THYMIC NEUROENDOCRINE CARCINOMA (CARCINOID): A CLINICOPATHOLOGIC STUDY OF FOURTEEN CASES

The medical records and histologic documents of 14 patients treated at our institution for a thymic carcinoid tumor were reviewed. There were 3 women and 11 men with an age range from 35 to 71 years. One patient had a multiple endocrine neoplasia syndrome; another had a neurofibromatosis. Twelve tumors were revealed by local symptoms and two were asymptomatic. One patient had Cushing's syndrome that appeared secondarily and was related to metastases. Tumors ranged from 6 to 20 cm and had the characteristic histologic appearance of atypical carcinoid tumor. Immunohistochemical evaluations were done. Tumors were positive for cytokeratin (92%), neuroendocrine markers (100%), and p53 oncoprotein (29%). S-100 protein antibody revealed numerous sustentacular cells in one case. Overall survival was 46% and 31% at 3 and 5 years, respectively. However, all patients died of the disease within 109 months as a result of local progression ($n = 5$), local relapse ($n = 3$), distant metastases ($n = 8$), or a combination of these reasons. Median survival was 71, 30, and 5 months for patients who had total resection ($n = 4$), partial resection ($n = 5$), or simple biopsy ($n = 4$), respectively ($p = 0.023$). In conclusion, thymic carcinoid tumors can be considered thymic neuroendocrine carcinomas because of their malignant behavior and histologic appearance of atypical carcinoid tumors. Complete surgical resection offers the best hope for long-term survival. (J THORAC CARDIOVASC SURG 1996;111:134-41)

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Mediastinal or thymic carcinoid tumors are extremely rare and only a few small series have been reported in the literature.[1-7] Among malignant epithelial tumors of the thymus, these carcinoid tumors are presently sharply separated not only from thymomas but also from thymic carcinomas.[8, 9] To provide more diagnostic, prognostic, and histologic data about this unusual neoplasm and to discuss the nosologic features of thymic carcinoid tumors and their relations with thymic carcinomas, we present the cases of 14 patients who underwent operation at our institution.

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Material and methods

Between 1960 and 1990, 17 patients underwent operation for a mediastinal carcinoid tumor at our institution. Clinical data were obtained from patients' records and follow-up information from the referring physician. Three cases were excluded from this study; two were considered metastatic lesions from an associated large bronchial atypical carcinoid tumor and a pancreatic neuroendocrine carcinoma. A third case was excluded because of insufficient histologic material. The 14 remaining cases, which form the basis of the current study, presented as primary mediastinal neoplasms. A primary lung tumor was ruled out by bronchoscopy ($n = 8$) and radiographs, tomographs, or computed tomographic scan of the chest. Tumor size was determined from the surgical specimen or, when the tumor was not resected, from imaging studies of the chest. Tumor location was assessed from these imaging studies and from surgical report.

Tissue for light microscopy and immunochemistry was fixed in buffered 10% formaldehyde and embedded in paraffin. All cases were stained with hematoxylin and eosin and Grimelius stains. A mean of five paraffin blocks was available for each case. Atypical carcinoid tumor was defined according to the criteria used for bronchopulmonary neuroendocrine tumors.[10] Immunohistochemical study was done with LSAB Kit peroxidase (Dako, Trappes, France). The following primary antibodies were used with the indicated dilutions: rabbit anti-human

