Virchows Archiv A Pathol Anat (1991) 419:257–260

Virchows Archiv A
Pathological Anatomy and Histopathology

Editorial

Tumours of the thymus and their nomenclature

Herwart F. Otto

Pathologisches Institut der Universität Heidelberg, Im Neuenheimer Feld 220/221, W-6900 Heidelberg, Federal Republic of Germany

Received March 27, 1991 / Accepted April 22, 1991

Primary tumours of the thymus are rare and the thymus is often considered to be an organ which rarely undergoes neoplastic transformation. However, 5–10% of all mediastinal tumours and 20–30% of those found in the anterosuperior mediastinum are primary thymic tumours (Levasseur et al. 1976; Salyer and Egglestone 1976; Otto 1984). Controversy about thymic organogenesis (theories of dualistic immigration and unitary transformation) and its complex ontogenesis and function, have led to several contradictory classifications of primary thymic tumors (for review see Otto 1984).

Apart from the mesenchymal tumours such as thymolimpomas (Otto et al. 1982) there are four cell types which may represent the cellular origins of primary neoplastic lesions of the thymus: thymocytes (T-lymphoblastic lymphomas); epithelial cells (thymomas/thymic carcinomas), neuroendocrine cells (carcinoid tumours of the thymus – neuroendocrine carcinomas), thymic B-lymphocytes (thymic lymphoma of the B-cell type, primary large- or clear-cell lymphoma of the thymus).

T-lymphoblastic lymphoma

Malignant lymphomas (Hodgkin's disease and non-Hodgkin's lymphoma) are the most common malignant tumours of the anterior and anterosuperior mediastinum (Lichtenstein et al. 1980). The mediastinal lymph nodes and/or the thymus itself may give rise to the lesions and many of the malignant lymphomas localized in the mediastinum are clearly primary thymic neoplastic lesions.

Most mediastinal non-Hodgkin's lymphomas in children are T-lymphoblastic lymphoma of convoluted-cell type, which usually presents radiographically as a lobulated mediastinal mass. Frequently, patients with malignant T-lymphoblastic lymphoma develop acute lymphoblastic leukaemias, sometimes described as "tumour growth in the anterosuperior mediastinum with acute lymphoblastic leukaemia" (Nathwani et al. 1976; Bernard et al. 1981; Rosen et al. 1987). It is widely accepted that this high grade malignant lymphoma is of primary thymic origin. Approximately 90% of these lymphomas possess characteristics corresponding to immature thymocytes. The distinctive features of this clinical syndrome has been reported by Sternberg in 1916 ("Leukosarkomatose" and "Myeloblastenleukämie"), and it is known as Sternberg's lymphoma of the thymus.

Epithelial tumours of the thymus: thymomas

Thymomas are epithelial tumours of the thymus associated with various numbers of lymphocytes (Castleman 1955; Mottet 1964; Rosai and Levine 1976; Levine and Rosai 1978). The morphology of epithelial tumour cells and the number of associated lymphocytes have both been used in different classification schemes of thymomas using light microscopy. Predominantly lymphocytic, mixed lymphocytic/epithelial, predominantly epithelial and pure epithelial thymomas were distinguished by some authors (for review: Otto 1984) on the basis of the number of associated lymphocytes. Large or epitheloid cell thymomas, spindle cell thymomas and mixed types have been classified by Rosai and Levine (1976) and others on the basis of the epithelial tumor cell morphology. To provide an organotypical classification of cortical, medullary or mixed (cortico-medullary) type thymomas, Marino and Müller-Hermelink (1985) used the morphological similarity of thymoma epithelial cells to their counterparts in the normal thymus.

Embryological studies (ectoderm-endoderm), as well as histological, immunohistological (cytokeratins, MHC antigens, T-cell restricted differentiation antigens), electronmicroscopic, enyzme-histochemical (Mg^{2+}-dependent adenosine triphosphatase, nonspecific alpha-naphthyl acetate esterase, 5'nucleotidase, acid phosphatase, esterase, beta-glucuronidase, alkaline phosphatase and several other enyzmes) and functional/morphological (thymopoietin, thymosin alpha 1 and beta 3) investigations have shown that different types of thymic epithelial cells can be differentiated by function (thymic microenvi-

ronment) or morphology: subcortical, cortical and medullary epithelial cells, epithelial nurse cells and cells of the Hassall's corpuscles (Haynes et al. 1984; Hofmann et al. 1987; Pallesen et al. 1987; Ritter and Haynes 1987; Schuurman et al. 1987; Takacs et al. 1987; Hirokawa et al. 1988). Attempts to classify the different epithelial cell types of the epithelial thymic tumours on the basis of its histogenentic and functional characteristics in normal conditions ("medullary-type thymoma", "cortical-type thmoma", "mixed-type thymoma" (Marino and Müller-Hermelink 1985; Müller-Hermelink et al. 1985; Hofmann et al. 1985; Müller-Hermelink 1986)) have been unsatisfactory, as have conventional histological classifications ("epithelial", "lymphocytic", "mixed-epithelial and lymphocytic", "spindled") (Otto 1984; Takacs et al. 1987; Willcox et al. 1987; Kornstein et al. 1988; Hofmann et al. 1989).

