Thymic Neuroendocrine Tumor (Thymic Carcinoid): A Clinicopathologic Study in 15 Patients

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Background. **Thymic neuroendocrine tumor (carcinoid tumor) is rare, and prognosis for patients with this tumor has been difficult to predict.**

Methods. **The medical records of 15 patients were reviewed, and the patients were classified according to tentative TNM classification and histologic grade.**

Results. **Ten (66.7%) of 15 patients were male. Lymph node metastases were identified in 9 (60%) of 15 patients at the time of resection. There were one grade 1, nine grade 2, and five grade 3 tumors. Total resection was possible in 13 patients. Distant metastases developed in 10 (76.9%) of these 13 patients, although no local recurrence developed. Of these 10 patients, 6 died of distant metastases 5 to 25 months after the recurrence. Three patients are still alive, with metastases to the bone, spleen, and pleura 1 to 24 months after the diagnosis of recurrence. Two patients are presently tumor free (T1N0, grade 3 and T3N2, grade 2), but only 1 has survived beyond 5 years.**

Conclusions. **Thymic neuroendocrine tumor must be regarded as a malignant neoplasm that is prone to metastasize to mediastinal lymph nodes and to distant sites, even after total excision. Neither T and N classification nor histologic grade has been successful in predicting the outcome of a patient with this tumor. More aggressive management, including adjuvant therapies and reexcision of subsequent tumors, may result in increased survival.**

(Ann Thorac Surg 1999;67:208–11)

Thymic carcinoid is a distinct clinicopathologic entity that was confused with thymoma before Rosai and Higa [1] described this tumor as a separate entity in 1972. Histologically, most of these tumors are identical to well-differentiated neuroendocrine carcinoma of foregut derivation [2, 3]. It is a potentially malignant tumor and often develops distant metastases, sometimes after long intervals [3–5]. However, the behavior of this unusual tumor is unpredictable [4], and there has been no satisfactory classification system to predict its progression. In 1991, we reported that in patients with thymic neuroendocrine tumor, the percentage with stage IVB disease was much higher than that in patients with thymoma [6]. Lymphogenous spread was observed around the thymus or in the mediastinum in noninvasive cases [6]. These findings have led us to propose a TNM classification for thymic neuroendocrine tumor (Table 1) [6]. To provide prognostic data about this unusual tumor, we looked for a relation between long-term prognosis, tumor–node classification, and histologic appearance.

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Accepted for publication June 18, 1998.

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Material and Methods

Thymic epithelial tumors seen at multiple hospitals in Japan over an 8-year period (1981 to 1989) were reviewed. Fifteen cases of thymic neuroendocrine tumor were identified. The criterion for selection included the absence of a primary neuroendocrine tumor at sites other than the mediastinum at the time of presentation. The classification of each case at presentation was established according to the staging proposed for thymomas [7] and TNM classification (Table 1) [6]. Follow-up was possible for all patients.

All tumor tissue was fixed in 10% formalin and embedded in paraffin. All tissue was stained with hematoxylin and eosin and Glimerius stains, and sections were examined by two pathologists (T.E., T.M.). Tumors were subclassified into three groups according to histologic grade. Grade 1 thymic neuroendocrine tumors are those composed of round to polygonal cells exhibiting little pleomorphism. Mitoses are rare. Grade 2 tumors show mild to moderate cellular pleomorphism with one or two mitotic figures per 20 high-power fields (×400). Grade 3 tumors have a higher degree of cellular pleomorphism and a higher nuclear to cytoplasmic ratio than grade 2 tumors (Fig 1). Mitoses were identified more easily, with six to eight mitoses per 10 high-power fields (×400) (Table 2). Grade 1 tumor corresponds to the carcinoid tumor, which is a distinct subset of neuroendocrine

Published by Elsevier Science Inc

0003-4975/99/$20.00
PII S0003-4975(98)01063-7

Table 1. Tentative TNM Classification of Thymic Neuroendocrine Tumor

Classification	Description
T1	Macroscopically completely encapsulated and microscopically no capsular invasion
T2	Macroscopic adhesion or invasion into surrounding fatty tissue or mediastinal pleura, macroscopic invasion into capsule
T3	Invasion into neighboring organs, such as pericardium, great vessels, and lung
T4	Pleural or pericardial dissemination
N0	No lymph node metastasis
N1	Metastasis to anterior mediastinal lymph nodes
N2	Metastasis to intrathoracic lymph nodes, except for anterior mediastinal lymph nodes
N3	Metastasis to extrathoracic lymph nodes
M0	No hematogenous metastasis
M1	Hematogenous metastasis

tumors, comprising the better differentiated members of that category [2]. Grades 2 and 3 tumors correspond to well-differentiated neuroendocrine carcinomas [2].