Table I. *Initial clinical and radiologic features, treatment, and follow-up*

Patient no.	*Age, sex*	*First symptom, duration*	*Clinical findings at diagnosis*	*Tumor size (cm) and location*	*Initial operation*	*Postoperative treatment*	*Relapse and metastasis*	*Total survival after diagnosis*
1	53, M	Chest pain, 6 mo	Normal	7 × 5.5 × 3, sup., ant., and left	Total Tx	No	Local R at 25 mo treated by RT and CT	79 mo with progression of local R
2	66, M	None	Normal	12 × 10 × 6, sup., ant., and left	Total Tx	RT (60 Gy)	Local R at 68 mo	71 mo
3	71, M	Pain, cough, 5 mo	Normal	13 ϕ, sup., ant., and left	Subtotal Tx	RT and CT	Symptomatic treatment for vertebral met. at 49 mo	56 mo, suicide, progression of met.
4	54, M	Dyspnea, 6 mo	Severe dyspnea, asthenia	20 ϕ, all ant. mediastinum	Debulking	RT	Local progression	6 mo
5	49, F	None	Normal	6 × 4 × 4, middle mediastinum	Total Tx and 5 mm lung Mx	No	Vertebral Mx at 60 mo, brain Mx at 84 mo	109 mo with new brain met.
6	56, F	Chest pain, 3 mo	Dyspnea, left RP, asthenia	7 ϕ, middle mediastinum	Biopsy	No (refused)	Not known	Not known
7	55, M	Not known	SVC syndrome, pleural effusion	Not known,* ant. and sup.	Biopsy	Symptomatic	Local progression	1 mo
8	39, M	Chest pain, 1 yr	Weight loss	12 ϕ, all sup. mediastinum	Biopsy	RT	Osseous and brain met.	5 mo
9	58, M	Pain, dyspnea, 5 mo	Asthenia, dyspnea	10 × 10 × 6, ant. and sup.	Subtotal Tx	RT (50 Gy) and CT	Left pleural carcinosis at 16 mo	20 mo
10	38, M	Chest pain, 1 yr	Dyspnea, weight loss	10 ϕ, ant. and sup.	Subtotal Tx	Not known	CT for local R and lung Mx at 14 mo	64 mo with disseminated disease
11	35, M	Chest pain, 3 mo	SVC syndrome, dysphonia	8 × 7 × 4, ant. and sup.	Subtotal Tx	RT† and CT	CT for cervical LN met. at 30 mo	40 mo with progression of LN met.
12	68, M	SVC syndrome, 2 mo	SVC syndrome	8 × 7 × 3, ant., sup., and left	Total Tx	RT (60 Gy)	RT for cervical LN and vertebral met. at 18 mo	36 mo with Cushing's syndrome
13	47, M	Dysphonia, 1 yr	Left RP, SVC syndrome, subclavicular mass	8 ϕ, ant. and sup.	Biopsy (cervical LN met.)	Not known	Not known	10 mo
14	55, M	Chest pain, 1 mo	SVC syndrome, dysphonia	10.5 × 9.5 × 9, ant., sup., and left	Biopsy	RT (40 Gy) and CT	Local progression	14 mo

M, Male; *F,* female; *sup.,* superior; *ant.,* anterior; *Tx,* tumor resection; *R,* relapse; *RT,* radiation therapy; *CT,* chemotherapy; *met.,* metastasis; *Mx,* metastasis resection; *RP,* recurrent paralysis; *SVC,* superior vena cava; *LN,* lymph node.

*Massive right pleural effusion.

†40 Gy before operation and 20 Gy after operation.

neuron-specific enolase (Dako, 1/50), monoclonal mouse anti-human chromogranin A (Dako, 1/40), rabbit anti-cow S-100 (Dako, 1/200), monoclonal mouse antikeratin (KL1, Dako 1/50), monoclonal mouse anti-human p53 protein (Dako, 1/25), monoclonal mouse anti-human macrophage CD68 (KP1, Dako, 1/50), rabbit anti-synthetic human adrenocorticotropic hormone (ACTH) 1-24 (Dako, 1/200), rabbit anti-bombesin (Euromedex, Schiltigheim, France, 1/1000), polyclonal rabbit anti-glucagon (Unipath, Dardilly, France; prediluted), rabbit anti-insulin (Unipath, prediluted), rabbit anti-pancreatic polypeptide (Unipath, prediluted), and rabbit anti-somatostatin (Unipath, prediluted). Normal pancreas was used as positive control for insulin, glucagon, pancreatic polypeptide, and somatostatin. Normal pituitary gland was used as positive control for ACTH and fetal lung was used for bombesin.

For statistical analysis, survival was calculated from the date of operation until death estimated with the product-limit method, and differences on its distribution were calculated with the log-rank test.

