Carcinoid tumours of the thymus

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Abstract

Background **– Carcinoid tumours of the thymus are rare. The clinical manifestations, radiographic findings, and cytological features of eight histopathologically verified thymic carcinoid tumours have been assessed.**

Methods **– One hundred and sixty two patients of mean age 52 (range 31–68) years with malignant mediastinal tumours were reviewed retrospectively and eight cases of thymic carcinoid were identified. Four of the eight patients were diagnosed by percutaneous ultrasound guided fine needle aspiration biopsy via a parasternal approach.**

Results **– Two patients had Cushing's syndrome at presentation and four had symptoms and signs secondary to mediastinal compression. Two were asymptomatic. Local extension of the tumour to pleura, pericardium, great vessels, phrenic nerve or regional lymph nodes, or both, were found in seven patients. Only one had the tumour confined to the thymus at diagnosis. Distant metastases were found in two patients, one to both lungs and the other in the iliac bone. Local recurrence or distant metastases developed 15–60 months after surgery in four of the five patients who underwent radical resection of the thymic tumour. Three patients died at 17 months, 34 months, and 10 years after diagnosis. The other five patients are alive at 9–51 months.**

Conclusion **– Thymic carcinoid is a slow growing tumour with a poor prognosis because of its tendency to local and distant spread. Cytological examination of samples obtained by ultrasound guided fine needle aspiration may provide a useful method for diagnosis in selected patients.**

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Thymomas are the commonest tumours of the anterior mediastinum. Thymic carcinoid tumours have long been confused with thymoma, and in 1972 Rosai and Higa identified carcinoid tumour of the thymus as a specific entity.[1] It originates from the thymic cells of the neuroendocrine system.[2,3] About 85% of the carcinoid tumours are located in the intestine and 10% in the lung.[4] A primary carcinoid tumour arising in the thymus is rare and only about 100 cases have been reported in the world literature.[5-7] Diagnosis of thymic carcinoid tumours is made either at thoracotomy or by open biopsy.[3-7] Diagnosis by ultrasound guided aspiration cytology has not previously been reported. We present eight cases of histopathologically proven thymic carcinoid tumours, four of which were diagnosed by ultrasound guided fine needle aspiration cytology, later confirmed histologically. Their clinical manifestations, radiographic findings, and cytological features are reported.

Methods

The medical records of all malignant mediastinal tumours (total 162 cases) seen between 1978 and 1993 at the National Taiwan University Hospital were reviewed and eight cases (six men and two women) of histopathologically proven thymic carcinoid tumour were identified. The histological sections of these 162 patients were reviewed again by two independent pathologists.

Clinical evaluation included chest radiography, computed tomographic scanning of the chest, ultrasonography of the chest, abdominal ultrasonography, and isotopic bone scanning in all patients. The extent of the thymic tumour was divided into three stages: (1) confined to the thymus; (2) local extension to adjacent tissues – for example, pleura, pericardium, regional lymph nodes, great vessels, or the sternum; and (3) distant metastases.

The technique of ultrasound guided fine needle aspiration and Tru-Cut biopsy has been detailed in our previous studies.[8-11] The indications for performing this technique included: (1) mediastinal tumour in contact with the chest wall detectable by ultrasonography; (2) no coagulopathy or bleeding tendency present; and (3) cooperative patient. With their permission, four of the patients (nos 2, 4, 6, and 8) underwent percutaneous ultrasound guided fine needle aspiration biopsy and Tru-Cut biopsy of their thymic tumour. Patients 3 and 7 refused ultrasound guided fine needle aspiration biopsy for fear of disseminating the disease. Cytological specimens were routinely stained by Papanicolaou's and Riu's methods. Special stains for adrenocorticotrophic hormone were made if necessary. Patient 5 underwent mediastinoscopy because he had multiple pulmonary metastases. Patients 1, 3, and 7 underwent surgical exploration of the thymic tumour without prior biopsy.

