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Well-differentiated thymic carcinoma: a clinico-pathological study

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Summary. Well-differentiated thymic carcinoma (WDTC) is a recently described epithelial tumour of the thymus previously classified as cortical or predominantly epithelial thymoma. The authors have reviewed a series of 15 cases of WDTC with the aim of further defining the clinicopathological features of this neoplasm. Histologically, the number of lymphocytes was always low; perivascular spaces and epithelial palisading around blood vessels and/or along fibrous septa were prominent features; 6 cases (40%) were associated with areas of typical cortical thymoma. All cases showed slight to moderate cytological atypia and nuclear grooving was frequently detected. Mitotic activity was variable but usually low. Clinically, all but 3 cases (80%) were invasive at surgery; myasthenia gravis was present in 9 cases (60%); 5 patients (33.3%) died due to disease and 2 additional patients (13.3%) had tumor recurrence. Our study indicates that WDTC has fairly distinctive clinicopathological features and that it is histologically and histogenetically related to cortical thymoma. The definition "well-differentiated carcinoma" is justified because of low-grade cytological atypia and retention of some organotypical histological features, in a tumour otherwise often displaying aggressive and sometimes clear-cut malignant clinical behaviour.

Key words: Thymus – Thymoma – Thymic carcinoma – Well-differentiated thymic carcinoma

Introduction

Epithelial tumours of the thymus are usually subgrouped according to the degree of cytological atypia of neoplastic cells. Tumours with no or with minimal cytological atypia are defined as thymomas, irrespective of whether they are invasive (Levine and Rosai 1978); conversely, tumours with obvious cytological atypia are more properly classified as thymic carcinomas (Levine and Rosai 1978; Snover et al. 1982). In addition, thymomas are as a rule characterized by the presence of distinctive histological features – perivascular spaces, epithelial palisading, epithelial rosettes, gland-like structures, areas of medullary differentiation, Hassall's corpuscles – altogether referred to as "organoid" (Rosai 1989) or "organotypical" (Kirchner and Müller-Hermelink 1989). These features are usually absent in thymic carcinomas. However, in a number of thymic epithelial tumours there is a degree of cytological atypia intermediate between conventional thymoma and thymic carcinoma, together with the presence of signs of organotypical differentiation. Such tumours have been recently defined as well-differentiated thymic carcinoma (WDTC) (Kirchner and Müller-Hermelink 1989). With the aim of further defining the nosological profile of this recently described thymic neoplasm, we have reviewed the pathological and clinical features of 15 cases of WDTC.

Materials and methods

The histological material of 75 cases of epithelial tumours of the thymus have been collected from the files of the II Pathological Anatomy of the University of Rome, "La Sapienza". Routinely stained slides from formalin-fixed paraffin-embedded blocks were available. The 75 patients had been treated surgically at the Division of Thoracic Surgery of the same university, between 1975 and 1990. The histological material was independently examined by two of us (E.P., S.R.) and scored for the presence of the diagnostic criteria of WDTC proposed by Kirchner and Müller-Hermelink (1989). In particular, the number of lymphocytes, mitotic activity (number of mitotic figures per high power field), presence of capsular and/or neighbouring tissue infiltration and of areas of necrosis, presence of "organotypical" features such as perivascular spaces, epithelial palisading, "starry" sky pattern, areas of medullary differentiation and Hassall's bodies were carefully assessed. Furthermore, the degree of cytological atypia was evaluated on the basis of nuclear features such as size, shape, chromatin staining and distribution, and the presence of nucleoli. Fifteen cases fulfilling the diagnostic criteria of WDTC were included in the present study.

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In all selected cases detailed clinical records (age, sex, clinical stage at surgery, and association with myasthenia gravis) were available. Follow-up data were obtained in 14 cases and varied from 6 months to 11 years. One patient was lost to follow-up. Survival curves were plotted according to the actuarial method of Kaplan and Meier and analysed through the log-rank test.