Results

Clinical and radiologic findings. Selected data at presentation are summarized in Table I. Patient 8

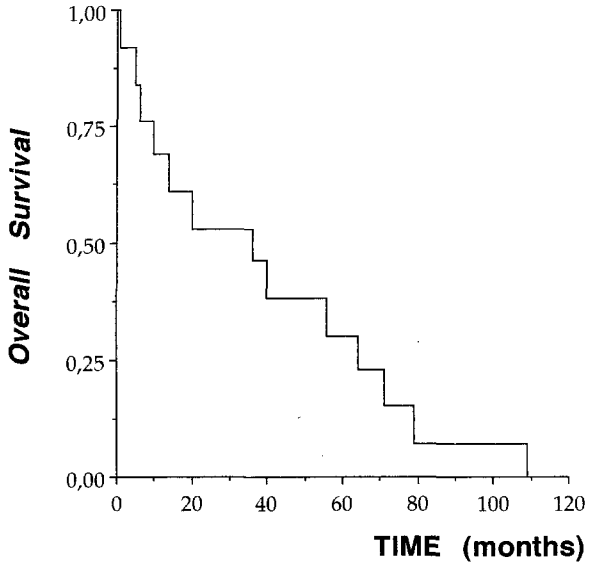

Fig. 1. Survival curve of thymic carcinoid tumors: overall survival.

had a von Recklinghausen's disease with "café au lait" spots and multiple thoracic dermal neurofibromas: symptoms similar to those of the male parent. He had no evidence of gastrointestinal tumor. Patient 5 had multiple endocrine neoplasia (MEN) syndrome. This patient's brother had Zollinger-Ellison syndrome; she herself was treated for a parathyroid adenoma 6 years after diagnosis of the mediastinal carcinoid tumor. Patient 7 had a severe chronic psychosis. At presentation, none of the patients had manifestations of abnormal secretion. In particular, none had carcinoid syndrome. Five patients were heavy smokers. All patients had abnormal findings on chest roentgenograms, and tomograms or computed tomographic scans specified size and location of the tumor. A bronchoscopy was done in eight cases and showed normal findings in two. In the six others, bronchoscopy revealed an extrinsic compression of trachea or major bronchi. Tracheobronchial biopsy provided no tumoral material.

Laboratory findings. Serum carcinoembryonic antigen level was normal in six cases and elevated in case 8 (24 ng/L, normal <5). Calcium level was normal in 11 cases. The patient with MEN syndrome had hypercalcemia (2.7 mmol/L, normal <2.6) with elevated alkaline phosphatase levels (166 IU/L, normal <90). These abnormalities were probably related to the parathyroid adenoma later discovered. Patient 10 also had hypercalcemia (3.16 mmol/L, normal <2.6) but normal alkaline phosphatase levels. No patient underwent further investigation in the search for hyperparathyroidism at that time. Serum ionic concentrations were normal in all cases and no patient had hypokalemia that could indicate a possible hypercortisolism. Urinary 5-OH-indoleacetic acid value was normal in the three tested cases. The patient with neurofibromatosis had a normal urinary vanillylmandelic acid level (20 μmol in 24 hours, normal <30).

Treatment and follow-up data (Table I). Tumoral resections were often extended to invaded adjacent structures: pericardium in five cases, lung (wedge resection) in two cases, innominate vein in one case, and vena cava in two cases. Invaded thymus could be identified in three cases. Subtotal resection was done in four cases in which tumoral tissue was left by one phrenic nerve when the two were invaded (3 cases), in the trachea (1 case), in the left carotid artery (1 case), and in the subclavian artery (1 case). Adjuvant treatments were not standardized. Three years after initial diagnosis, Cushing's syndrome developed in patient 12 with high and irregular ACTH serum levels. There was no sign of mediastinal tumoral relapse and Cushing's syndrome was related to a T12 vertebral metastasis. Overall survival was 46% and 31% at 3 and 5 years, respectively; however, all patients died of the disease within 109 months with a median survival of 28 months (Fig. 1). Death was related to local progression (5 cases), local relapse (3 cases), and distant metastases (8 cases). Median survival was 71, 30, and 5 months for patients who had total resection ($n = 4$), partial resection ($n = 5$), or simple biopsy ($n = 4$), respectively ($p = 0.023$) (Fig. 2).