Results

The clinical presentations of these eight patients are summarised in table 1. Their ages ranged from 32 to 68 years at diagnosis. Four (nos 1, 2, 3 and 4) had symptoms and signs of mediastinal compression including superior

Table 1 Summary of clinical findings in eight patients with thymic carcinoid tumours

Patient no.	Age (years)/ sex	Presentation	Tumour size (cm)	Diagnostic method	Initial treatment	History of thyroid cancer
1	40/M	Cough, SVC syndrome	3×3×2	Thoractotomy	Surgery	No
2	65/M	Dyspnoea, back pain	25×20×15	UGFNA and biopsy	Radiotherapy and chemotherapy	Yes
3	32/M	Chest pain	9×7×6	Thoracotomy	Surgery	No
4	68/M	Hoarseness	12×10×8	UGFNA and biopsy	Radiotherapy	No
5	51/F	Cushing's syndrome	4×4×4	Biopsy through mediastinoscopy	Radiotherapy	Yes
6	47/M	Cushing's syndrome	4×6×4	UGFNA and biopsy	Surgery	No
7	55/M	Asymptomatic	8×5×4	Thoracotomy	Surgery	No
8	59/F	Asymptomatic	20×20×15	UGFNA and biopsy	Surgery	Yes

SVC = superior vena cava; UGFNA = ultrasound guided fine needle aspiration.

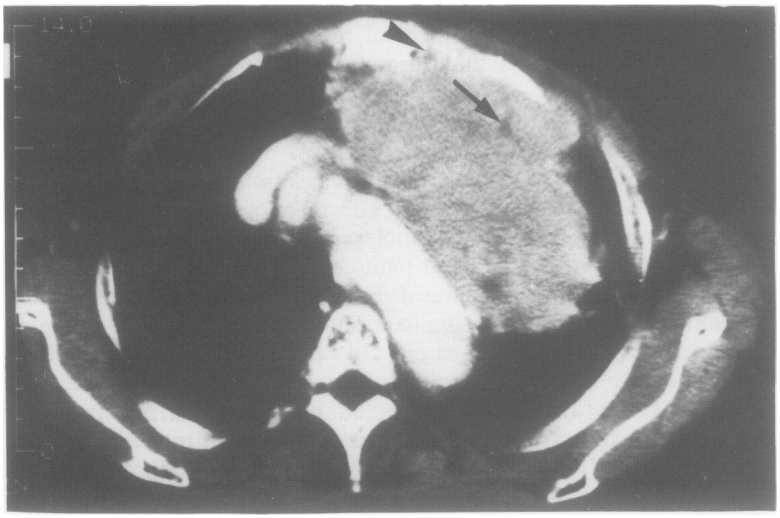

Figure 1 Computed tomographic scan of the chest showing a large tumour with ill defined margin and chest wall invasion (arrowhead). Poor contrast enhancement in the central part of the tumour represents central necrosis and cystic degeneration (arrow).

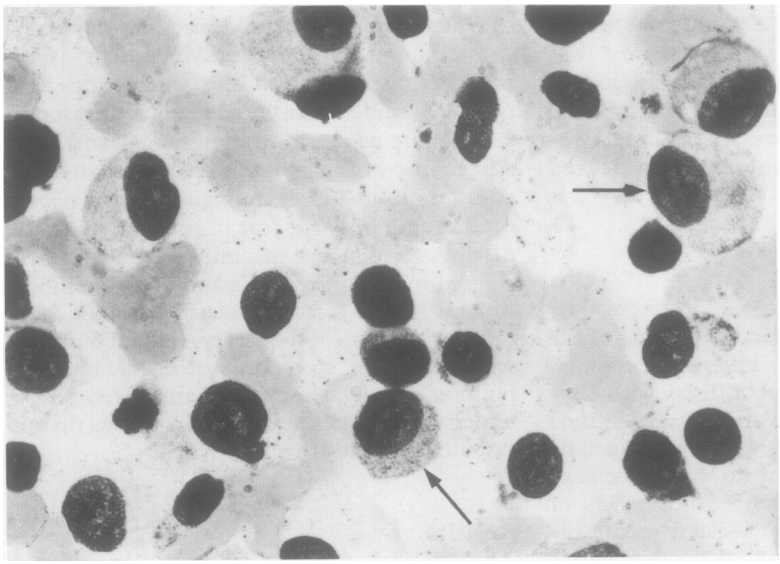

Figure 2 Carcinoid tumour cells from fine needle aspiration specimen. Note the characteristic uniform individual small round tumour cells with scanty cytoplasm, round to oval nuclei, and finely granular chromatin. Some tumour cells show abundant cytoplasm with macronucleoli and characteristic neurosecretory granules (arrows). Riu's stain, original magnification × 1000, reduced to 82% during origination.

vena caval obstruction, chest discomfort, and hoarseness. Two patients (nos 5 and 6) had Cushing's syndrome with hypernatraemia, hypokalaemia, and elevated serum levels of adrenocorticotrophic hormone (ACTH) and cortisol. Two patients were asymptomatic and their thymic tumours were found coincidently on chest radiography.