Results

There were 9 female and 6 male patients (F:M=1.5:1) whose age ranged from 27 to 60 years; myasthenia gravis was present in 9 patients (60%). Twelve cases (80%) were invasive at surgery and 1 of them had also endothoracic metastases. Seven patients are alive and disease-free 6 months to 11 years after surgery; 2 patients had tumour recurrence. Three patients died because of disease 6 months to 5 years after surgery, and 2 elderly patients with myasthenia gravis died during the post-operative period. The main clinical features are reported in Table 1. The actuarial survival curve of WDTC is shown in Fig. 1, together with the actuarial survival curve of the overall series of thymic epithelial tumours on which this study was based. Interestingly, there was a statistically significant difference ($P<0.01$) between the two groups.

Histologically, 9 cases were classified as pure WDTC and 6 cases as WDTC with associated areas of cortical thymoma (WDTC+CT). Eight cases showed a lobulated pattern, with broad and irregular fibrous septa (Fig. 2A); the remaining cases had a diffuse growth pattern. Lymphocytes were always rather few in number (Fig. 2A), ranging from less than 10% of total cell count in pure WDTC to 10–30% in WDTC+CT. Well-formed perivascular spaces were a constant and prominent feature, present in all but 1 case; furthermore, in 10 cases perivascular spaces (PVS) were dilated and frequently contained lymphocytes, erythrocytes and extravasated fluid (Fig. 2B). Palisading of epithelial neoplastic cells around blood vessels and along fibrous septa was present in all cases (Fig. 2C). Capsular infiltration was histologically detected in 11 cases and was associated with microscopic evidence of pleural and lung infiltration in 4 instances (Fig. 2D). Foci of necrosis were present in 3 cases and Hassall's corpuscles in only 1. Vascular invasion was observed in 3 cases. In the 6 cases diagnosed as WDTC+CT the transition between WDTC and CT areas was characterized by a clear-cut increase in the number of lymphocytes (Fig. 3A, B); starry-sky pattern was restricted to the periphery of CT areas. Remnants of non-neoplastic thymic tissue were noticed in 5 cases: 2 were characterized by lymphoid follicular hyperplasia, 1 was normal and 2 were involuted thymuses. In 1 case a few germinal centres were also observed within the tumour. Areas of medullary differentiation (AMD) and spindle-cell areas with storiform and/or haemangiopericytoma-like pattern were never observed.

Cytologically, all cases consisted of broad sheets of rather polyhedral and cohesive cells, often with sharply defined cytoplasmic borders and showing mild to moderate atypia. Nuclei were either round or oval with medi-

Table 1. Well-differentiated thymic carcinoma: clinical features

Case	Sex	Age	MG	Invasion at surgery	Follow-up
1	F	50	–	+	Died (6 months)
2	F	27	+	–	A and W (11 years)
3	F	53	–	+	Died (5 years)
4	F	34	–	+	A and W (3 years)
5	M	36	–	+	Lost to follow-up
6	F	42	–	+	Tumour recurrence (1 year)
7	F	50	+	+	Post-operative death
8	M	60	+	+	Post-operative death
9	F	46	–	–	A and W (10 years)
10	M	33	+	+	Died (2 years, 1 month)
11	M	54	+	+	A and W (3 years)
12	M	55	+	–	A and W (1 year, 6 months)
13	M	57	+	+	A and W (6 months)
14	F	48	+	+	Tumour recurrence (23 months)
15	F	55	+	+	A and W (3 years)

