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Thymoma and thymic carcinoma

Relation of thymoma epithelial cells to the cortical and medullary differentiation of thymus*

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Summary. Based on the light microscopical features of normal thymic epithelial cells, human thymoma was divided in different types, namely cortical, medullary, and mixed ones, according to the epithelial cell (EC) type. Lymphoid cell populations with morphological features of either cortical or medullary thymocytes were found according to different types of EC in thymoma. The histological variation of the different types of thymoma are demonstrated. In a retrospective study of 58 thymomas and 13 thymic carcinomas, malignant invasive character as well as the occurrence of myasthenia gravis were both found to be related to the neoplastic proliferation of the cortical epithelial cells, whereas in the usual mixed type of thymoma and the medullary type no gross invasion or metastases were noticed.

These results are discussed in view of recent concepts and immunological findings of thymus microarchitecture.

Key words: Thymus epithelial cells – Thymoma – Myasthenia gravis

Several reports have pointed out the complex microtopographical organization of the thymus. Ultrastructural and ontogenetic studies in human thymus (Bloodworth et al. 1975; Rosai and Levine 1976; v. Gaudecker and Müller-Hermelink 1980; v. Gaudecker 1985), immunological investigations in the mouse (Wekerle et al. 1980; Rouse and Weissman 1981; Raedler et al. 1983), and man (Ritter et al. 1981; Haynes et al. 1983; Steinmann and Müller-Hermelink 1984; Müller-Hermelink and Steinmann 1984; Janossy et al. 1985), and enzyme histochemical observations in man (Müller-Hermelink 1977; Hirokawa et al. 1983) have dealt with the heterogeneity of thymic epithelial cells (EC). According to these studies the two basic cellular com-

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partments of the thymus, cortex and medulla, present different microenvironments necessary for normal production of T lymphocytes. At least five topographically and phenotypically distinct EC types have been defined: a flat layer covering the thymic lobules, thymic nurse cells (TNC) localized in the subcapsular cortex, dendritic cortical epithelial cells, medullary epithelial cells, and squamous epithelial cells forming Hassall's bodies. The presence of neuroendocrine cells in the human thymus is very likely (Rosai and Higa 1972); these cells were extensively studied in the avian thymus (Håkanson et al. 1974), where granule-containing cells were found close to or joined to myoid cells (Kendall and Frazier 1979). In addition to EC, different non-lymphoid mesenchymal cells are present: macrophages in the thymus cortex, medulla, and around cortico-medullary junction; interdigitating reticulum cells (IDC) in the medulla (Kaiserling et al. 1974). In the human thymus, myoid cells were observed early in fetal life (v. Gaudecker and Müller-Hermelink 1980); they are constantly found in postnatal life (Ito et al. 1969; Drenckhahn et al. 1979).

All these cells may be considered to be a complex epithelial-stromal microenvironment in which the proliferation and differentiation of T cells takes place and which is intimately involved in the regulation of cellular events in the thymus.

Several morphological (v. Gaudecker and Müller-Hermelink 1980; v. Gaudecker 1985), immunological (Weissman 1973; Bhan et al. 1980; Janossy et al. 1980; Weissman et al. 1982), functional (Papiernik and Laroche 1982), and enzymatic (Palestro et al. 1980) features may be used to distinguish cortical and medullary thymocytes. The outer thymic cortex represents the site of lymphoblastogenesis with large immature lymphoid cells as predominant cellular component. In the deep cortex small thymocytes prevail (Weissman et al. 1982) whereas in the medulla mostly mature peripheral-type T cells are localized (Scollay et al. 1980).

Although the epithelial structure of the thymus is obscured by the lymphoid component the two main complex microenvironments of the thymus, the cortex and medulla, may be recognized by distinct EC types in normal biopsy material. This prompted us to study the epithelial thymic tumours, the thymomas, in order to identify microstructural features related to the normal EC of the thymus. We were able to define different types of thymoma: namely cortical, medullary, and mixed. The following paper deals with the cytological and histological features of thymoma defined according to the light microscopical characteristics of their EC. It provides data of clinical relevance of a retrospective study on our material. Since cytological features of EC are essential for the distinction of different types of thymoma, we will first briefly illustrate the main light microscopical features of cortical and medullary EC in routine paraffin sections.

Material and methods

Normal thymic tissue. Thymuses from 70 patients undergoing cardiac surgery were examined. Their age varied from 4 months up to 71 years; no alterations of the immune system were found during the clinical preoperative examination. Tissue samples were fixed in Bouin's fixa-

Table 1. Clinical and histopathological data of 58 cases of thymoma

Case No.	Age/sex	Assoc. syndrome	Biopsy site	Histol diagnosis	Remarks
1	40 y, F	–	Mediast. tum.	Cort.	Tumour with infiltration of adipose tissue
2	45 y, M	–	Mediast. tum.	Cort.	After 4 years recidive with pleural infiltration
3	57 y, M	Myasthenia	Mediast. tum.	Cort.	–
4	45 y, F	–	Mediast. tum.	Cort.	Mediastinal, pleural and diaphragmatic infiltration
5	7 y, F	–	Mediast. tum.	Cort.	–
6	72 y, F	–	Thoracal wall	Cort.	Mediastinal tum. with parasternal and intrathoracal metastases

tive or in buffered formalin, and embedded in Paraplast. Five μ thin sections were stained with Haematoxylin-Eosin, Giemsa, PAS, and Gomori's silver stain.

Epithelial thymic tumors. A total of 71 epithelial thymic tumours received in a 16 years period (1967–1983) were examined; 45 derived from the Lymph Node Registry at the Institute of Pathology in Kiel, 26 from the Katharinenhospital in Stuttgart[1]. Only biopsy material was considered. Non-epithelial tumours, or epithelial tumours of possible metastatic origin were discarded; a thymic hamartoma was also excluded. All the biopsies considered were derived from completely or subtotally resected mediastinal tumors, with the exceptions of 3 cases, in which intrathoracic (2 cases) or extrathoracic (1 case) metastases were examined: however, in all these cases the existence of a histologically and/or clinically diagnosed primary mediastinal tumour was certain.

Due to the character of "reference" center of the Institute of Pathology of Kiel for tumours of the lymphoid system, many tumours were received after the sampling was accomplished elsewhere. Therefore the macroscopical appearance of the tumour was not always reported; no obvious variations were noticed comparing the described aspects (Rosai and Levine 1976; Snover et al. 1982). The number of samples examined for each tumour varied: in 35 cases several fragments were available; in 26 cases 2 specimens and in 10 cases only 1 sample could be examined. In all cases HE, Giemsa, PAS, and silver stained sections were available.

Clinical features of thymoma. The essential clinical features of 58 thymoma cases are reported in Table 1 and 3. Due to the retrospective character of our study "malignant" or "benign" behaviour refers mainly to the clinical evaluation at the moment of the surgical intervention, i.e. the malignant tumours being designated by the local invasiveness (Batata et al. 1974) and/or the presence of intrathoracal metastases. When available, follow-up data were included in Table 1.

The invasive tendency of the tumours is judged histologically: malignant growth was assumed if invasion of either large veins, adipose tissue or adjacent organs is seen. Encapsulated tumours often show invasion of the inner aspect of the capsular area. Therefore, like in endocrine tumours, malignant growth was assumed only if the tumour obviously break through the whole capsule and invade the surrounding tissue.

All consulting pathologists and surgeons got a questionnaire asking for detailed follow-up data. Due to the long period needed for the collection of cases and the diverse hospitals involved in the primary care of the patients, many patients, however, were lost from the files. Therefore long-time follow-up data were available only in a minority of cases, these data are included in Table 1.

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Table 1 (continued)

Case No	Age/sex	Assoc. syndrome	Biopsy site	Histol. diagnosis	Remarks
7	62 y, M	–	Mediast. tum.	Cort.	–
8	44 y, F	Low grade myasthenia; hypergamma-globulinaemia	Mediast. tum.	Cort.	Pleural infiltration
9	42 y, F	–	Mediast. tum.	Cort.	Locally invasive tumour
10	48 y, F	–	Mediast. tum.	Cort.	Capsule infiltration
11	66 y, F	–	Mediast. tum.	Cort.	Local invasion. Death in the same year
12	32 y, M	–	Mediast. tum., thoracal and diaphragmatic metastases	Cort.	Inoperable tum. infiltrating paravertebral region and both sides of diaphragm
13	30 y, M	–	Pleural metastasis	Cort.	Mediastinal tum. with multiple pleural metastases
14	51 y, F	–	Mediast. tum.	Cort.	Inoperable tum. with lung and diaphragmatic metastases
15	16 y, M	–	Mediast. tum.	Cort.	–
16	58 y, F	–	Mediast. tum.	Cort.	Pleural, diaphragmatic, and lung metastases
17	49 y, F	–	Mediast. tum.	Cort.	–
18	51 y, M	Myasthenia since 10 years	Mediast. tum.	Cort.	Lung infiltration; myocardial metastases
19	52 y, F	Myasthenia	Mediast. tum.	Cort.	Infiltration of lung and pericardium. Death 20 days after surgical intervention (bronchopneumonia)
20	62 y, M	–	Mediast. tum.	Cort.	Capsule infiltration
21	56 y, F	Myasthenia	Mediast. tum.	Cort.	8 months later development of a lymphoblastic lymphoma, convoluted-type
22	51 y, M	–	Supra-clavicular lymph node	Cort.	1 year before biopsy, diagnosis of lymphocyte-rich thymoma in a mediastinal tumour
23	45 y, F	Collagenose	Mediast. tum.	Cort.	Mediastinal tum. with intrathorocic metastases (pleura, lung, pericardium)
24	28 y, M	Myasthenia	Mediast. tum.	Cort.	Histologically capsule infiltration
25	72 y, M	–	Mediast. tum.	Cort.	Inoperable mediast. tum. with local infiltration, pleural and lung metastases
26	not det., M	Myasthenia	Mediast. tum.	Mixed, common	–
27	70 y, F	–	Mediast. tum.	Mixed, common	–
28	63 y, M	–	Mediast. tum.	Mixed, common	Clinically benign
29	46 y, F	–	Mediast. tum.	Mixed, common	Histologically incomplete capsule

Table 1 (continued)