Results

Results are summarized in Table 3. The age of our patients at the time of diagnosis ranged from 19 to 73 years, with an average age of 50.6 years. Ten (66.7%) of 15 patients were male. Lymph node metastases were identified in 9 (60%) of 15 patients at the time of resection. There were one grade 1, nine grade 2, and five grade 3 tumors. Computed tomographic scans successfully revealed the lesions in all patients (Fig 2). Total resection was possible in 13 (86.7%) of 15 patients (Fig 3). One biopsy (patient 15, T3N3) and one subtotal resection (patient 14, T4N0) were performed. Two patients had Cushing's syndrome. Patient 1 was admitted to the Nagoya City University Hospital after having been diagnosed with myasthenia gravis. Computed tomographic scans revealed a large cystic mass in the right lobe of the thymus and a small homogenous solid mass in the left lobe of the thymus. Microscopically, the cystic tumor was found to be thymoma, and the solid tumor was a thymic neuroendocrine carcinoma. Electron microscopy revealed numerous neurosecretory granules in the neoplastic cells of the solid tumor [8]. Eight patients received adjuvant irradiation. Of these 8, 2 patients (patients 11 and 13) received neoadjuvant chemotherapy that gave little benefit. Distant metastases developed in 10 (76.9%) of 13 patients who received total resection, although no local recurrence developed. Of these 10 patients, 6 died of distant metastases 5 to 25 months after recurrence. Three patients are still alive, with metastases to the bone, spleen, and pleura 1 to 24 months after the diagnosis of recurrence. In these patients, the metastases did not become evident until 99, 72, and 73 months after the initial operation, respectively. Two patients are presently tumor free (T1N0, grade 3 and T3N2, grade 2), but only 1 has survived beyond 5 years. The best prognosis was observed in patient 14 (T4N0, grade 3) who received adjuvant irradiation and chemotherapy. He lived 127 months with disseminated pleural disease. The earliest recurrence was noted 4 months after the operation in patient 7 (T1N1, grade 1).

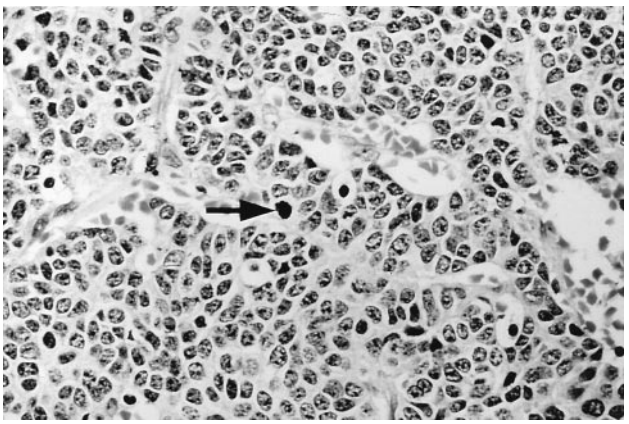

Fig 1. (Patient 9, T2N1.) Grade 3 neuroendocrine tumor of thymus. Arrow *indicates mitosis. (Hematoxylin and eosin; ×400 before 32% reduction.)*

Comment

Since Rosai and Higa [1] described thymic carcinoid tumor as a separate entity in 1972, this tumor has been the subject of several reports indicating that it (1) occurs predominantly in male subjects; (2) can be complicated by endocrine abnormalities, either because of adrenocorticotrophic hormone secretion by the thymic carcinoid itself or its association with other endocrine neoplasms; and (3) develops distant metastases in approximately 20% to 30% of patients, often with a protracted clinical course [3]. Long-term follow-up of the 15 patients in our series showed that metastases occurred in 10 (76.9%) of 13 patients despite total resection. Only 3 of 13 patients did not develop distant metastases, but in only 1 was follow-up longer than 5 years. These results indicate that the long-term prognosis of patients with this tumor is poor [9–11].