MG, Myasthenia gravis

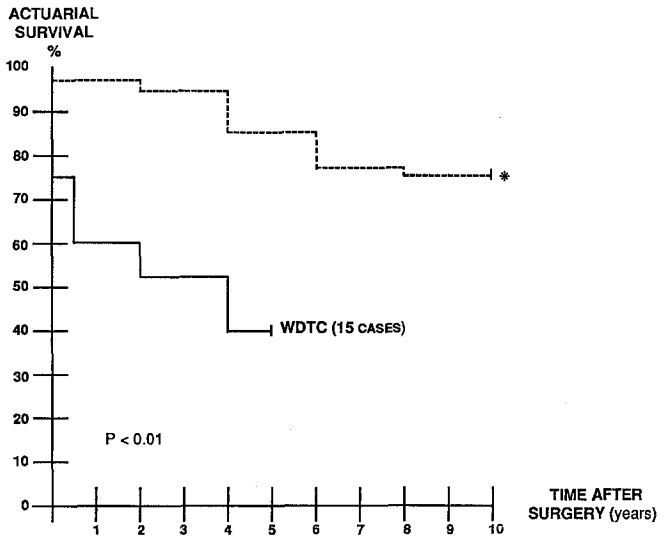

Fig. 1. Actuarial survival of well-differentiated thymic carcinoma (15 cases) compared to the actuarial survival of the series of 75 cases of thymic epithelial tumours upon which this study has been based (*asterisk*). The difference is highly significant statistically ($P<0.01$)