Case No	Age/sex	Assoc. syndrome	Biopsy site	Histol. diagnosis	Remarks
30	63 y, F	Suspect of latent myasthenia	Mediast. tum.	Mixed, common	–
31	49 y, F	–	Mediast. tum.	Mixed, common	Clinically benign
32	54 y, M	–	Mediast. tum.	Mixed, common	Clinically benign
33	not det., M	–	Mediast. tum.	Mixed, common	Clinically benign
34	39 y, F	–	Mediast. tum.	Mixed, common	Clinically benign
35	60 y, F	–	Mediast. tum.	Mixed, common	Clinically benign
36	49 y, M	–	Mediast. tum.	Mixed, common	Clinically benign
37	66 y, M	–	Mediast. tum.	Mixed, common	–
38	54 y, F	–	Mediast. tum.	Mixed, common	Histologically incomplete capsule
39	50 y, F	–	Mediast. tum.	Mixed, common	–
40	55 y, F	–	Mediast. tum.	Mixed, common	Clinically benign
41	55 y, F	–	Mediast. tum.	Mixed, common	Clinically benign
42	56 y, M	–	Mediast. tum.	Mixed, common	–
43	60 y, F	Myasthenia	Mediast. tum.	Mixed, common	Clinically benign
44	53 y, M	Myasthenia	Mediast. tum.	Mixed, common	Clinically benign
45	48 y, M	–	Mediast. tum.	Mixed, common	Capsule micro infiltration
46	69 y, F	Myasthenia since 3 months	Mediast. tum.	Mixed, common	Clinically benign
47	65 y, F	–	Mediast. tum.	Mixed, cort. predom.	–
48	53 y, M	Myasthenia since 8 weeks	Mediast. tum.	Mixed, cort predom.	Histologically: perineural infiltr. 15 months later the patient was living and without recurrence
49	27 y, F	Hypergamma-globulinaemia	Mediast. tum.	Mixed, cort. predom.	Mediast. tum. with pleural, lung and pericardial infiltration
50	not det., M	–	Mediast. tum.	Mixed, cort. predom.	–
51	54 y, M	–	Mediast. tum.	Mixed, cort. predom.	Capsule infiltration
52	47 y, F	–	Mediast. tum.	Mixed, med. predom.	–
53	38 y, F	–	Mediast. tum.	Mixed, med. predom.	Clinically benign
54	62 y, M	–	Mediast. tum.	Mixed, med. predom.	–
55	50 y, M	–	Mediast. tum.	Mixed, med. predom.	Clinically benign
56	56 y, F	–	Mediast. tum.	Medullary	Clinically benign
57	49 y, M	–	Mediast. tum.	Medullary	–
58	67 y, M	–	Mediast. tum.	Medullary	Clinically benign

Results

Morphology of cortical and medullary epithelial cells in routine sections

In the normal human thymus, EC form a lymphocyte-entrapping meshwork, showing zonal differences in density and cytology. At the light microscopical level, the EC of the thymic cortex are recognized as large cells, with round-oval nucleus, showing a very loose chromatin structure and a distinct, medium-sized, round nucleolus (Fig. 1 a). The cytoplasm is hardly seen. Sometimes eosinophilic, only faintly stained cytoplasmic processes are found in between adjacent lymphatic cells. At the surface of the thymic lobules, a layer of smaller, flattened EC is seen, that borders a continuous basal lamina seen in reticulin stain. In the deep cortex, the density of EC is lower, however, the morphology of cortical cells has the same character as in the outer cortex; cell cytoplasm and processes are hidden by tightly packed thymocytes (Fig. 1 b). The large lymphoid cells ("lymphoblasts") are mainly distributed in the outer cortex. They are often observed close to cortical epithelial cells (Fig. 1 a). Many mitoses occur in the lymphoid cell population.

In the medulla, EC are more polymorphic. Some cells show the criteria of cortical EC. The main epithelial component contains a smaller, oval or spindle shaped nucleus. The chromatin structure is coarser than in the cortical EC; 1–2 small nucleoli may be observed. The cytoplasm is fusiform and eosinophilic; EC processes form a connecting network (Fig. 1 c). Scattered Hassall's bodies are formed by squamous EC that frequently are surrounded by fusiform EC of medullary type. In the medulla, the lymphocytes are small, with the dark pleomorphic nucleus of the mature T lymphocyte. No mitoses are seen. Macrophages and other blood cells are easily discernible. IDC are difficult to recognize in paraffin sections.

At the cortico-medullary junction a mixture of cortical and medullary EC is observed. The perivascular spaces are surrounded by a flat layer of EC; within these spaces lymphoid cells of different cytological features

Table 2. Differential characteristics of cortical and medullary thymic EC in light microscopy

	Cortical	Medullary
Shape	Stellate	Spindle with cytoplasmic processes
Nucleus		
Shape	Oval-round	Oval-spindle, often with irregular contour
Size	Medium-large	Small-medium
Character	Thin and distinct nuclear membrane, very loose chromatin (clear nucleus)	Distinct nuclear membrane, finely distributed heterochromatin
Nucleolus	1, often prominent, round, central	+/−, little, not prominent
Cytoplasm	Scant, clear or faintly eosinophilic	Scant, dense eosinophilic, mostly represented by the cellular processes
Cytoplasmic processes	Very thin, faintly eosinophilic	Long, thin, eosinophilic

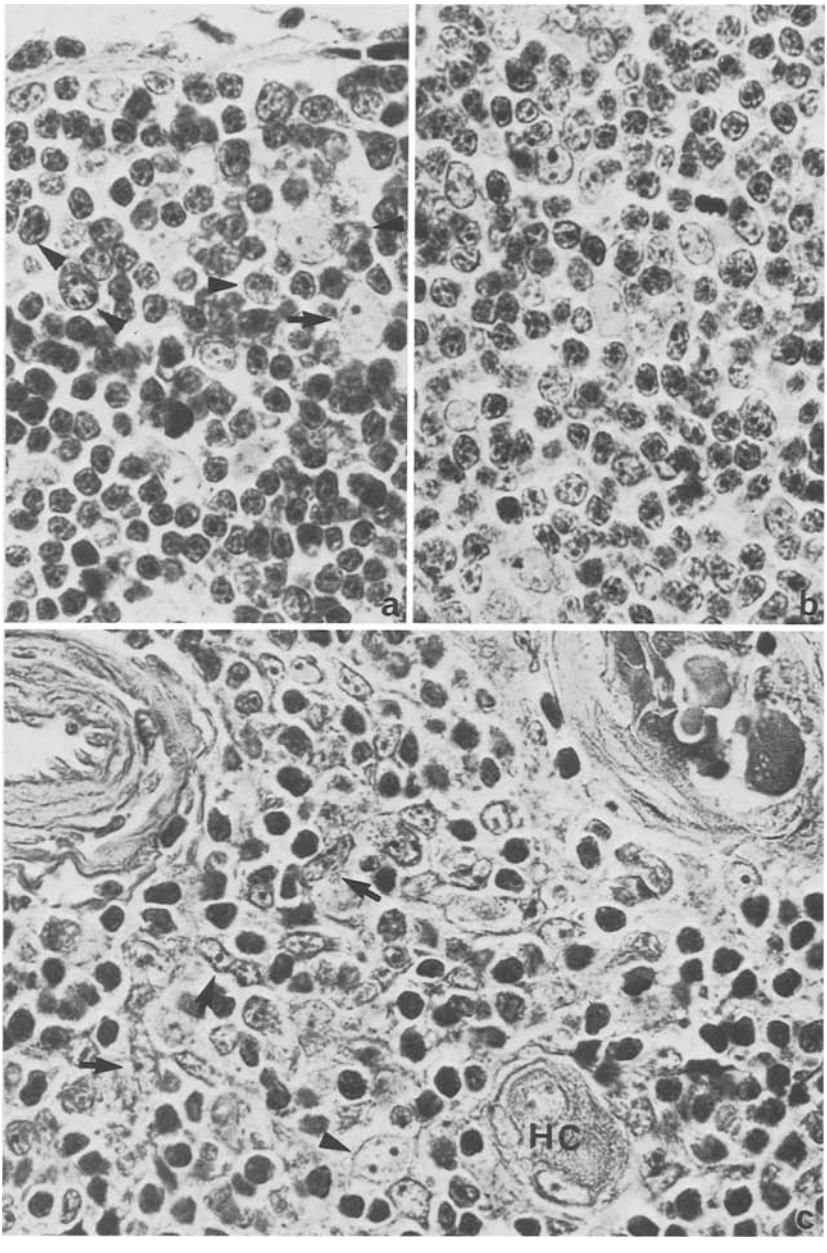

Fig. 1 a–c. EC in thymus. **a** Outer cortex: round-oval nuclei of EC of cortical type, with conspicuous nucleoli (*arrow*) are seen in between small, medium and large (*arrow head*) lymphocytes. Flattened EC surround the lobule. **b** Deep cortex: cortical type EC surrounded by the cortical type of lymphoid cell population. Mitoses are seen. **c** Medulla: EC of medullary type with spindle-shaped nucleus, coarser chromatin structure, small nucleoli, and long anastomosing cell processes (*arrow*) surrounded by small lymphoid cells with dark, pleomorphic nucleus. A large EC of cortical type is seen (*arrow head*). Two Hassall's bodies are present (HC) (15 months-old boy). Giemsa, 900 ×

including plasma cells are found. The cytological characteristics of the two basic cortical and medullary type of thymic EC are summarized in Table 2. The description refers to Giemsa stained tissue sections.

Thymic epithelial tumours

Microscopic findings: 71 cases of primary thymic epithelial tumours were divided in two groups: 58 cases were diagnosed as thymoma and 13 as thymic carcinoma. The term *thymoma,* as usual, was applied for all the neoplasms of thymic EC (Castleman 1955; Rosai and Levine 1976; Levine and Rosai 1978) without or with minimal cytological atypia, irrespective of their clinical behaviour. These tumours often have a high, but varying content of non-neoplastic lymphoid cells. The thymoma in this definition includes the usual cases of thymoma and the category I of malignant thymoma, according to Levine and Rosai (1978). The term *thymus carcinoma* has been used for all tumours characterized by an invasive almost pure EC growth. EC differ from the normal thymic EC and show cytologically all criteria of malignancy. These tumours may be classified like carcinoma of other sites and organs. In our series this group corresponds to the category II of Levine and Rosai (1978).

Thymoma

From the cytological features of EC, 3 types of thymoma were distinguished: I. cortical, II. mixed, showing the proliferation of cortical and medullary EC, and III. medullary. In the mixed type the relative amount of cortical and medullary EC was judged arbitrarily. Therefore, an almost equal mixture of the different EC was called "common" and distinguished from cases with predominance of either cortical or medullary EC.