The cellular and structural differentiation patterns of epithelial thymic tumours are always heteromorphic. This variable phenotype does not correspond to the organogenetic and histogenetic features of the normally functioning organ. For prognostic and therapeutic purposes, it is thus important that a clear-cut tumour classification is based on the growth and degree of aggressive behaviour of thymomas in relation to their neighbouring structures and organs, using the clinical staging of Bergh et al. (1978); Masaoka et al. (1981) or Verley and Hollmann (1985). Subtle histomorphological classifications should not be used. In this way, difficulties with exceptions, such as thymic carcinomas with cytological atypia, undifferentiated lesions and those which are lymphoepthelioma-like, squamous, basaloid, clear cell, mucoepidermoid or sarcomatous, can be avoided (Thomson and Thackray 1957; Shimosata et al. 1977; Snover et al. 1982; Wick et al. 1982).

In addition to these intrinsic problems differential diagnoses between thymomas and other mediastinal tumours (germ cell tumours including teratomas, lymphomas, histiocytic tumours and tumour-like lesions) primary or metastatic, as well as between extramediastinal tumours and metastasizing thymomas may present a challenge. The association of thymomas with T-lymphocytes, predominantly of cortical type, might prove a good diagnostic tool if a tumour is associated with lymphocytes and if fresh frozen material is available (Hofmann et al. 1987, 1989).

Carcinoid tumours (neuroendocrine carcinomas) of the thymus

In 1972, Rosai and Higa identified neuroendocrine tumours of the thymus as a specific lesion distinctly different from thymomas. The authors proposed that the tumours they designated as "thymic carcinoid" be separated from "true" thymomas by virtue of its clinical, histomorphological, immunohistological and structural differences. Since then, carcinoid tumours of the thymus have been defined as a clinicopathological entity (Rosai et al. 1974; Hosoda et al. 1975; Wick et al. 1980 and 1982; Wick and Scheithauer 1984; Herbst et al. 1987; Wick and Rosai 1988). This group of tumour, however, is rare. Among the tumours of the anterior medistinum, carcinoid of the thymus represents a very small group with 2.5% to 4%. These tumours are derived from the foregut and their biological characteristics are similar to those of other carcinoids. Marino and Müller-Hermelink (1985) classify thymic carcinoids (and small cell carcinomas of the thymus/mediastinum) as neuroectodermal carcinomas.

The neuroectodermal nature of these tumours is reflected by their reactivity for cytokeratins in virtually all cases (Miettinen 1977). Neurofilament reactivity has also been reported in some thymic neuroendocrine neoplasms (Miettinen et al. 1983). Histochemically, the tumour cells are nonargentaffin but argyrophil. Formalin-induced fluorescence and alpha-glycerophosphate dehydrogenase can also be demonstrated in thymic carcinoids. Ultrastructurally, the tumour cells contain membrane-bound, dense-core neurosecretory granules ranging in size from 100 to 450 nm. Thymic carcinoids are able to produce alpha-MSH, somatostatin, parathormone, serotonin, calcitonin, met-enkephalin, leu-enkephalin, beta-endorphin, cholecystokinin and neurotensin. In many cases the tumour cells contain ACTH. Some induce paraneoplastic syndromes such as Cushing's syndrome, hyperparathyroidism or Zollinger-Ellison syndrome (Herbst et al. 1987; Wick and Rosai 1988). They may also be associated with Multiple Endocrine Neoplasia (MEN I and II).

In recent years, several general immunohistochemical markers of neuroendocrine differentiation have been characterized, including neuron-specific enolase (NSE), chromogranin and synaptophysin. These markers proved useful tools for the cellular (diagnostic) characterization of the thymic neuroendocrine tumours (Müller-Hermelink et al. 1986; Herbst et al. 1987; Wick and Rosai 1988).