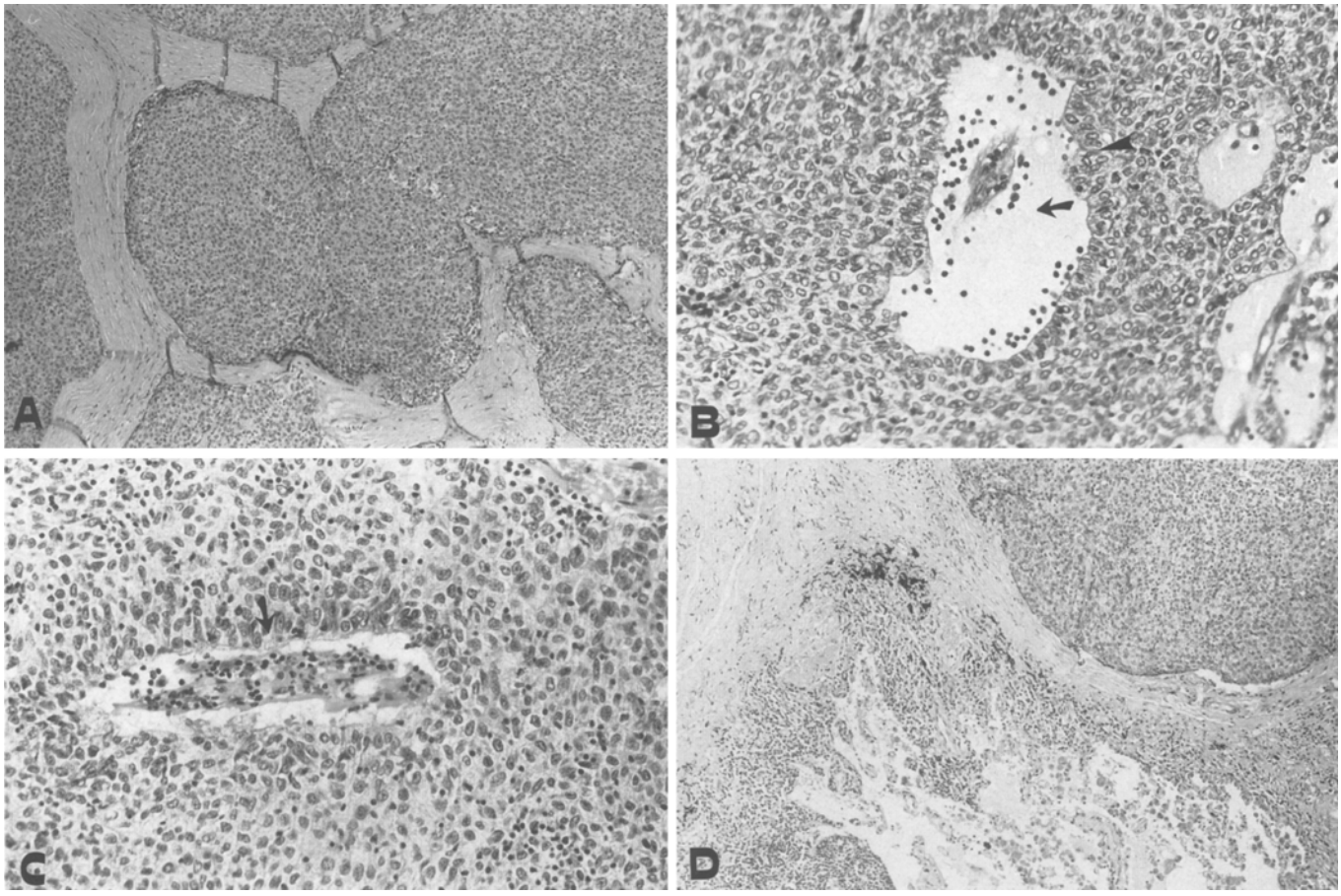

Fig. 2. **A** Low power field of well-differentiated thymic carcinoma showing a marked lobulation with broad fibrous septa and the typical small number of lymphocytes. H&E, ×40. **B** A dilated perivascular space (*arrow*) with epithelial perivascular palisading (*arrowhead*), H&E, ×100. **C** Prominent epithelial perivascular palisading (*arrow*) is shown. H&E, ×100. **D** Well-differentiated thymic carcinoma invading the lung (*arrow*). H&E, ×40

Table 2. Well-differentiated thymic carcinoma: histological features

Case	Lobulation	Necrosis	PVS	Palisading	Nuclear groove	Storiform pattern	"Starry-Sky" pattern	AMD	Hassall's bodies	Histological diagnosis
1	+	−	+	+	+ (Focal)	−	−	−	−	WDTC
2	−	−	++ (D)	++	+++	−	−	−	+	WDTC
3	+	−	−	+	−	−	−	−	−	WDTC
4	−	+	+ (D)	++	+ (Focal)	−	−	−	−	WDTC
5	−	−	+	+	+ (Focal)	−	−	−	−	WDTC
6	+	+	+ (D)	+	−	−	−	−	−	WDTC
7	+	−	++ (D)	+	+	−	−	−	−	WDTC
8	++	−	+	+	−	−	−	−	−	WDTC
9	+	−	++ (D)	++	+++	−	−	−	−	WDTC
10	−	−	+ (D)	+	+ (Focal)	−	−	−	−	WDTC+CT
11		−	+ (D)	++	+ (Focal)	−	−	−	−	WDTC+CT
12	+	−	+ (D)	++	++	−	+ (Focal)	−	−	WDTC+CT
13	−	−	+ (D)	++	−	−	+ (Focal)	−	−	WDTC+CT
14	−	+	+ (D)	++	−	−	−	−	−	WDTC+CT
15	+	−	+	+	+	−	+ (Focal)	−	−	WDTC+CT

PVS, Peri-vascular spaces; D, dilated;
AMD, areas of medullary differentiation;
WDTC, well-differentiated thymic carcinoma;
WDTC+CT, well-differentiated thymic carcinoma with associated areas of cortical thymoma