In view of the histologic features, most tumors of thymic origin should fall into the category of well-differentiated neuroendocrine carcinomas [2, 3]. So-

Table 2. Histologic Features of Grade 1, 2, and 3 Thymic Neuroendocrine Tumors

Grade	Cellular Pleomorphism	Mitosis	N/C Ratio
1	Little	Extremely rare	Moderate
2	Mild–moderate	1 per 20 high-power view	Moderate
3	High	6–8 per 10 high-power view	High

N/C = nuclear to cytoplasmic ratio.

Table 3. Summary of Clinicopathologic Findings in 15 Patients with Thymic Neuroendocrine Tumor

Patient No.	Age (y)	Sex	T	N	Stage*	Grade†	Operation	Complication	Adjuvant/ Therapy	Site of Postoperative Recurrence	Interval Between Operation and Recurrence (mo)	Survival after Diagnosis (mo)	Status
1	60	M	1	0	I	3	Total Tx	MG				103	ANT
2	20	F	1	0	I	2	Total Tx	Cushing		Bone	48	53	DOD
3	57	F	2	0	II	3	Total Tx		Postop RT	Lung, bone	26	40	DOD
4	52	M	3	0	III	2	Total Tx		Postop RT	Spleen	99	100	AWT
5	61	M	3	0	III	2	Total Tx			Bone, brain, pleura	29	58	DOD
6	36	M	1	1	IVB	2	Total Tx		Postop RT	Bone	72	92	AWT
7	19	M	1	1	IVB	1	Total Tx	Cushing	Postop RT	CLN (resected)	4	15	Suicide
8	35	M	2	1	IVB	2	Total Tx		Postop RT	Pleura	73	97	AWT
9	35	M	2	1	IVB	3	Total Tx			Bone	9	34	DOD
10	68	M	2	2	IVB	3	Total Tx			CLN, lung	14	34	DOD
11	54	M	3	2	IVB	2	Total Tx		Preop and postop RT, preop CT	CLN, bone	27	34	DOD
12	70	F	3	2	IVB	2	Total Tx		...	...	...	49	ANT
13	53	F	3	3	IVB	2	Total Tx		Preop CT, postop RT	...	...	47	Suicide
14	63	M	4	0	IVA	3	Subtotal Tx		Postop RT and CT	...	...	127	DOD
15	73	F	3	3	IVB	2	Biopsy		CT	...	...	18	DOD

* Classification of Masaoka and colleagues [7]. † Histologic grade.

ANT = alive with no tumor; AWT = alive with tumor; CLN = cervical lymph node; CT = chemotherapy; Cushing = Cushing's syndrome; DOD = died of disease; MG = myasthenia gravis; RT = radiotherapy; Tx = tumor resection.

called carcinoid tumors, a distinct subset of neuroendocrine tumors, comprising the better differentiated tumors, are rare [2, 3]. Well-differentiated neuroendocrine carcinoma could be subclassified into grades 2 and 3 by the degree of cellular atypia and mitotic activity.

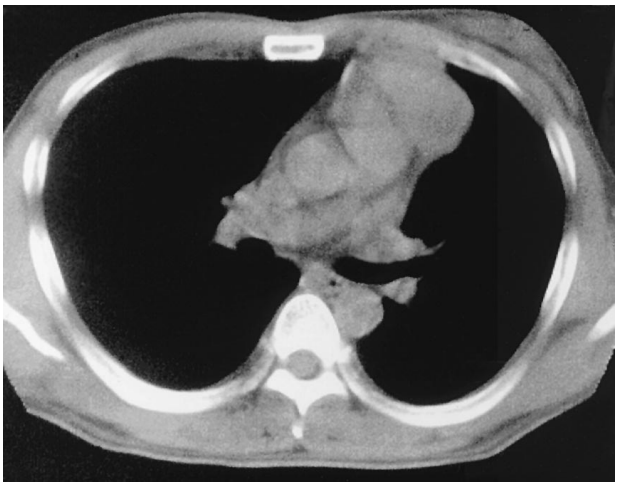

Fig 2. (Patient 6.) Computed tomographic scan of the chest reveals a large mass in the anterior mediastinum.

However, our series illustrates the difficulty of predicting the outcome of a patient according to histologic grade alone. Even the patient with grade 1 tumor (so-called carcinoid tumor) showed anterior mediastinal lymph node metastasis at the time of presentation (T1N1) and developed cervical lymph node metastases only 4 months after the initial operation.