I. Cortical type of thymoma

Thymoma of cortical type contain EC morphologically similar to the cells found in the normal thymus cortex. Furthermore, the lymphocytes resemble the cortical thymocytes. The relative amount of EC is much higher than in the normal thymus. Areas of almost pure epithelial growth may be found.

The cytological features of cortical types of thymoma are as follows:

(1) Cortical EC: In the neoplastic cortical EC the nuclei may be of the same size or often larger and the cytoplasmic processes are broader and more conspicuous than in the normal thymus cortex. Cortical cell nuclei are of round or oval shape. The nuclear staining of these EC is always very clear. In the center of the nucleus one round, very prominent nucleolus is seen (Fig. 2a). The cytoplasm is scant and may hardly be seen in between adjacent lymphoid cells. Sometimes, however, the EC form continuous sheets showing a broad, faintly eosinophilic cytoplasm. Occasionally. EC form the border of small cysts, giving the appearance of a microcystic transformation (Fig. 2b, c). Epithelial mitoses are not obvious and, if at all, are observed very rarely.

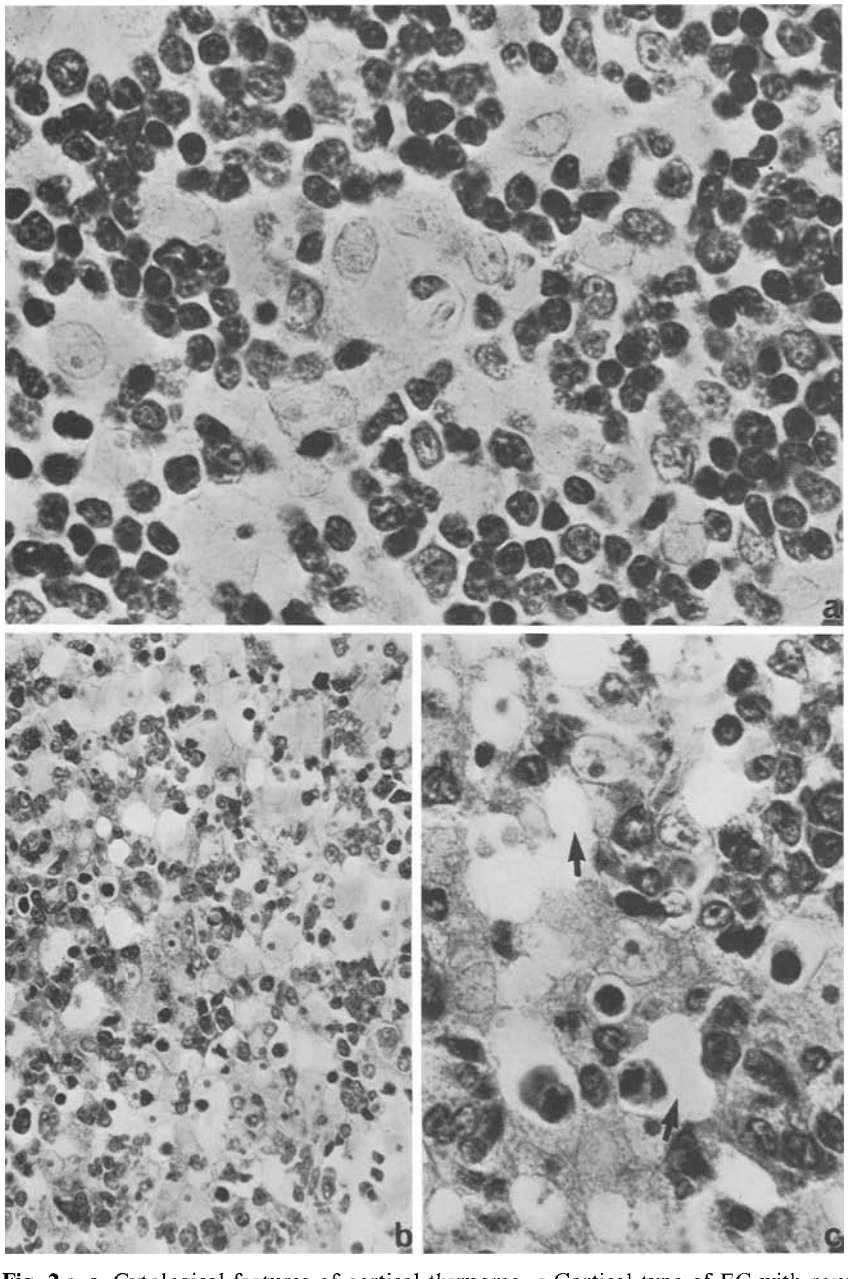

Fig. 2 a–c. Cytological features of cortical thymoma. **a** Cortical type of EC with round-oval, large, clear nucleus, surrounded by small, medium and some large lymphoid cells (case no. 24). Giemsa 900×. **b** TNC containing thymoma: Sheets of EC with morphological features of cortical EC containing grouped lymphoid cells in the cytoplasm as typical for the normal TNC (case no. 10). Giemsa, 350×. **c** TNC-like EC at high magnification: In the large cytoplasm numerous lymphoid cells, small, medium-sized or large with irregular nuclear outlines are found. Some mitoses are seen. The cytoplasms of TNC form sometimes the border of small cysts (*arrow*) (case no. 10). Giemsa, 900×

(2) Thymic nurse-cell (TNC): In all cortical thymoma we observed EC recalling the structural features of thymic "nurse-cell" (Wekerle et al. 1980; Ritter et al. 1981; v.d. Wijngaert et al. 1983). These cells or cell complexes differ from the normal type of cortical EC by an enlarged cytoplasm that is loaden with lymphoid cells in variable number up to 10–15 (Fig. 2b). The EC are connected to each other by enlarged faint eosinophilic cytoplasmic processes. The lymphoid cells lying in the cytoplasm have a vital appearance and undergo mitosis (Fig. 2c). The amount of these cells varied in different thymoma. Some tumours consisted almost exclusively of EC with features of TNC.

(3) Lymphoid cells: Cortical thymoma contain the "cortical" type of thymocytes, i.e. in addition to small round lymphocytes, many medium-sized, round and large lymphoid cells ("lymphoblasts") with round or convoluted nuclei and narrow basophilic cytoplasm are present (Fig. 2). The relative amount of lymphoblasts is variable up to tumours predominantly containing lymphoblasts (even in a metastasis) (Fig. 10). Very frequent lymphoid mitoses are observed in these tumours. A narrow contact of EC to lymphoid cells is always seen. The lymphocytes in TNC are mostly of medium size, round or large with irregular or convoluted outlines (Fig. 2b, c).

Histological pattern of cortical type of thymoma. Cortical thymoma show a nodular growth pattern forming tumour nodules of different size; tumours with high EC/lymphocyte ratio tend to be organized into smaller nodules than tumours rich in lymphocytes. Thin connective bands may partially or totally delimit or separate a tumour nodule (Fig. 3a). The whole tumour may either be well circumscribed by fibrous tissue; sometimes, however, the border of the nodules is unsharp giving the impression of invasive growth. The invasion of adjacent tissue (large veins, mediastinal fat tissue, pleura or lung) is frequently found (Fig. 3b). Cortical EC are able to form rather ordered lobular structures, reminescent of the normal thymic cortex. An epithelial continuous row of parallel cells is then seen at the nodule boundary, with PAS-positive, basal-membrane-like material and/or a layer of small flat EC surrounding the lobules. The relative EC density often decreases from the external to the internal part of the lobule. In lymphocyte-rich tumours a careful search is needed to see the epithelial component and to recognize the typical cytological features. Macrophages are frequently seen, containing cellular debris, giving a typical starry sky appearance (Fig. 3c).

Cortical thymoma may show the cortical type of epithelial and lymphoid cells exclusively. However, in some cases, scattered, circumscribed areas are seen where the lymphocytes are smaller and more pleomorphic, similar to mature small lymphocytes. Here some fusiform EC resembling the normal thymic medullary EC may be seen. Hassall's bodies are very rare. These areas correspond to a medullary differentiation as described by Rosai and Levine (1976). The predominating large cortical areas surrounding small "medullary" areas give rise to an organoid pattern strongly suggestive of