Pathologic findings. All tumors demonstrated the characteristic neuroendocrine architecture of carcinoid tumors, often with palisading or rosette patterns. In 12 cases, the tumor contained irregular areas of necrosis, sometimes with foci of dystrophic calcification. The stroma was usually scant and fibrovascular, but in six cases it was focally fibrous and in case 11 (treated by radiation) the tumor had a dense hyalin fibrous stroma (Fig. 3). Tumoral cells were of large size and regular. Their nucleus was oval to round with finely granular chromatin. Cytoplasm was eosinophilic or pale. These cells had a polygonal shape but were fusiform in case 5 associated with MEN syndrome (Fig. 4) and in a small area in case 2. There was no small cell component. Mitotic figures could be observed in all cases but were never greater than 10 per 10 high-power fields

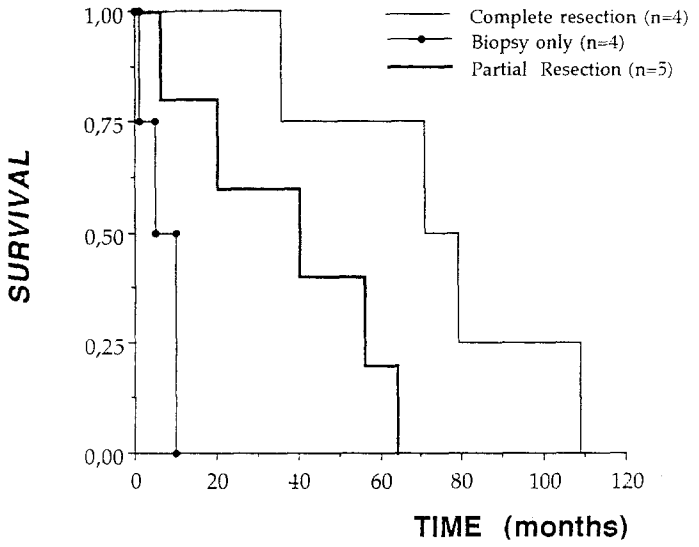

Fig. 2. Survival curve of thymic carcinoid tumors: survival according to type of operation ($p = 0.023$).

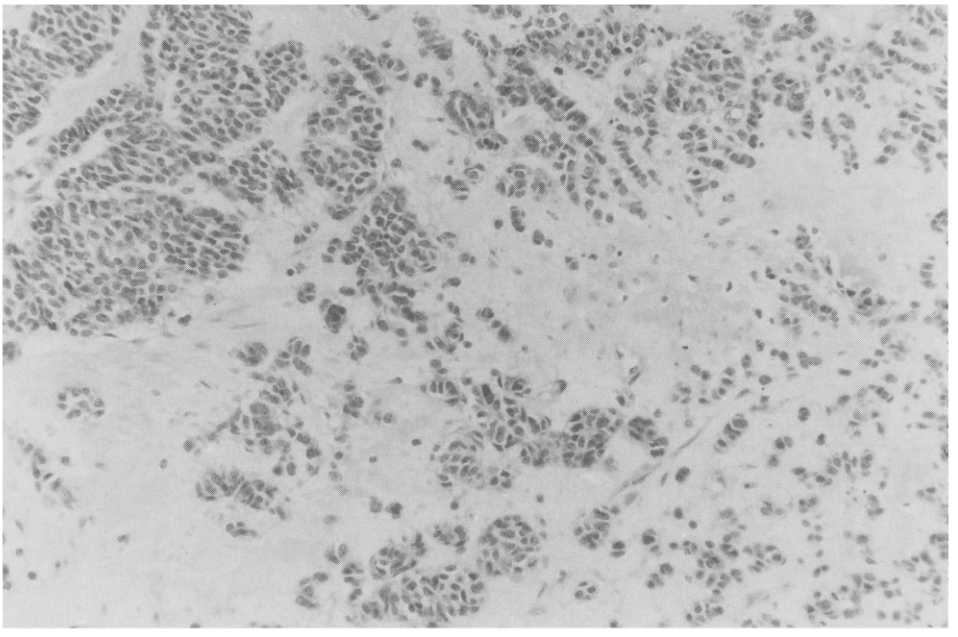

Fig. 3. Case 11. Nonsterilized thymic carcinoid tumor displaying abundant hyalin fibrous stroma after preoperative radiation therapy.