Chest computed tomographic scanning showed the diameter of tumours to range from 3 to 25 cm. All were located in the anterior mediastinum and appeared as heterogeneous masses with central necrosis and cystic degeneration (fig 1). The borders of the tumour were sharp and well demarcated in only one patient (no. 7). The other seven were ill defined and infiltrated the adjacent tissues.

Cytological and histological examination of the fine needle aspirate yielded characteristic carcinoid tumour cells (fig 2) in all four patients from whom biopsy specimens were taken. Histologically the tumours exhibited a lobular, ribbon-like growth pattern with rosette formations and fibrovascular stroma (fig 3). The tumour cells were small, oval or round, with eosinophilic cytoplasm and uniformly round nuclei. There were areas with haemorrhage and necrosis. Immunohistochemically the tumour cells were all argyrophilic by Grimelius stain. The staining pattern for the neuroendocrine marker (neurone specific enolase) was characterised by a clear intracytoplasmic positivity in both the primary tumour and in the metastases in all four cases. Moreover, in the tumours of patients 5 and 6 ACTH immunostaining showed a granular intracytoplasmic reaction.

Local extension of the tumour to adjacent tissues was found in seven of the patients (table 2). Furthermore, two patients showed evidence of distant metastases at diagnosis (iliac bone in patient 2, both lungs in patient 5). Only in patient 7 was the tumour confined to the thymus.

Radical resection of the tumour and adjacent involved tissues was performed in five patients (nos 1, 3, 6, 7, and 8, table 1). Patients 2 and 5 did not undergo surgery because of metastases, and patient 4 did not undergo surgery because of poor pulmonary function. Patients 2, 4, and 5 received local radiotherapy (4000 cGy in 20 fractions) to the anterior mediastinum and patient 2 also received chemotherapy (5-fluorouracil 350 mg/m^2/day for five days every three weeks for two courses).

Four of the five resected patients developed local recurrence or distant metastases, or both, 15–60 months after surgery (table 2). The patient whose tumour was confined to the thymus at the time of surgery (no. 7) developed both local recurrence and distant metastases to the lung 15 months after surgery. Patient 8 showed no evidence of relapse nine months after surgery. Recurrence was treated by re-excision or radiotherapy, or both.

No significant reduction in the size of the thymic tumour was seen in the patients who underwent radiotherapy to the anterior mediastinum. There was no response to chemotherapy in patient 2. The two patients

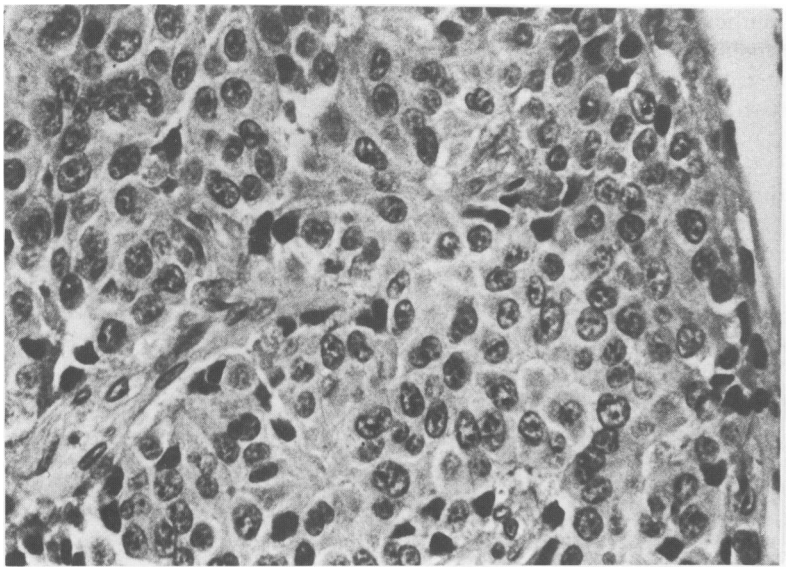

Figure 3 Histological section showing relatively uniformly round tumour cells with rosettes and ribbon-like growth pattern separated by fibrovascular septa. Stain: haematoxylin and eosin. Original magnificatioin × 530, reduced to 82% during origination.