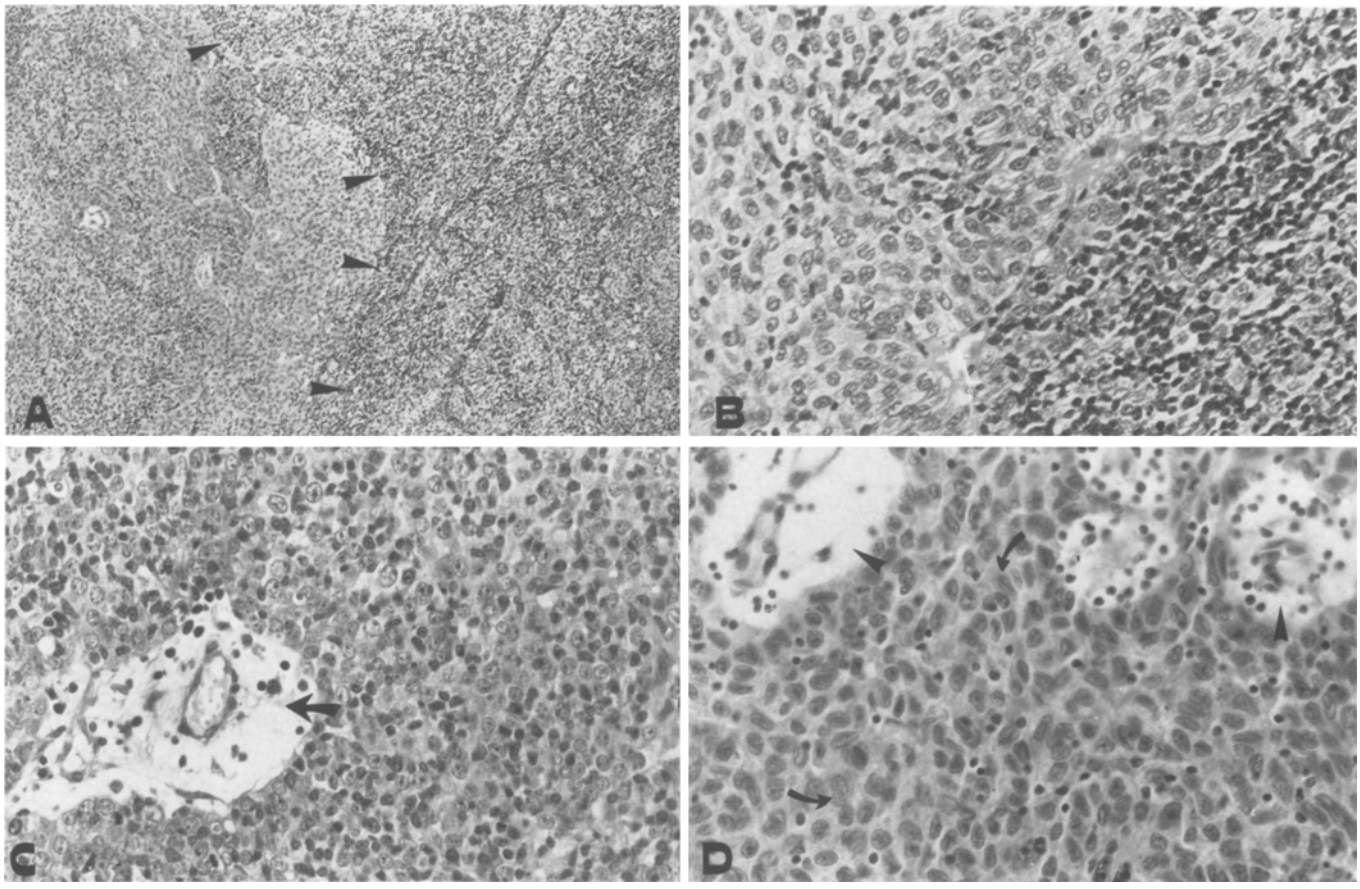

Fig. 3. **A** Well-differentiated thymic carcinoma (*left*) with an associated area of cortical thymoma (*right*): the *arrowheads* indicate the transition between the two lesions. H&E, ×40. **B** Transition between an area of lymphocyte-poor well-differentiated thymic carcinoma (*left*) and an area of lymphocyte-rich cortical thymoma (*right*): the morphological appearance of epithelial cells is very similar. H&E, ×400. **C** Cytological detail of well-differentiated thymic carcinoma: this case is featured by round-oval cells with prominent nucleoli. A somewhat dilated perivascular space is present on the left (*arrow*). H&E, ×400 .**D** Cytological detail of well-differentiated thymic carcinoma: this case is characterized by cells with irregular nuclei; a nuclear groove (*arrows*) is present in most cells. Some perivascular spaces are also shown (*arrowheads*). H&E, ×400

um-sized nucleoli (Fig. 3C), or irregular with prominent grooving and inconspicuous nucleoli. Nuclear grooving (Fig. 3D) was frequent in 3 cases and focally present in 6. Areas of cells with clear cytoplasm were frequently observed. Mitotic figures ranged from 1 to 5 per 10 high power fields in all but 2 cases, which displayed a considerably higher proliferative activity (11 and 30 mitoses per 10 high power fields). The main histological features of WDTC are reported in Table 2.