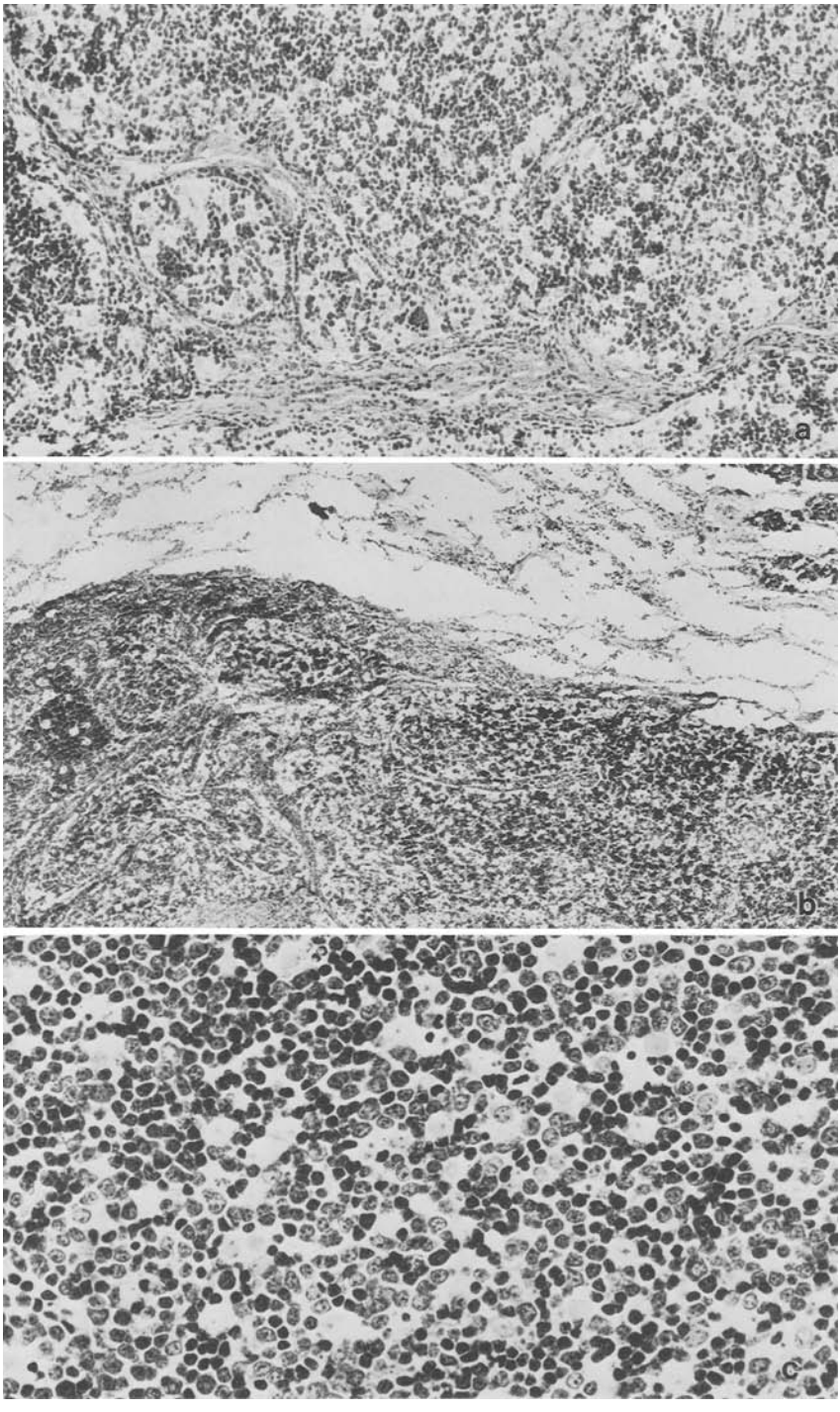

Fig. 3 a–c. Histological features of cortical thymoma. **a** Nodular growth pattern with formation of smaller lobules by thin connective bundles. Numerous EC are seen by their clear appearance contrasting to the lymphoid background (case no. 19). Giemsa, 140×. **b** Invasive growth of cortical type thymoma into lung tissue (case no. 19). Giemsa, 60×. **c** Lymphocyte-rich cortical type of thymoma: scattered EC of cortical type are seen. Many macrophages containing cellular debris confer a starry-sky aspect. Lymphoid cells are small, medium or large. Note resemblance to normal thymus cortex (case no. 17). Giemsa, 350×

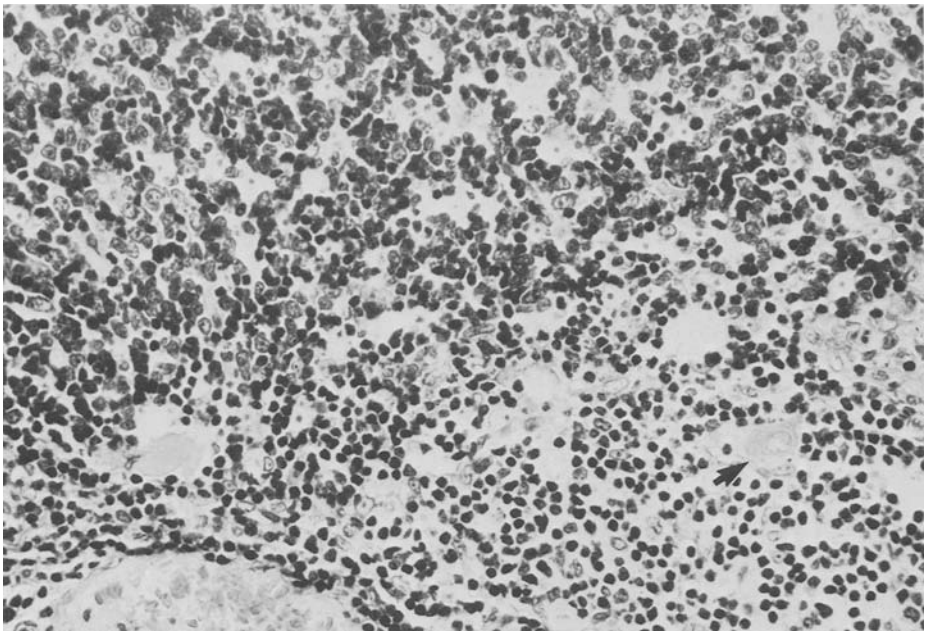

Fig. 4. Organoid pattern in cortical thymoma. Cortical EC combined with a lymphoid cell population of cortical type surround a lighter area rich in EC of medullary type; lymphoid cells in this area are of medullary type, too. A small Hassall's body is seen (*arrow*). An organoid picture, with "cortex" surrounding "medulla" is seen (Case no. 1). Giemsa, 350 ×

the normal thymic structure (Fig. 4). However, in these "medullary" areas the content of cortical type EC is at times higher than in the normal medulla. As additional characteristic feature EC often form conspicuous perivascular palisading or ordered, columnar, radial structures around perivascular spaces. The latter are rare in this tumour group and are mainly found in tumors rich in lymphocytes.

II. Mixed type of thymoma

The mixed thymoma are characterized by the proliferation of both cortical and medullary EC types. They grow together, forming loose or dense meshworks, with a variable ratio of cortical and medullary EC types in different cases. The epithelial/lymphocyte ratio also shows a wide range of variation in different areas of the same tumour. The lymphocyte number, however, is usually high. The usual mixture of EC types in mixed tumours is referred as the common type, while the predominance of areas similar to pure cortical or pure medullary thymoma (more than 75% of tumour area) is referred as mixed thymoma with cortical or medullary predominance.

The cytological features of mixed type of thymoma are as follows:

(1) Epithelial cells: The cytological appearance of most EC types is quite similar to their normal counterparts in cortex and medulla (Fig. 5). Thus, also the cortical EC type is usually not as large as often found in the

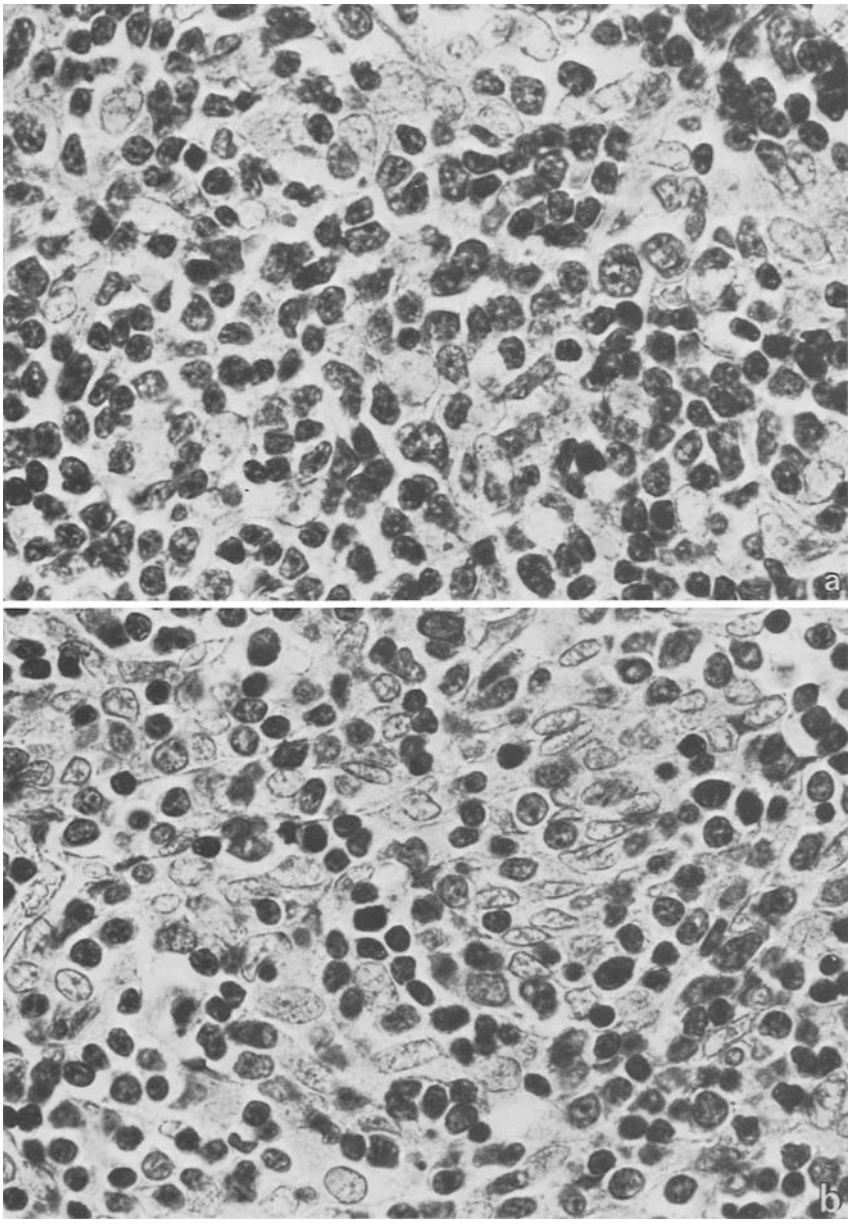

Fig. 5 a, b. Cytological features of mixed type of thymoma. EC of cortical type with large, round-oval, clear nucleus and round nucleolus grow tightly intermingled with spindle-shaped medullary type EC. Small and medium-sized lymphocytes predominate. Regional differences in the amount of cortical and medullary type of EC and in the morphology of the lymphoid component are seen. **a** Region rich in cortical type EC. **b** Region rich in medullary type EC (case no. 38). Giemsa, 900 ×

thymoma of cortical type. The clear nuclear staining and a distinct nucleolus are present as in the normal cortical EC. In the loose network of EC often the nuclei of cortical cells are slightly elonged. Medullary cells have a smaller oval spindle-shaped nucleus with coarser chromatin. Thin, anastomosing cell processes of both cell types are seen when loose networks are formed. The cytoplasm is hardly seen.

Not all EC, however, correlate strictly to the cortical or medullary type of EC. There are also EC cytologically intermediate to cortical or medullary EC types. These cells often are seen also at the border of perivascular spaces and in papillary structures (see below). These cells are of cylindroid shape, their nucleus is medium-sized, round-oval, without prominent nucleoli, and their cytoplasm has indistinct borders (Fig. 7). From the cytological features and their distribution these cells are reminescent of the subcapsular layer of EC cells at the thymus surface and the perivascular spaces.

(2) Lymphoid cells: Predominantly small and medium-sized, round lymphocytes, in high number, accompany the epithelial growth. Lymphoblasts are found mainly in areas rich in cortical EC. In these regions lymphoid mitoses are more frequent than in the areas populated mostly by small lymphocytes. The amount of immature cells is considerably lower than in cortical thymoma.

Histological pattern of mixed type of thymoma. (a) Mixed type of thymoma, "common": Most often, cortical and medullary EC are found intermingled. However, EC density and the ratio of cortical and medullary EC may vary considerably also in individual cases in different areas of the tumour. The histological features are also different in tumours with high or low content of lymphoid cells.