Extracapsular invasion of mediastinal structures at the initial exploration may indicate a poorer prognosis [4, 5]; however, neither T nor N classification is a good predictor of the prognosis of the patient with well-differentiated neuroendocrine carcinoma. The prognosis depends on the development of distant metastases or the lack thereof. In the present study, there were no survivors who lived longer than 25 months after the development of recurrence. It is safe to say that the earlier the recurrence, the poorer the prognosis.

It has been implied that Cushing's syndrome on clinical presentation is associated with a poorer prognosis [2]. Despite the same tumor–node classification (T1N0) and higher histologic grade in patient 1 than in patient 2, the clinical outcome of these 2 patients was considerably different. Patient 2, who had Cushing's syndrome, died of bone metastases 53 months after operation. Patient 1, without Cushing's syndrome, is now in good condition

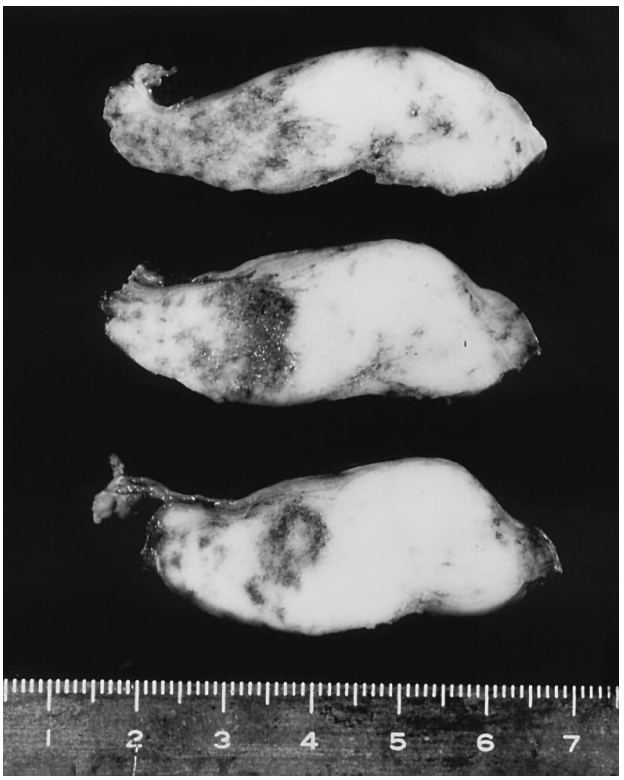

Fig 3. (Patient 6.) Gross appearance of thymic neuroendocrine tumor. The tumor lacks internal fibrous septation. Foci of hemorrhage are apparent.

103 months after operation. Patient 7, who also had Cushing's syndrome, developed cervical lymph node metastasis only 4 months after operation, despite a grade 1, very well differentiated neuroendocrine tumor. We speculate that the degree of neuroendocrine potential of the tumor may reflect the malignancy itself.

No local recurrence was reported. Seven of 13 patients in whom total resection was possible received postoperative radiation therapy. Although the role of adjuvant irradiation has not been adequately assessed, radiotherapy may be helpful in preventing local recurrence after total excision. The role of chemotherapy is uncertain.

Economopoulos and colleagues [5] have claimed that long-term survival can only be achieved by aggressive excision not only of the initial tumor but of subsequent recurrences and metastases. This approach would be possible only in patient 4 who developed splenic metastasis 99 months after the initial operation, and splenectomy is now under consideration.

In conclusion, thymic neuroendocrine tumor (even grade 1) must be regarded as a malignant lesion that is prone to metastasize to mediastinal lymph nodes and to distant sites even after total excision. Unfortunately, neither T and N classification nor histologic grade has been successful in predicting the outcome of a patient with this tumor. More aggressive management, including routine adjuvant therapy and reexcision of the subsequent recurrent tumor, might result in increased survival.

We thank the following physicians for providing follow-up information about their patients and histologic specimens: Dr. Yasushi Yamato, Niigata University, Niigata; Dr. Tetsuya Mitsudomi, Aichi Cancer Center, Nagoya; Dr. Yoshinori Kusajima, Toyama City Hospital, Toyama; Dr. Masahiro Yoshimura, Hyogo Medical Center for Adults, Akashi; Dr. Norimichi Nemoto, Nippon University, Tokyo; Dr. Yukio Shimizu, Gunma Cancer Center, Ota; Dr. Koji Kawano, Naha City Hospital, Naha; Dr. Yuji Matsumura, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan.

Dr Masaoka is the organizer of the project "Function of Thymoma," which is supported by a grant from the Ministry of Health and Welfare of Japan.

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