Discussion

Thymic carcinomas are rare tumours with morphological and clinical evidence of malignancy; most of them are of the epidermoid or lymphoepithelioma-like types although other more unusual histological variants have been also described (Snover et al. 1982; Kuo et al. 1990; Truong et al. 1990). These carcinomas are characteristically devoid of those histological features, referred to as "organoid" (Rosai 1989) or "organotypical" (Kirchner and Müller-Hermelink 1989), typical of thymomas. Thus, thymic carcinomas are histologically very similar to analogous tumours arising in other sites, and usually lack histological hallmarks suggestive of thymic origin; the latter is often only assumed on the basis of the antero-superior mediastinal location of the tumour in the absence of other clinically detectable neoplasms. However, rare cases of thymic carcinoma arising from a background of typical thymoma have been also reported (Morinaga et al. 1987). In the present paper we have studied the clinical and pathological features of 15 cases of a thymic epithelial tumour classified as WDTC using the histological criteria recently proposed by Kirchner and Müller-Hermelink (1989). The term WDTC at present refers to a distinctive subgroup of thymic neoplasms previously classified as cortical thymoma (Marino and Müller-Hermelink 1985; Müller-Hermelink et al. 1986) or predominantly epithelial thymoma (Rosai and Levine 1976). The original study of Kirchner and Müller-Hermelink (1989) suggested that the clinical behaviour of WDTC was consistent with that of a rather malignant tumour, 16 out of 22 cases (72%) being invasive at surgery. Our results parallel

those of Kirchner and Müller-Hermelink both pathologically and clinically. However, some points deserve further consideration. Our findings, demonstrating the presence of areas of typical CT in 6 out of 15 cases (40%) of WDTC indicate, on morphological grounds, that WDTC and CT are histogenetically related. This interpretation is further supported by the fact that we have detected areas of WDTC in 7 of 21 cases (33%) of cortical thymoma (unpublished observations) and, on clinical grounds, by the evidence that CT, like WDTC, also often displays aggressive clinical behaviour (Ricci et al. 1989; Pescarmona et al. 1990). According to our observations the most relevant diagnostic histological features of WDTC are perivascular spaces (often dilated) and epithelial palisading. Both these organotypical traits are suggestive of thymic origin and were present in all but 1 of our cases: in addition, lymphocytes were typically scanty. Cytologically, nuclear grooving was a rather typical and previously undescribed feature.

The overall incidence of WDTC in our series (15 out of 75 thymic epithelial tumours = 20%) is very similar to that originally reported by Kirchner and Müller-Hermelink (22 of 88 = 25%), thus confirming that WDTC represents a significant percentage of thymic epithelial tumours. Moreover, this entity is often associated with myasthenia gravis as demonstrated in the present study (60%) and in the previous study of Kirchner and Müller-Hermelink (86%).

From the prognostic standpoint, the analysis of actuarial survival curves shows that prognosis of WDTC is significantly worse than that of the overall series of thymic epithelial tumours considered in the present study. In particular, aged myasthenic patients with invasive neoplasms seem to be at high risk of post-operative death and tumour recurrences are not unusual; conversely, long-term survivals are usually associated with non-invasive tumours.

We conclude that WDTC is a distinctive epithelial tumour of thymic origin, histologically and histogenetically related to cortical thymoma, with histological features suggestive of partial cortical differentiation. The term well-differentiated carcinoma is justified by the low-grade cytological atypia and by the presence of signs of organotypical differentiation in a neoplasm otherwise displaying aggressve and often clear-cut malignant clinical behaviour.

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