Lymphocyte-rich tumours or tumour areas: In some cases EC form loose meshworks entrapping many lymphocytes. Then very large tumoral nodules are formed, that are delimited by dense strands of fibrous connective tissue. Fibrous trabeculae may partially delimit and traverse these nodules (Fig. 6a). At low magnification the picture is monotonous. Perivascular spaces are often present, bordered by EC that are not so prominent as in the pure type of cortical thymoma. Often the perivascular space is dilated and may contain densely packed lymphocytes (Fig. 6b). Some areas are reminiscent to medullary differentiation; an organoid pattern, however, is encountered mainly in the cases with cortical predominance described later.

EC-rich tumours or tumour areas: In areas rich in EC the two EC types grow tightly intermingled surrounded by bundles of spindle cells (Fig. 6c). The lymphocyte content is usually low. Plump, round-oval clear EC nuclei of cortical type are seen alternating with the smaller spindle-shaped nuclei of medullary EC. The EC are variably orientated, sometimes they are arranged in a rosette configuration, with polar peripheral nuclear localization and centripetal slightly eosinophilic cytoplasm. In such areas perivascular spaces are rare. In both histological patterns we observed the intermediate EC already mentioned, forming almost pure epithelial sheets with pseudoglandular and cystic structures (Fig. 7), surrounding perivascu-

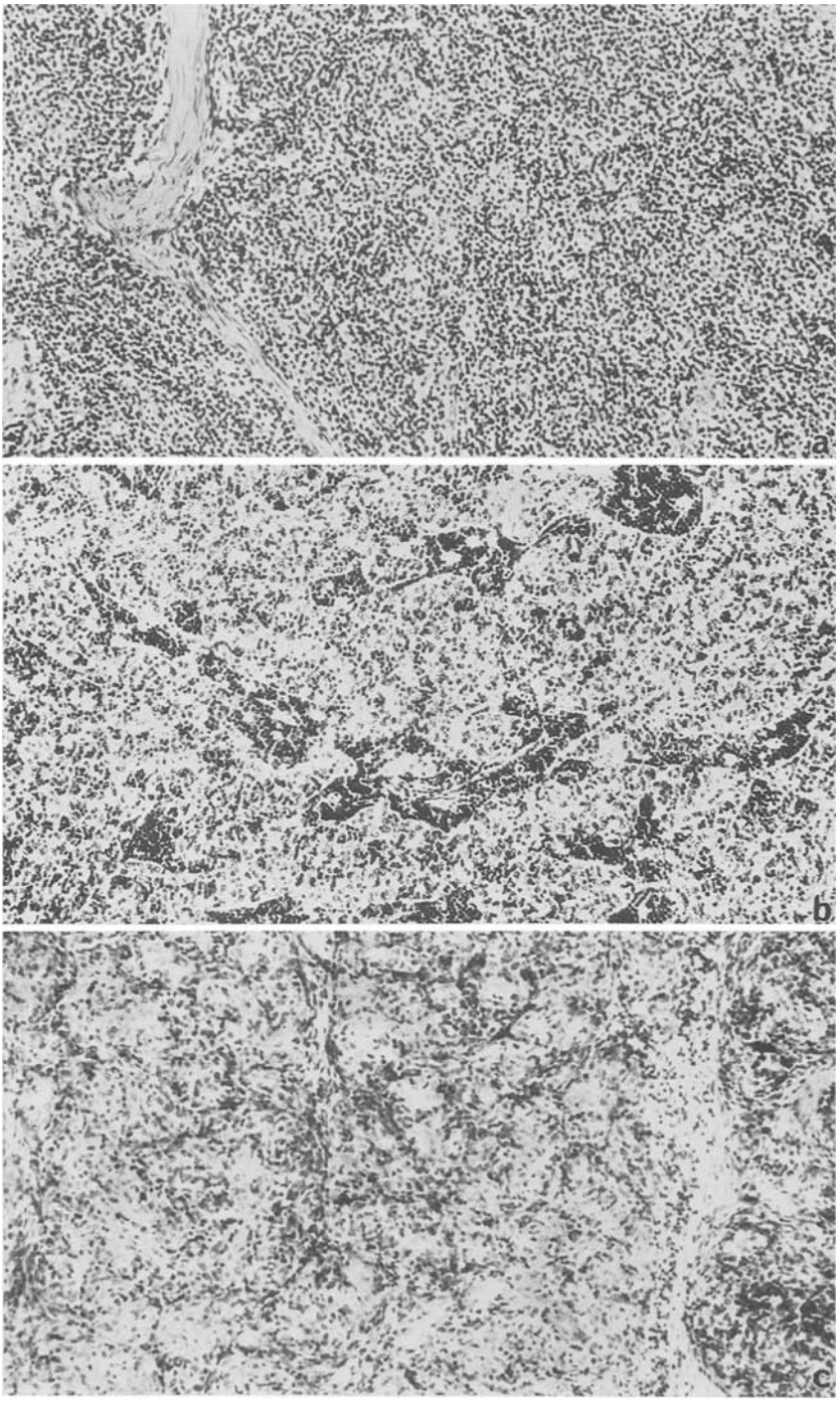

Fig. 6 a–c. Histological features of mixed type of thymoma. **a** Lymphocyte-rich area delimited by fibrous connective tissue: monotonous picture (case no. 39). Giemsa, 60×. **b** EC-rich area of thymoma, densely packed lymphoid cells in the perivascular areas (case no. 34). Giemsa, 140×. **c** Formation of small lobules (case no. 43). Giemsa, 140×

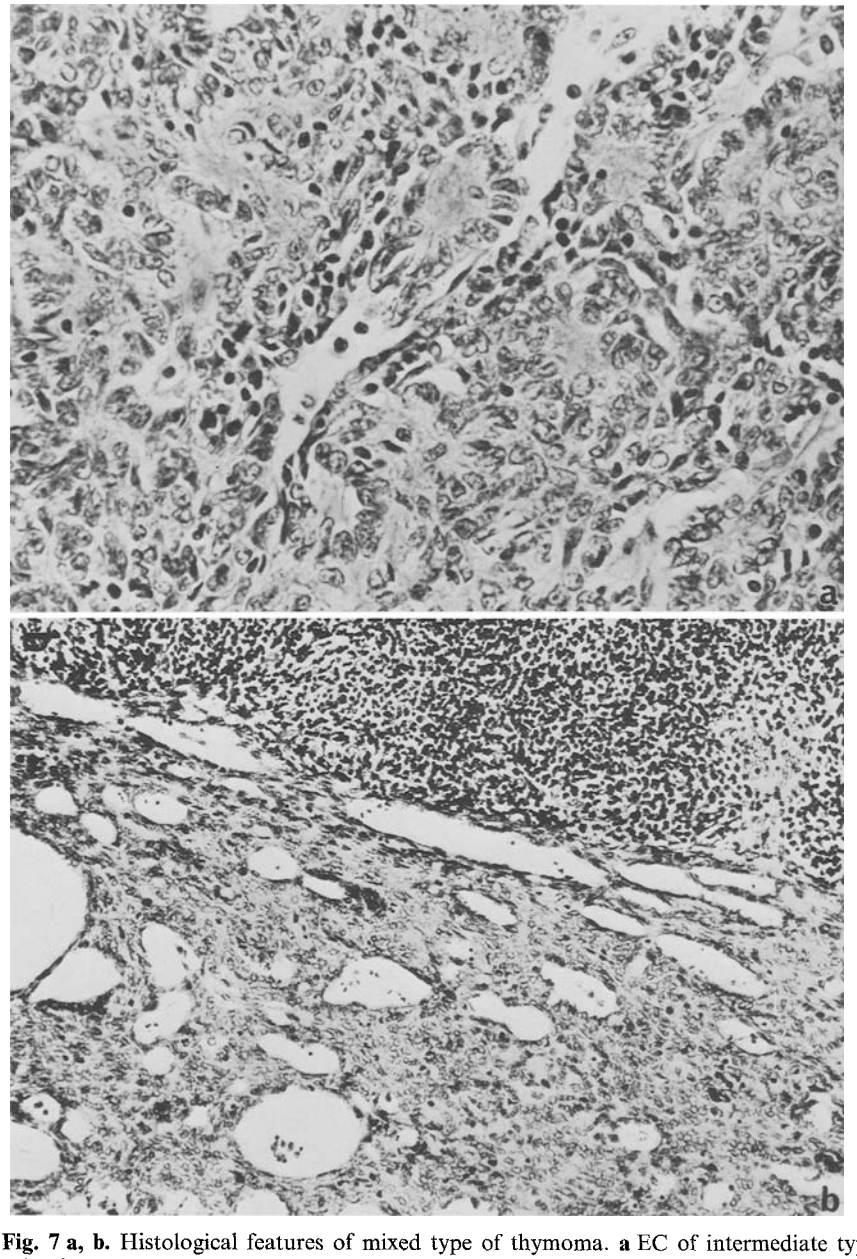

Fig. 7 a, b. Histological features of mixed type of thymoma. **a** EC of intermediate type and EC of medullary type bordering perivascular spaces and showing rosette-like arrangement (case no. 42). HE, 350×. **b** Lymphoid cell-rich and pure epithelial part of mixed type of thymoma. In the area rich in EC mostly EC of intermediate and medullary type form solid sheets and dilated perivascular spaces (case no. 33). Giemsa, 140×

lar spaces or dilated blood vessels. Similar cells are also observed in papillary structures that are found projecting in dilated perivascular spaces. Hassall's bodies may be rarely seen. With regard to the lymphoid component, medium and large lymphocytes are found in areas rich in cortical EC; mature small lymphocytes are more likely to colonize the areas rich in medullary EC. The amount of more mature appearing small lymphocytes is higher in the mixed than in the cortical type of thymoma.

(b) Mixed type with cortical predominance: In addition to areas similar to the described pattern of the mixed, common type of thymoma, large areas are found corresponding to the typical appearance of cortical thymoma. An organoid pattern of the tumours often is the result of the concomitant occurrence of areas of medullary differentiation (Fig. 8). The lymphocyte number is usually high, and their morphology is similar to that observed in cortical thymoma.

Mixed thymoma with cortical predominance may show in rare instances invasivity to surrounding tissues similar to the cortical thymoma (see below).