Table 2 Extent of disease and outcome in eight patients with thymic carcinoid tumours

Patient no.	*Extent of disease at diagnosis*	*Sites of relapse after surgery*	*Interval between surgery and relapse (months)*	*Survival after diagnosis (months)*	*Status*
1	Local extension to RLN, pleura, great veins	Chest wall, RLN, diaphragm, cervical spine	60	120	Expired
2	Local extension to RLN; distant metastasis to iliac bone	—	—	17	Expired
3	Local extension to RLN, phrenic nerve	Both lungs	36	51	Alive
4	Local extension to RLN, pleura, pericardium	—	—	30	Alive
5	Local extension to RLN, sternum; distant metastases to both lungs	—	—	34	Expired
6	Local extension to RLN	RLN, CLN, left lung	16	23	Alive
7	Confined to thymus	RLN, right lung	15	32	Alive
8	Local extension to pleura, pericardium, left pulmonary artery and vein	No evidence of relapse	—	9	Alive

RLN = regional lymph node; CLN = cervical lymph node.

with distant metastases at diagnosis survived 17 months and 34 months, respectively. Patient 1 survived 10 years after diagnosis. The remaining five patients (nos 3, 4, 6, 7, and 8) are still alive 9–51 months after the diagnosis.

Three of the eight patients had a history of previously excised thyroid cancer (follicular carcinoma, papillary carcinoma, and medullary carcinoma). Patients 5 and 6 had Cushing's syndrome at diagnosis. Patient 5 developed an osteoblastic metastasis to the lumbar spine one year after local radiotherapy to the anterior mediastinum and ACTH was found in the tumour cells in the excised lumbar spine lesion. In patient 6 ACTH and cortisol levels returned to normal after surgery but became elevated again at relapse.

Discussion

Thymic carcinoids have long been confused with thymoma, but have been recognised as a different histological entity since 1972.[1] According to previous reports, a male predominance and an association with Cushing's syndrome (20–35%) were found in patients with thymic carcinoid, although we found that the presence of Cushing's syndrome was not related to the tumour size or the extent of the disease. Thymic carcinoid tumours associated with a multiple endocrine neoplasia syndrome are rare.[6 7 12–14] In this study three of eight cases had a previous history of thyroid cancer. The association of carcinoid tumour with medullary carcinoma of the thyroid has been reported previously.[15]

Thymic carcinoid tumours can be diagnosed either by surgical exploration or by open biopsy of the tumour at mediastinoscopy. Diagnosis by percutaneous fine needle aspiration cytology has not previously been reported. In our experience the incidence of track implantation by malignant cells following the procedure is rare.[8 10 11] In the current series the diagnosis was correctly made by ultrasound guided percutaneous fine needle aspiration cytology in four patients. However, in two cases with small tumours ultrasonography failed to detect the lesion because it was hidden behind bony structures and normal aerated lung.

Cytomorphologically thymic carcinoid tumour cells can be confused with small cell carcinoma, lymphoma, adenocarcinoma, plasmacytoma, or neuroblastoma.[16 17] However, certain features are characteristic of carcinoid tumours including predominantly single cells and occasional small loose clusters of cells with uniformly round or oval contours, scanty cytoplasm, evenly distributed finely granular chromatin, and inconspicuous nucleoli. A few larger tumour cells with abundant granular cytoplasm or prominent nucleoli are also present. The characteristic cytoplasmic neurosecretory granules can be seen clearly by argyrophilic or Riu's staining (fig 2). From our experience it should be emphasised that, as cystic necrosis of the thymic carcinoid tumour is common, aspiration should be performed under ultrasound guidance to avoid aspiration from necrotic tissue.

Invasion of adjacent structures occurs in 30–50% of cases.[7 18 19] Intrathoracic lymph node metastases were documented in over 40% and distant metastases, commonly to the lung, bone, and liver, in about 30%.[7 18–22] In this study local invasion of the adjacent tissues was found in 88% of thymic carcinoid tumours at diagnosis.

Surgical resection is the treatment of choice although recurrence is common,[19 23] up to 67%.[19] In this study recurrence occurred in four of the five patients who underwent surgery, despite extensive resection including adjacent involved tissues. The high recurrence rate may be partly explained by the advanced stage of thymic carcinoid tumours encountered in this study. However, even in a well encapsulated tumour without invasion of adjacent tissues (patient 7) local recurrence and distant metastases developed 15 months after thoracotomy.

Radiotherapy and chemotherapy have been suggested by some investigators.[19 21 24] In our study the three cases who received radiotherapy, chemotherapy, or both, showed no improvement.

In conclusion, thymic carcinoid is a slow-growing tumour which commonly invades adjacent tissues. Despite extensive resection, recurrence may occur years later. Ultrasound guided fine needle aspiration cytology may be helpful for diagnosis in selected patients.

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