Primary large- or clear-cell (B-cell) lymphoma of the thymus

Primary mediastinal, non-lymphoblastic, non Hodgkin's lymphoma has recently been recognized as a distinct clinicopathological entity (Möller et al. 1986a, b; Perrone et al. 1986; Menestrina et al. 1986). Its B-cell nature was first demonstrated by Möller et al. (1986a) and Addis and Isaacson (1986). Different names have been used to describe this lymphoma, for example "mediastinal diffuse large cell lymphoma with sclerosis" (Perrone et al. 1986), "large cell lymphoma of the mediastinum" (Addis and Isaacson 1986), "primary large-cell lymphoma of the thymus" (Davis et al. 1990) or "primary mediastinal clear-cell lymphoma of B-cell type (Möller et al. 1986b). There are some lines of evidence that this lymphoma is a tumour of thymic origin. A basis for this assumption has been found in the normally occurring B-cells within the thymus medulla (Addis and Isaacson 1986; Isaacson et al. 1987; Hofmann et al. 1988a, b; Möller et al. 1989a, b). Antigenetically, this lymphoma is characterized as CD5−, CD10−, CD19+, CD20+,

CD21−, CD22+, CD30−, CD37+, CDw40+ and by frequent expression of CD11c and CD23, while other antigens are expressed inconsistently. Most of these lesions are immunoglobulin-negative (Möller et al. 1987; Scarpa et al. 1987; Brandter et al. 1989; Knauf et al. 1989). Finally, the neoplastic B-cells have severe defects in the expression of major histocompatibility complex (MHC) antigens (Möller et al. 1986b, 1987; Momburg et al. 1987), reflecting the high grade of malignancy of clear-cell lymphoma of the thymus.

Conclusion

During the past two decades, substantial progress has been made in the understanding of the biology of the thymus gland and, therefore, in the pathology and clinical behaviour of thymic tumours (Levine and Rosai 1978; Janossy et al. 1980; CIBA Foundation Symposium No. 84 1981; Otto 1984; Müller-Hermelink 1986; Hofmann et al. 1989). Thymic tumors are classified according to their morphological features and presumed histogenesis. They include tumors arising from thymic epithelial cells (thymomas, thymic carcinomas), neuroendocrine cells (carcinoid tumours of the thymus, neuroectodermal carcinomas), lymphoid cells (malignant non-Hodgkin's lymphomas of T- and B-cell types and Hodgkin's disease), and adipose tissue (thymolipomas). All other tumours (myoid and histiocytic) and tumour-like lesions (cysts, hyperplasia) are extremely rare.

References

Addis BJ, Isaacson PG (1986) Large cell lymphoma of the mediastinum: a B-cell tumour of probable thymic origin. Histopathology 10:379–390

Bergh NP, Gatzinsky P, Larsson S, Lundin P, Ridell B (1978) Tumors of the thymus and thymic region: I. Clinicopathological studies on thymomas. Ann Thorac Surg 25:91–98

Bernard A, Boumsell L, Reinherz EL, Nadler LM, Ritz J, Coppin H, Richard Y, Valensi F, Dausset J, Flandrin G, Lemerle J, Schlossmann SF (1981) Cell surface characterization of malignant T cells from lymphoblastic lymphoma using monoclonal antibodies: evidence for phenotype differences between malignant T cells from patients with acute lymphoblastic leukemia and lymphoblastic lymphoma. Blood 57:1105–1110

Brandter LB, Smith CIE, Hammarström L, Lindemalm C, Christensson B (1989) Clonal immunoglobulin gene rearrangements in primary mediastinal clear cell 1 lymphoma. Leukemia 3:122–129

Ciba Foundation Symposium, No 84: Microenvironments in haemapoietic and 1 lymphoid differentiation. Pitman: London

Davis RE, Dorfman RF, Warnke RA (1990) Primary large-cell lymphoma of the thymus: A diffuse B-cell neoplasm presenting as primary mediastinal lymphoma. Hum Pathol 21:1262–1268

Haynes BF, Scearce RM, Lobach DF, Hensley LL (1984) Phenotypic characterization and ontogeny of mesodermal-derived and endocrine epithelial components of the human thymic microenvironment. J Exp Med 159:1149–1168

Herbst WM, Kummer W, Hofmann WJ, Otto HF, Heym C (1987) Carcinoid tumors of the thymus. An immunohistochemical study. Cancer 60:2465–2470

Hirokawa K, Utsuyama M, Moriizumi E, Hashimoto T, Masaoka A, Goldstein AL (1988) Immunohistochemical studies in human thymomas. Localization of thymosin and various cell markers. Virchows Arch [B] 55:371–380

Hofmann WJ, Möller P, Manke HG, Otto HF (1985) Thymoma – A clinicopathologic study of 98 cases with special reference to three unusual cases. Path Res Pract 179:337–353