(c) Mixed type with medullary predominance: In some cases of mixed tumors a predominance of medullary type EC is present. Small pleomorphic mature and small round lymphocytes characterize these thymoma; moreover the amount of lymphocytes is usually lower than in cortical areas or the common type of mixed thymoma. Perivascular spaces are seldom present here and palisading of EC around vessels is not found. In EC rich areas the spindle-shaped medullary cells show different spatial orientation, thus forming a storiform growth pattern. In internodular areas thin-walled vessels, at times dilated, are present; however, true perivascular spaces are rare. Sometimes formation of epithelial rosettes occurs.

III. Medullary type of thymoma

Medullary thymoma are characterized by the proliferation of EC of the medullary type. Furthermore, lymphoid cells resemble the medullary lymphocytes of normal thymus.

The cytological features of medullary type of thymoma are as follows:

(1) Epithelial cells: The medullary EC is medium-sized and spindle shaped. The nucleus is oval or fusiform and contain a homogenous chromatin pattern that is more dense than in the cortical EC. A small nucleolus may be seen. The cell body is thin, elonged, the cytoplasm is scant and eosinophilic. The cellular processes are orientated to the long axis of the nucleus (Fig. 9a).

(2) Lymphoid cells: Lymphocytes are mostly small, with dark, round or often pleomorphic nucleus. Some medium-sized lymphoid cells are present and some of them are in mitosis.

Histological pattern of medullary type of thymoma. The arrangement of medullary-type EC and the amount of lymphocytes give these tumours different histological patterns, often encountered in the same tumour: or dense sheets of spindle EC, following different orientations where lymphocytes are ob-

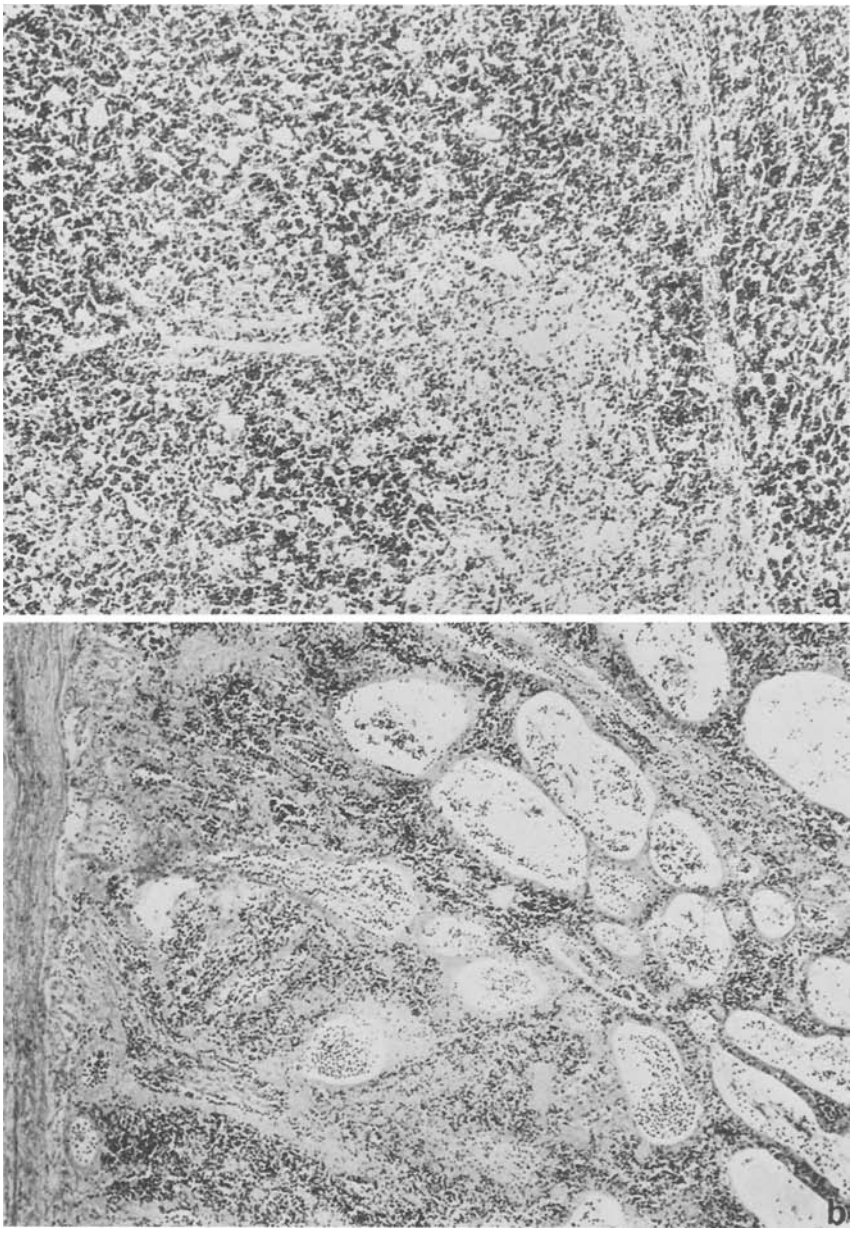

Fig. 8 a, b. Histological features of mixed type of thymoma, with cortical predominance. **a** Typical cortical area comprising mostly of the tumour. **b** Mixed type area with dilated, pseudoglandular perivascular spaces only present in a very limited part of this case (case no. 48). Giemsa, 140 ×

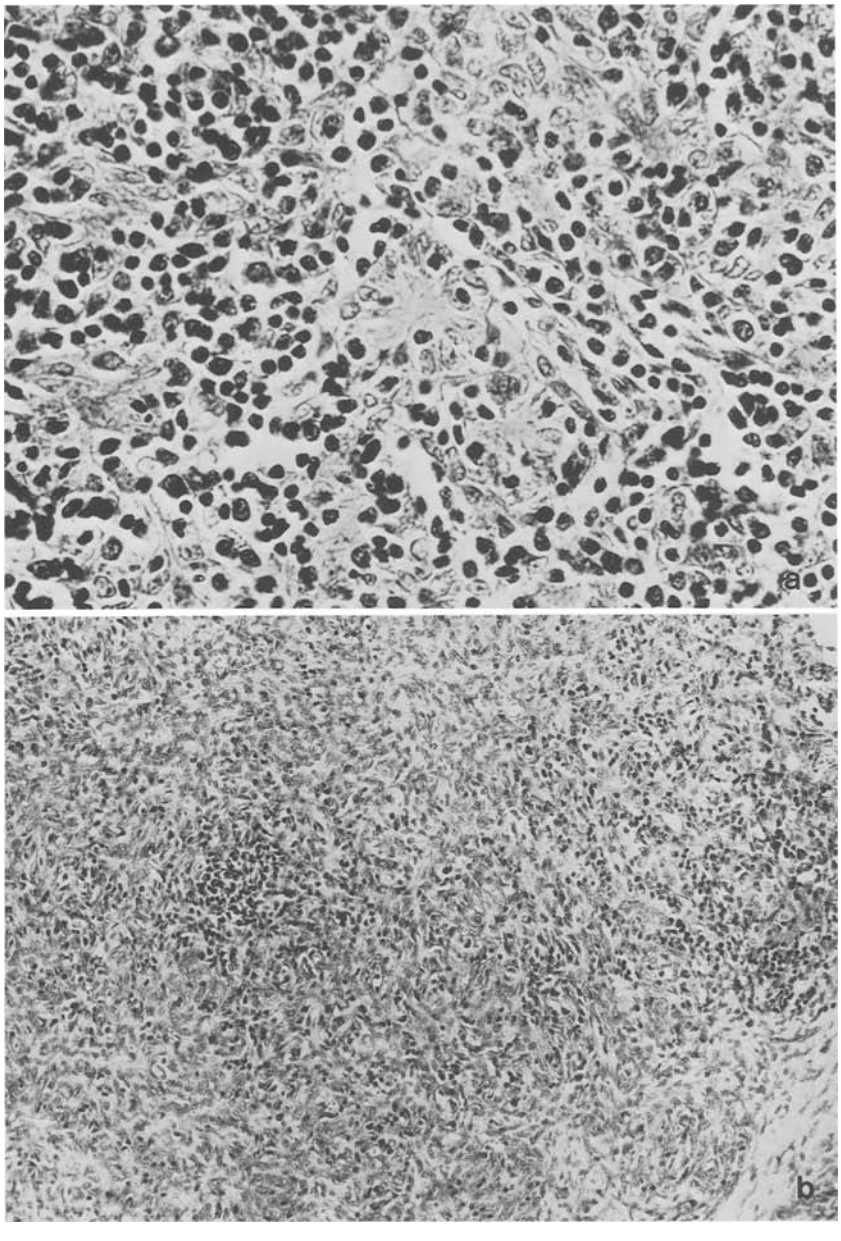

Fig. 9 a, b. Medullary thymoma. **a** Cytological features: EC of spindle shape, with spindle-shaped nucleus and thin anastomosing cellular processes. Nucleoli are not prominent. The lymphocytes are scant, predominantly small, with dark, often pleomorphic nucleus (case no. 57). Giemsa, 350×. **b** Histological features. Spindle-shaped EC grow in dense sheets with few lymphocytes in between. Tumour nodules have ill-defined borders where spindle shaped EC merge with connective tissue fibroblasts (case no. 58). HE, 140×

Table 3. Clinico-pathological characteristics of 58 cases of thymoma

Histological diagnosis	*n*	Malignant	Myasthenia	Other syndromes
Cortical	25	15	6	3[a]
Mixed				
Common	21	–	5	–
Cortical pred.	5	1	1	1[b]
Medullary pred.	4	–	–	–
Medullary	3	–	–	–
	58	16	12	4

[a] Collagen disease (1); hypergammaglobulinemia (1); lymphoblastic lymphoma, convoluted-type (1)
[b] Hypergammaglobulinemia

served only in low number (Fig. 9) or lymphocyte-rich areas with a loose epithelial network are found. However, even then the lymphocyte content is not as high as in the cortical or even mixed tumours. Often the tumour forms large nodules. In the capsule or septae dense bundles of spindle-shaped EC merge with the fibroblasts of connective tissue origin (Fig. 9b). In epithelial-rich areas of tumours, the dense sheets of spindle EC may give the impression of a mesenchymal tumour; the formations of cysts and rosettes may occur, whereas perivascular spaces are only rarely encountered. We never observed Hassall's body formation in pure medullary tumours.

Clinical features of thymoma (Table 1, 3).

