2002; Kondo et al., 2004). Okumura et al. reported that types B2 and B3 thymomas had a higher recurrence rate and poorer prognosis than types A, AB, and B1 thymomas (Okumura et al., 2002); In stage I and II thymomas, the WHO subtype is an independent influencing factor (Chen et al., 2002).

Thymic tumors often occur in patients over the age of 40, with a similar incidence in men and women. In this study, representation of men and women was similar, while the average age was 48. Thymic tumors are rarely found in children or adolescents. The youngest patient in this study was 18 years old. There was no significant difference in age or gender between the different pathological classification groups, consistent with reports in the literature (Sadohara et al., 2006). CT data is an important basis for the selection of treatment for thymic tumors. In the literature, thymic epithelial tumors are divided into low-risk thymomas (types A, AB, and B1), high-risk thymomas (types B2 and B3), and thymic carcinomas. Tumor invasiveness increases gradually. CT signs reflect tumor characteristics well (Sadohara et al., 2006; Priola et al., 2010). In this study, tumor size, tumor shape, necrosis or cystic change, capsule integrity, invasion of the adjacent tissue, lymphadenopathy and the presence of pleural effusion were significantly different between the different pathological types of thymic tumors. The malignant characteristics of type B2 and B3 thymomas and thymic carcinomas were obvious, consistent with previous reports (Tomiyama et al., 2002; Han et al., 2003; Sadohara et al., 2006).

The size of thymic tumors is associated with classification. The greater the tumor mass, the higher the probability the tumor is malignant (Yanagawa and Tomiyama, 2011). In particular, thymomas >10 cm are often type B or thymic carcinoma (Yanagawa and Tomiyama, 2011). In this study, 7 (7/12, 58%) cases of type B3 and 11 (11/21, 52%) cases of thymic carcinoma were greater than 10 cm in size. Type A and type AB thymic tumors are often round or oval with a clear, smooth edge and a uniform density (Figure 2A); Type B and thymic carcinomas are often irregular in shape or lobulated, though; the lobulation rate is greater than 60% (Tomiyama et al., 2002). Chen et al. reported a lobulation rate of 89% (Okumura et al., 2004). In this study, 91% and 74% of type A and type AB thymomas, respectively, were round or oval, while 46%, 75%, and 85% of type B2 thymomas, type B3 thymomas, and thymic carcinomas, respectively, were irregularly shaped, supporting the aforementioned point of view.

Sadohara et al. (2006) reported that necrosis or cystic change occurred in 67% of thymic carcinomas. In this study, necrosis or cystic change occurred in 67% and 57% of type B3 thymomas and thymic carcinomas, respectively, consistent with the previous study. Tomiyoma et al. reported that calcification is most common in type B thymomas (Tomiyama et al., 2002). In this study, the calcification rate in type B thymomas was 25-33%, higher than that of the other types of thymic tumors. Our results are consistent with Tomiyoma et al.'s results.

It is reported that the capsule was intact in the majority of type A and type AB thymomas, but capsular infiltration might occur in some of them (Figure 2B) (Chen et al., 2002). Capsule destruction is an important CT manifestation of type B thymoma and thymic carcinoma. Surrounding organ invasion (which mainly refers to the invasion of the pleura, pericardium, and great blood vessels) and distant metastasis occur only in type B and thymic carcinoma (Figure 2C, D) (Marom, 2010; Marom et al., 2011). Relying on the fuzzy capsule in CT images as the determining criteria for capsular invasion would lead to errors. Research suggests that MRI is superior to CT in displaying tumor capsule, septum, and intratumoral hemorrhage (Sadohara et al., 2006). In this study, capsule destruction occurred in one case of type A thymoma. The incidence of capsule destruction was 83% in type B3 thymomas and 100% in thymic carcinomas. In types B1, B2, and B3 thymomas as well as in thymic carcinomas, the incidence of capsule destruction increases with increased atypia. The axial CT images and combined multi-planar reconstruction may be used to accurately identify thymic tumor invasion of the adjacent blood vessels, pericardium, and lung tissue (Figure 3A, B). In this study, adjacent tissue invasion occurred in 75% and 81% of type B3 thymomas and thymic carcinomas, respectively, similar to the percentage reported in the literature (Jung et al., 2001; Sadohara et al., 2006). The prognosis is poor if vascular invasion occurs.

Using CT to determine the clinical stage of thymic tumors may help in the selection of treatment protocol as well as in determining the prognosis (Nakagawa et al., 2003; Yanagawa and Tomiyama, 2011). If the malignant thymoma has a cast-like relationship with great blood vessels, the tumor is unresectable (Maher and Shepard, 2005; Marom, 2010; Yanagawa and Tomiyama, 2011). Tian et al. (2003) reported that CT could reach a staging accuracy of 87.5%, a specificity of 90%, and a sensitivity of 83.3%. Imaging assessment plays an important role in the clinical diagnosis and treatment of thymic tumors (Yanagawa and Tomiyama, 2011). Complete resection of the tumor is the best treatment method and the most important prognostic factor (Kondo and Monden, 2003; Strobel et al., 2004). Types A, AB, and B1 thymomas require no further treatment after complete resection. Stage I and II types B2 and B3 thymomas require adjuvant radiotherapy after complete resection. The recurrence rate is 34% in incompletely resected types B2 and B3 thymomas, and in stage III or higher thymomas after adjuvant radiotherapy; it is 78% in patients who do not receive radiotherapy (Strobel et al., 2004). If a tumor has a smooth margin, homogeneous density, and

no obvious necrosis or cystic change, it often can be resected completely. If a tumor is lobulated or irregular in shape and has heterogeneous enhancement, it is often a highly invasive thymoma or thymic carcinoma. MRI is recommended for further assessment as MRI facilitates the assessment of local invasion (Tomiyama et al., 2002).

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