(Fig. 4). Because of necrosis and mitotic activity, all cases were classified as atypical carcinoid tumors.

Tumors were partially encapsulated. A pseudocapsule was sometimes identified as a thickened fibrous mediastinal pleura. Tumoral infiltration of adipose tissue was observed in 5 of the 10 resection specimens and was associated with tumoral lymphangitis in two cases.

Histochemical and immunohistochemical findings (Table II). All tumors expressed at least two of the three neuroendocrine markers used in this evaluation. In case 3, anti–S-100 protein antibody revealed numerous cells with morphologic features of the sustentacular cells seen in paraganglioma (Fig. 5). These cells did not express the CD68 histiocytic marker. Otherwise, tumoral cells were S-100 protein

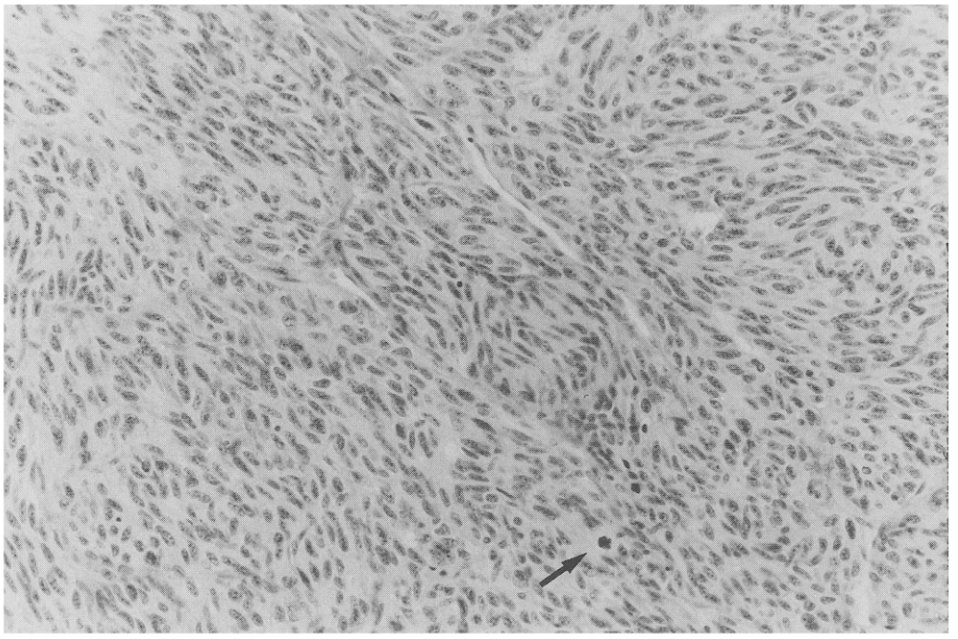

Fig. 4. Case 5 (associated with MEN syndrome). Thymic carcinoid tumor made up of spindle cells. This morphologic appearance can be confused with that of spindle cell thymoma, but lack of lymphoid component and immunohistochemical data permitted diagnosis. Mitotic feature is indicated with *arrow.*

Table II. *Grimelius stain and immunohistochemical findings*

	Case													
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
Grimelius	−	+	−	+	−	−	+	−	+	+	+	+	−	+
Cytokeratin	+	+	+	+	+	−	+	nd	+	+	+	+	+	+
NSE	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromogranin	+	+	−	+	+	+	−	−	+	−	+	+	−	−
Protein S-100	−	−	+*	−	−	−	−	−	−	−	−	−	−	−
p53	+	−	−	−	+	+	+	−	−	−	−	−	−	−

nd, Not done; *NSE,* neuron-specific enolase.
*Sustentacular cells.

negative in all cases. Cytokeratin was strongly expressed in 10 cases including the one with sustentacular cells, weakly in case 12, and focally in case 5 with fusiform cells. Antibody to p53 stained strongly most of the tumoral cell nuclei in case 7 and weakly few of these nuclei in three other cases. No secretion product was detected by immunohistochemistry. In the patient in whom Cushing's syndrome later developed, testing for ACTH was negative in the primitive tumor.