Cortical type of thymoma: In our series 25 tumours were classified as cortical; at the moment of surgical intervention 14 cases were malignant, 1 case showed a tumour recurrence with pleural infiltration 4 years later and was therefore also considered to be malignant. In the recurrent tumour the cortical character of the thymoma was unchanged. The degree of malignancy was usually of low-grade, showing only local invasion but no distant metastases. The local findings were characterized by extensive infiltration of the mediastinum and of surrounding tissues and by concomitant intrathoracal implants. Distant lymphogenous or hematogenous metastases were seen in 1 case: in case no. 22 a supraclavicular lymph node was involved. Furthermore, in case no. 12 the tumour infiltration extended to the inferior diaphragmatic wall. For the cases not clinically documented, 3 showed invasion through the capsule, in 1 case the tumour showed growth into fat histologically. In 6 cases no histological signs of malignancy were observed.

In 6 cases a clinical diagnosis of myasthenia gravis was reported. In 1 case absolute hypergammaglobulinaemia was associated and in 1 case a collagen disease was mentioned. Case no. 21, a few months after diagnosis of a typical EC-rich thymoma a lymphoblastic lymphoma, convoluted type developed.

Table 4. Clinico-pathological characteristics of 13 cases of thymic carcinoma

		Number of cases	Age/Sex	Remarks
Squamous cell carcinoma[a]		1	65 y/m	Myasthenia was associated
Lymphoepithelioma-like		2	14 y/m	Local infiltration and intrathoracal metastases
			21 y/m	Death 3 years later with distant metastases
Undifferentiated		5	19 y/m	Local infiltration. Death 1 year later
			45 y/f	Lung infiltration and intrathoracal metastases
			58 y/m	–
			24 y/m	Local infiltration
			59 y/f	Local infiltration
	Oat-cell type	2	26 y/m	Local infiltration
Neuroectodermal carcinoma of the thymus			44 y/m	Distant metastases
	Carcinoid type	3	20 y/m	Local infiltration
			19 y/m	Cushing was associated. Death with distant metastases
			42 y/m	Distant metastases

[a] Well differentiated

Mixed type of thymoma: (a) Common: 21 cases were diagnosed as mixed, common. In 12 cases clinically benign behaviour was mentioned. In the remaining cases: 2 were not good delimited (partial capsular absence), 1 showed capsule microinfiltration. In the remaining 6 cases no clinical information was reported and no histological signs of malignancy were observed. Five cases were myasthenic.

(b) With cortical predominance: 5 tumours were included in this group. One was malignant (no. 49): this was a large predominantly cortical tumour, extensively sampled, in which only small areas of the mixed type were observed in a cortical type of growth. In the remaining cases, 1 showed infiltration through the capsule, 1 perineural infiltration. Two cases did not show histological signs of malignancy. Interestingly, the invasive parts of these tumours always were related to the parts showing all features of cortical thymoma. Myasthenia (1 case) and hypergammaglobulinaemia (1 case) were associated.

(c) with medullary predominance: Four cases were included. None was malignant. Two cases were clinically benign. In the other cases no histological signs of invasivity or aggressive behaviour were noticed. No myasthenia nor other syndromes were present.

Medullary type of thymoma: In our series only 3 tumours were diagnosed as pure medullary types. In 2 cases the clinical information was detailed and a benign behaviour could be assumed. In the third case no histological signs of invasive growth were found. No syndromes were associated.

Table 5. Differential histological features of thymoma types

	Cortical	Mixed cort. predominance	Mixed common	Mixed medul. predominance	Medullary
Clear epithelial cell predominance	+	+	−	−	−
Thymic nurse cells (TNC)	+	+	+/−	−	−
Starry sky pattern	+	+	+	−	−
Perivascular spaces	+/−	+/−	+	−	−
Epithelial perivascular palisading	+	+	−	−	−
Medullary differentiation areas	+	+	+/−	−	−
Epithelial cysts	−	−	+	+	+/−
Spindle cell predominance	−	−	−	+	+
Lymphoblasts	+	+	+/−	−	−

+ regularly present
+/− present in some cases
− not found

Thymus carcinoma (Table 4): 13 cases of almost pure epithelial tumours of the thymus were diagnosed as thymus carcinoma because of their cytologically and histologically unequivocal malignant character, according to the criteria of Levine and Rosai (1978). The tumours were usually locally invasive. Intrathoracal and/or distant metastases were reported in 6 cases. In our series, the observed morphological variants were comprised in previous descriptions (Rosai and Higa 1972; Rosai and Levine 1976; Shimosato et al. 1977; Snover et al. 1982; Wick et al. 1982; Wick and Scheithauer 1982). Table 4 illustrate the distribution of thymic carcinoma in our material.

Discussion

Since the work of Castleman (1955) showing that thymoma are tumours of thymic epithelial cells, much has been done to separate these tumours from others occurring in the thymic region and in the thymus, such as lymphomas, teratomas, dysgerminomas, and mesenchymal tumours (Bernatz et al. 1961; Lattes 1962; Legg and Brady 1965; Rosai and Levine 1976; Salyer and Eggleston 1976; Levine and Rosai 1978). Actually two kinds of thymic epithelial tumours have been defined: thymoma and thymic carcinoma (Rosai and Levine 1976; Levine and Rosai 1978). The latter are obviously cytologically and clinically malignant tumours, that frequently metastasize and have a poor prognosis (Rosai and Higa 1972; Rosai and Levine 1976; Shimosato 1977; Snover et al. 1982; Wick et al. 1982; Wick and Scheithauer 1982). Thymoma is referred to tumours composed of a mixture of EC and lymphocytes. There is general agreement on the neoplastic nature of the EC (Rosai and Levine 1976), whereas lymphocytes, belong-

ing to T cell lineage (Levine and Polliack 1975; Pedraza 1977; Cossman et al. 1978), are regarded as non neoplastic. Thymomas are usually encapsulated and behave as benign tumours; however, some of them recur, independently of the presence or absence of a capsule, other show local invasive growth at the time of diagnosis. Cases with intrathoracic and/or extrathoracic metastases have been reported (Gravanis 1968; Rosai and Levine 1976; Baud et al. 1981). Several thymoma classifications have been proposed, based on a variety of morphological (Bernatz et al. 1961; Lattes 1962; Legg and Brady 1965; Watanabe 1966) and histogenetical (Lowenhaupt 1948) variables and are discussed by Rosai and Levine (1976) and Otto (1984). A correlation between the histological features and the biological behaviour of these tumours, however, has not been found, although some relationship with clinical and functional features do exist (Castleman 1955; Bernatz et al. 1961, 1973; Lattes 1962; Legg and Brady 1965; Rosai and Levine 1976; Salyer and Eggleston 1976; LeGolvan and Abell 1977; Otto 1978; Gray and Gutowski 1979). The cytological variability of the thymoma EC is a well known feature: round-oval or spindle cells occur, or a mixture of both type. Rosai and Levine (1976) suggested to report the shape of the neoplastic EC in thymoma. The variations observed were interpreted as the morphological spectrum of one cell type (Rosai and Levine 1976; Gray and Gutowski 1979).

In recent years different lines of evidence indicated that thymic EC are heterogeneous in nature. Ontogenetic studies (v. Gaudecker and Müller-Hermelink 1980) have shown that the distinction between a cortical and medullary type of thymic EC is an early event in human fetal life, as early as the 8th gestational week. The electron microscopic differences attained by cortical and medullary EC persist in postnatal life (v. Gaudecker 1985) and the different ultrastructural morphology of cortical and medullary EC is a well known feature (Mandel 1968; Chapman and Allen 1971; Frazier 1973; Bloodworth et al. 1975; Rosai and Levine 1976; Singh 1981). Recently, immunological markers provided additional data to heterogeneity of thymic EC (Wekerle et al. 1980; Rouse and Weissman 1981; Ritter et al. 1981; Raedler et al. 1983; Haynes et al. 1983; Steinmann and Müller-Hermelink 1984; Janossy et al. 1985) and an immunohistological analysis of the human thymic epithelial framework has been performed elsehwere (Müller-Hermelink and Steinmann 1984). Medullary epithelial cells showed to be positive for HLA-ABC, HLA-DR, keratins and the Facteur Thymique Sérique (FTS), cortical EC did not react with some antibodies to non-squamous type of prekeratins and to FTS, while expressing HLA-ABC and HLA-DR. Additional features concern the EC of thymic surface and those bordering perivascular spaces; some of them are Leu7+ (Chan et al. 1984).

We have shown here that cortical and medullary thymic EC may be distinguished even at light microscopical level in routine histological material, since the two cell types exhibit different nuclear and cytoplasmic features.

Based on these light microscopical criteria, we studied a series of human thymomas. We found that cytological and histological patterns may be

related to the microarchitectural features of normal human thymus characterized thus far only by immunological means. The histological diagnosis of different thymoma types according to these criteria is done by the cytological recognition of the proliferating EC type. The Giemsa stain of thin sections gives a good contrast between the clear epithelial cells and the darkly stained lymphocytes. Moreover, the differences in nuclear chromatin structure are well appreciated. The presence in cortical cells of a distinct, prominent nucleolus supplies an additional important cytological criterium. The nuclear size is higher in cortical cells; the shape is round-oval in cortical and oval-spindle in medullary cells. The amount of cytoplasm is scanty in both cell types; however, the spindle-shaped cytoplasm of medullary cells is characteristic. Cellular processes are seen only when the epithelial growth is not dense, and they are more conspicuous in cortical cells. The peculiar cytological characteristics of TNC and their resemblance to cortical cells have been mentioned. EC of intermediate morphology also occur, mainly in the mixed type, and are found at the border of perivascular spaces. These cells may be morphologically related to cells bordering the outer aspect of the lobule and the perivascular spaces in normal thymus, and may represent an undetermined stage of thymic EC differentiation.

Regarding the lymphoid component, the prevalent association of medium- and large-sized lymphocytes (lymphoblasts) with pure cortical or with predominantly cortical EC-containing thymoma is a characteristic feature as well as the predominance of small pleomorphic lymphocytes in medullary or mixed tumours with medullary predominance. The close contact of lymphocytes to epithelial cells in cortical thymoma is different from the epithelial-lymphocyte relationship in medullary tumors. Lymphocyte number is high in cortical and mixed thymoma, whereas pure medullary tumours have a scanty or negligable lymphocyte component. In addition to the cytological differences, histological features belonging to different types were pointed out and summarized in Table 5. These morphological features have already been described (Castleman 1955; Bernatz et al. 1961; Lattes 1962; Legg and Brady 1965; Rosai and Levine 1976; Salyer and Eggleston 1976; LeGolvan and Abell 1977; Gray and Gutowski 1979; Otto 1984) as typical features present in some but not all types of thymoma. However, in our characterization of thymoma some proved to be characteristically associated with the cortical or medullary type of tumour proliferation.