Discussion

The observations made in this study provide evidence that thymic carcinoid tumors (1) may present with a variety of clinical onsets, (2) behave as malignant tumors, (3) have a prognosis related to the radicalness of the surgical resection, and (4) have a distinctive histologic and immunohistologic appearance. These neoplasms can either be asymptomatic, associated with symptoms related to local growth, or part of a MEN syndrome and can produce endocrinopathy,[1-9] especially Cushing's syndrome.[11, 12] The peculiarity of our case with Cushing's syndrome was that the endocrinopathy was not present at the time of diagnosis and appeared only in the late phase of the disease. MEN syndrome often comprises hyperparathyroidism, as in our case.[13] A tumor developed in one of our patients in association with neurofibromatosis, another systemic disease involving the neuroendocrine system. This is an unusual event because in this condition, carcinoid tumors are rare and almost exclusively gastrointestinal.[14]

Our study confirms the malignant behavior and the poor prognosis of thymic carcinoid tumors. In three previously published series, 4 of 7,[5] 7 of 8,[6] and 5 of 8[7] cases were reported as having locally invasive lesions and only 4 of our 14 cases could be totally resected. Relapse occurred in 3 of our 8 patients who underwent surgical resection. Distant metastases occurred in 7 of our patients and in 11 of 15,[2] 11

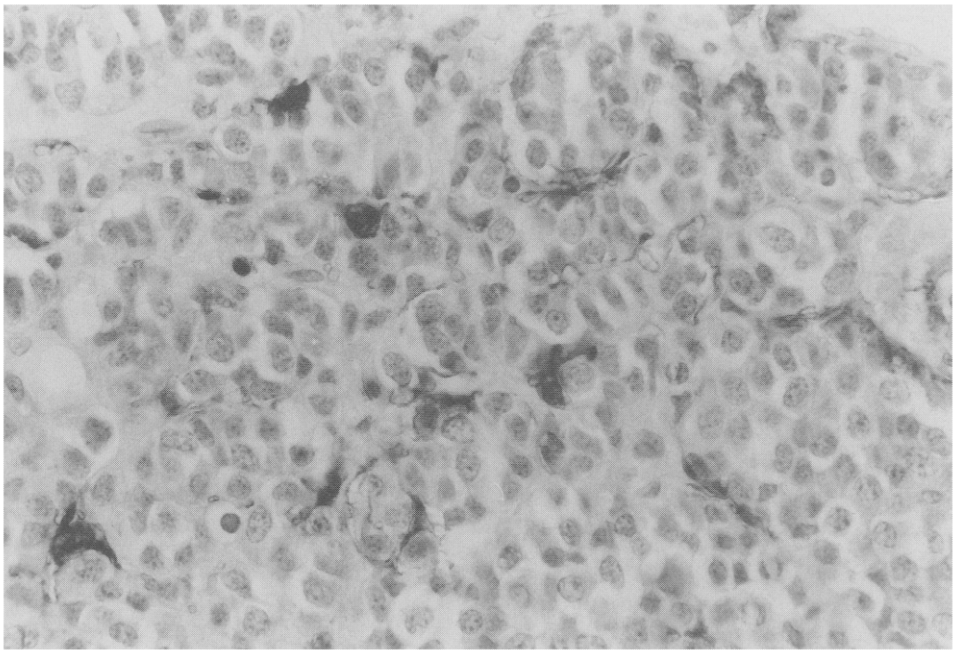

Fig. 5. Case 3. Sustentacular cells revealed by anti–S-100 protein in thymic carcinoid tumor.

of 12,[3] and 7 of 8[6] patients in three other series. Only 6 of 44 cases from four series,[2, 5, 7] including ours, have had a protracted course with a survival of more than 8 years. Median survival of 28 months in our series is in line with that reported by others.[2, 5] Operation is the most effective treatment[5] and complete resection offers the best hope for long-term survival.