Very large *tumour nodules,* showing a loose epithelial network and an *abundant lymphocytic content* are mainly observed in cortical and mixed types of thymoma. In cortical tumours and mixed ones with cortical predominance the light staining of large cortical cells and the associated frequent starry sky pattern provided by macrophages confer a "mottled" appearance. Microcystic growth pattern is a characteristic feature of the cortical tumour areas. Perivascular spaces are present mainly in mixed tumours, where they are surrounded by an inconspicuous epithelial palisade, and often are dilated. The cells bordering perivascular spaces in mixed thymoma and forming epithelial sheets and cysts are small, elonged and do not show nucleoli. This growth pattern differs from cortical type and mixed type with cortical

predominance, where the presence of a conspicuous perivascular palisade of large cortical cells is very characteristic. The occurrence of areas of medullary differentiation is restricted to cortical and mixed tumours mainly of cortical predominance. Hassall's bodies are very rarely found. An organoid growth pattern showing "cortex-like" and "medulla-like" areas associated to each other is a morphological feature of cortical type and mixed type with cortical predominance.

Tumours or areas of tumours *consisting almost exclusively of EC* may be found in all types of thymoma, however, EC and growth pattern are different and characteristical for the cortical or medullary type of thymoma. Papillary structures projecting in dilated perivascular spaces and rosettes were noticed in mixed type and medullary type of thymoma.

In the evaluation of extensively sampled tumours, despite to the variations in epithelial/lymphocytic ratio and their way of arrangement, an overall constancy in the type of proliferating EC was observed as already stressed by Castleman (1955): "The epithelial cells do vary in size, being from 3 to 10 times than the lymphocytes; in a given case, however, they are fairly uniform." Thymoma showing the combination of areas of cortical type largely prevailing over areas of typical mixed type were designated as mixed thymoma with cortical predominance. The inverse criteria were used for mixed thymoma with medullary predominance. Tumours containing a combination of pure cortical and pure medullary areas were not observed; however, due to the retrospective character of our study and to the inadequate sampling of some tumours, this possibility cannot be ruled out. The capsule of all types of thymoma is unsharp at its inner aspect irrespective of a benign clinical course. In these areas the cortical type of EC are prevailing. Small capsular infiltrates were observed very frequently by other authors (Jain and Frable 1974; Sundström 1975) and their clinical significance needs to be clarified. Complete invasion through the capsule, however, and invasion of surrounding adipose tissue and large veins were a feature formed only in the cortical type of thymoma and the cortical areas in mixed tumours.

The invasive tendency of cortical type of thymoma found a correspondence in the clinical behaviour of these tumours: 14 of 25 cases were locally invasive and/or intrathoracally (13) or extrathoracally (1) metastasizing, and 1 case recurred 4 years later infiltrating the pleura. 1 case with extrathoracal metastasis (no. 22; Fig. 10) exhibited EC of typical cortical type. This case was also very rich in lymphoblasts (see below). Only one other malignant case was found in the mixed group with cortical predominance. Also published cases of metastasizing thymoma, as judged by the pictures, are of cortical type (Baud et al. 1981).

Although the number of cases examined in our series does not allow a statistical analysis, we noticed that cortical tumours showed a tendency to occur in younger age than other thymoma types; furthermore, all the tumours affecting patients in the first two decades were cortical. In the literature, a generally poor prognosis for thymoma in childhood is reported (Rosai and Levine 1975; Dehner et al. 1977).

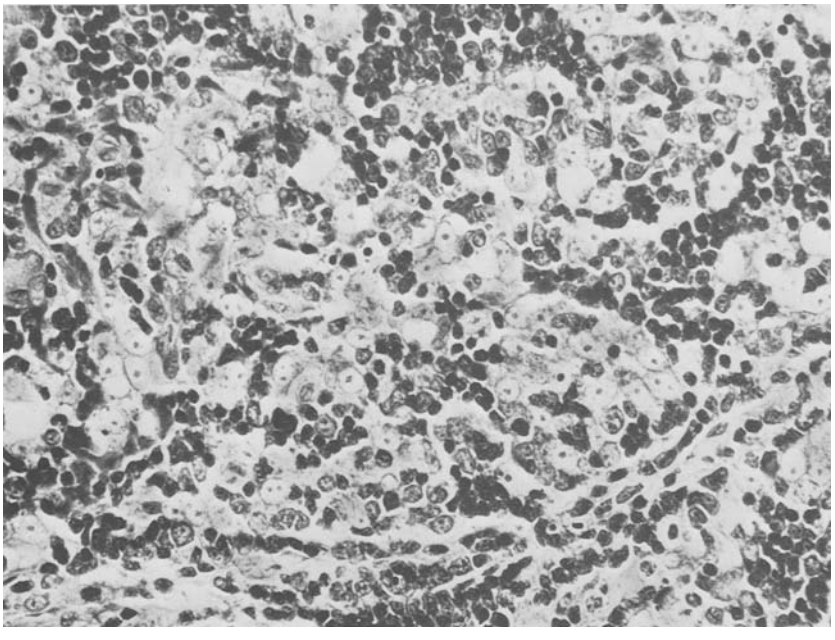

Fig. 10. Extrathoracal metastasis of thymoma (supraclavicular lymph node). Large EC of cortical type with prominent nucleoli. Thy lymphoid population is very rich in lymphoblasts; some of them have irregular nuclear contours (case no. 22). Giemsa, 350 ×

The medullary type of thymoma largely corresponds to the "spindle cell" thymoma (Levine and Bensch 1972). A further similarity of spindle cell thymoma to the thymic medulla is seen in a recent report (Lauriola et al. 1984). They describe the occurrence of IDC-like cells in thymoma, reactive with an anti-S-100 antibody. These cells were frequently found in spindle cell thymoma, and rarely in round-oval cell thymoma. In the normal thymus IDC were found only in the medulla (Kaiserling et al. 1974). In our study, medullary tumours and mixed ones with medullary predominance show a benign clinical behaviour. This corresponds to the benign character of spindle-cell epithelial thymoma (LeGolvan and Abell 1977; Levine and Rosai 1978).

The occurrence of myasthenia gravis associated with thymoma was found only in tumours containing the cortical type of EC.

The medullary type of thymoma or mixed type with medullary predominance did not show any associated syndrome in our series. However, the relationship of spindle cell thymoma with pure red cell aplasia (Lattes 1962; Gray and Gutowski 1979), or hypogammaglobulinaemia (Jeunet and Good 1968) but not with myasthenia gravis (Castleman 1955; Salyer and Eggleston 1976; Levine and Rosai 1978) is known, whereas myasthenia gravis was noticed to be associated with the occurrence of plump, clear cells (Castleman 1955; Bernatz et al. 1961; Rosai and Levine 1976; Gray and Gutowski 1979) to which cortical cells may correspond according to our criteria.

The frequent occurrence of neoplastic TNC in cortical thymoma was outlined. In mouse (Wekerle et al. 1980) and in man (v. d. Wijngaert et al. 1983) TNC have been reported to share ultrastructural features with thymic EC. These cells are situated in the mid/outer cortex, where thymocyte precursors first migrate and proliferate after the arrival in the thymus (Ritter et al. 1981) and are supposed to play a role in T-lymphocyte maturation.

We showed here that neoplastic TNC are similar to cortical EC and contain medium-sized, round and large lymphoid cells with irregular or convoluted outlines. These lymphoid cells are vital and are seen in mitosis. Previous reports described electron microscopic features of lymphocytic emperipolesis in EC of thymoma (Llombart-Bosch 1975; Levine et al. 1975). We can speculate that the observation of TNC in thymoma is related to the phenomenon of emperipolesis as described earlier. The functional meaning of TNC presence in thymoma, however, is not known.

The immunological and functional characteristics of thymoma T-lymphocytes have been subjected to several studies in recent years: thymoma lymphocytes are different from peripheral T cell and share several morphological and immunological characteristics with lymphocytes in the normal thymus (Lauriola et al. 1979, 1981; Reddick and Jeunette 1983), however, a high degree of phenotypic and functional variability is showed by lymphocytes in different thymoma (Musiani et al. 1982; Lauriola et al. 1983). A human thymoma with prothymocyte-like infiltration was reported (Piantelli et al. 1983) and might be classified according to the published picture as cortical thymoma. Correspondingly, some of our cortical thymomas contained a very high amount of immature lymphoid cells with convoluted nuclei.

Preliminary immunohistochemical data (unpublished observations) confirmed the heterogeneity of thymoma EC and their resemblance with cortical or medullary antigenic patterns. A recent report (Chilosi et al. 1984) also described the phenotypical similarity of EC from a thymoma with normal thymic EC. Mokhtar et al. (1984) reported some relationship of thymoma EC and lymphoid cells to their normal counterparts on the basis of immunohistological findings.

Thymic epithelial tumours included in category II of Levine and Rosai (1978) i.e. thymic carcinoma do not cause problems with regard to their malignant character. Several morphological variants were reported (Rosai and Higa 1972; Shimosato et al. 1977; Snover et al. 1982; Wick et al. 1982; Wick and Scheithauer 1982). Histogenetically these carcinoma are either derived from an endodermal (Snover et al. 1982) or ectodermal stem cell or their derivatives (e.g. hypobronchial ducts) included in the thymus anlage or from neuro-ectodermal cells (Rosai and Higa 1972; Rosai and Levine 1976), as discussed for the neuroectodermal carcinoma of carcinoid or oat cell type.

Although metastasis to extrathoracic sites is found more frequently in this group of thymic tumors, it is not restricted to them (Gravanis 1968; Rosai and Levine 1976); in a recent report on malignant thymoma (Baud

et al. 1981) cases of cortical type of thymoma and thymic carcinoma were included.

This paper showed that human thymoma may be related to the neoplastic proliferation of the cortical or medullary type of thymic EC or of both. In the mouse (Cordier and Haumont 1980) and in man (Norris 1938) ectoderm and endoderm contribute to the epithelial part of the thymus gland: however, the topographical distribution of ectodermal and endodermal derivatives in the normal postnatal thymus is at the moment unknown, as well as the amount of contribution of the two epithelial anlages. Moreover, our knowledge of the fetal and/or postnatal differentiative pathways of thymic EC is still rudimentary. Therefore, the proliferation of different EC types in human thymoma may reflect either the composite growth of different stem cells as occurring in hamartoma, or different phenotypic expression (= differentiation) of one epithelial stem cell. At the moment, the arguments to favour one of these hypotheses are insufficient; moreover the different possibilities need not to be mutually exclusive.

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