Histologic diagnosis of mediastinal carcinoid tumor is facilitated by recognition of its characteristic morphologic features. Areas of necrosis, sometimes calcified, are usual features.[9] Our case with hyalin fibrous stroma was interesting in that the tumor had been radiated with 40 Gy and was absolutely not sterilized. In the current series and in our recent study of 98 mediastinal germ cell tumors,[15] we did not encounter carcinoid tumors arising in a germ cell neoplasm like the one previously reported.[16] Our case with sustentacular cells is a variant not previously reported. Such "paraganglioid" tumors generally account for a variable percentage of bronchial and gastrointestinal carcinoid tumors and have no other relevant biologic significance.[17] ACTH is the neuropeptide most commonly detected in thymic carcinoid tumors,[2] but other secretory products, which do not usually correspond to manifestation of clinical symptoms,[4] have also been detected.[3, 4] Our immunohistochemical neuropeptide search had negative results. The p53 nuclear oncoprotein was detected in 45% of 22 pulmonary atypical carcinoid tumors but not in any of 15 typical carcinoids.[18] In our current series, 4 (29%) of 14 tumors were found to express p53. This expression had no prognostic value because two of these patients had a rapid fatal outcome and another had the longest survival.

The thymus is considered the principal origin for primary mediastinal carcinoid tumors.[9] These thymic tumors can be differentiated from other mediastinal neuroendocrine neoplasms.[19] A metastasis especially from a bronchopulmonary carcinoid tumor must be clinically formally excluded. Mediastinal parathyroid adenomas are not exceptional,[19] but only the rare and exceptionally nonsecreting mediastinal parathyroid carcinoma can be considered in the differential diagnosis of thymic carcinoid tumor with malignant behavior. Mediastinal paraganglioma[20] theoretically can be distinguished from carcinoid tumors by its constant lack of immunoreactivity for cytokeratin. Nonneuroendocrine mediastinal neoplasms, which can histologically be confused with carcinoid tumors, are infrequent thymomas without any lymphoid component. Immunohistochemical negativity for neuroendocrine markers can permit diagnosis.

Our study confirms that thymic carcinoid tumors represent a specific entity. This entity is usually

separated from the other malignant epithelial thymic tumors, namely, thymomas and thymic carcinomas. However, several elements suggest that thymic carcinoid tumors may be compared with the group of thymic carcinomas. This comparison is based on the following observations. First, thymic carcinomas are rare and not associated with immunologic disorders such as myasthenia gravis. These carcinomas have a propensity to produce lymph-node and extrathoracic metastases.[21-23] Such clinical features are shared with thymic carcinoid tumors and clearly distinguish these tumors from the more common and less aggressive thymomas. Furthermore, the prognosis in patients with thymic carcinoid tumors is close to the survival rate (33.3% at 5 years) reported for thymic carcinomas.[22] Second, all our 14 cases and all the 8 cases in a recent detailed pathologic series[7] were considered atypical carcinoid tumors. Typical carcinoid tumors of the thymus are exceptional.[7] In the lung, the term *atypical carcinoid tumor* is used as synonymous with *well-differentiated neuroendocrine carcinoma*.[10] The term *carcinoma* is suitable for thymic carcinoid tumors and is a better term to indicate an epithelial neoplasm with malignant behavior than *carcinoid,* which in some locations such as lung[10] corresponds to a benign or a low aggressive tumor. Third, there is no histologic evidence to exclude a well-differentiated neuroendocrine carcinoma in the heterogeneous group of thymic carcinomas. Obvious features of cytologic atypia are usually required for this diagnosis[21] but several thymic carcinomas, such as mucoepidermoid carcinoma, are of a low-grade histologic type.[22] The group of thymic carcinomas also includes small cell carcinoma,[22] which is another neuroendocrine neoplasm. Fourth, recognition of a carcinoid component in rare thymic carcinomas confirms a link between these two entities.[24, 25]

In light of these arguments, inclusion of thymic carcinoid tumors in the group of thymic carcinomas, as has already been suggested by a recent surgical series of thymic carcinomas including two carcinoid tumors,[23] appears justified. Therefore a thymic carcinoid tumor should be considered, as has already been proposed, a thymic carcinoma of a carcinoid type[26] or, rather, as a thymic well-differentiated neuroendocrine carcinoma. This would permit a more comprehensive classification of malignant thymic epithelial neoplasm by distinguishing all thymic carcinomas (neuroendocrine and others) from thymomas.

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