Hofmann WJ, Momburg F, Möller P, Otto HF (1988a) Intra- and extrathymic B cells in physiologic and pathologic conditions. Immunohistochemical study on normal thymus and lymphofollicular hyperplasia of the thymus. Virchows Arch [A] 412:431–442

Hofmann WJ, Momburg F, Möller P (1988b) Thymic medullary cells expressing B lymphocyte antigens. Hum Pathol 19:1280–1287

Hofmann WJ, Möller P, Otto HF (1987) Immunohistochemical analysis of five thymomas and one thymic carcinoma using the Workshop antibodies of the thymic epithelium panel. In: McMichael AJ [eds] Leucocyte typing III. White cell differentiation antigens. Oxford University Press: Oxford, New York, Tokyo, pp 253–257

Hofmann WJ, Pallesen G, Möller P, Kunze W-P, Kayser K, Otto HF (1989) Expression of cortical and medullary thymic epithelial antigens in thymomas. An immunohistological study of 14 cases including a characterization of the lymphocytic compartment. Histopathology 14:447–463

Hosoda S, Suzuki H, Kito H, Hiai H, Akamine Y, Murakami M, Kosukegawa K, Kato N, Yura Y, Miyachi Y (1975) Argyrophilic thymic carcinoid. Clinicopathologic study of four cases. Acta Pathol Jpn 25:717–740

Isaacson PG, Norton AJ, Addis BJ (1987) The human thymus contains a novel population of B lymphocytes. Lancet ii:1488–1490

Janossy G, Thomas JA, Bollum FJ, Granger S, Pizzolo G, Brandstock KF, Wong L, Ganeshagurn K, Hoffbrand AV (1980) The human thymic microenvironment: an immunohistologic study. J Immunol 125:202–212

Knauf WU, Möller P, Ho AD, Dörken B, Heger G, Hunstein W (1989) Mediastinal clear cell lymphoma – a distinct entity of B-cell derived lymphoma as shown by immunotyping and analysis of gene rearrangements. Blut 59:243

Kornstein MJ, Curran WJ, Turrisi AT, Brooks JJ (1988) Cortical versus medullary thymomas: A useful morphologic distinction? Hum Pathol 19:1335–1339

Levasseur Ph, Kaswin R, Rojas-Miranda A, N'Guimbous JF, Merlier M, LeBrigand H (1976) Profil des tumeurs chirugicales du mediastin. A propos dune serie de 742 operes. Nouv Presse med 42:2857–2859

Levine GD, Rosai J (1978) Thymic hyperplasia and neoplasia: a review of current concepts. Hum Pathol 9:495–515

Lichtenstein AK, Levine A, Taylor OR, Boswell W, Rossman S, Feinstein DI, Lukes RJ (1980) Primary mediastinal lymphoma in adults. Am J Med 68:509–514

Marino M, Müller-Hermelink HK (1985) Thymoma and thymic carcinoma. Relation of thymoma epithelial cell to the cortical and medullary differentiation of thymus. Virchows Arch [A] 407:119–149

Masaoka A, Monden Y, Nakahara K, Tanioka T (1981) Follow-up study of thymomas with special reference to their clinical stages. Cancer 48:2485–2492

Menestrina F, Chilosi M, Bonetti F, Lestani M, Scarpa A, Novelli P, Doglioni C, Todeschini G, Ambrosetti A, Fiore-Donati L (1986) Mediastinal large-cell lymphoma of B-type with sclerosis: Histopathological and immunohistochemical study of eight cases. Histopathology 10:589–600

Miettinen M (1987) Synaptophysin and neurofilament proteins as markers for neuroendocrine tumors. Arch Pathol Lab Med 111:813–818

Miettinen M, Partanen S, Lehto VP (1983) Mediastinal tumors: ultrastructural and immunohistochemical evaluation of intermediate filaments as diagnostic aids. Ultrastruct Pathol 4:337–347

Möller P, Mielke B (1989) Extrafollicular peripheral B-cells report.

In: Knapp W [eds] Leucocyte typing IV. White cell differentiation antigens. Oxford University Press: Oxford New York Tokyo, pp 213–215
Möller P, Lämmler B, Eberlein-Gonska M, Feichter GE, Hofmann WJ, Schmitteckert H, Otto HF (1986a) Primary mediastinal clear cell lymphoma of B cell type. Virchows Arch [A] 409:79–92
Möller P, Lämmler B, Herrmann B, Otto HF, Moldenhauer G, Momburg F (1986b) The primary mediastinal clear cell lymphoma of B-cell type has variable defects in MHC antigen expression. Immunology 59:411–417
Möller P, Moldenhauer G, Momburg F, Lämmler B, Eberlein-Gonska M, Kiesel S, Dörken B (1987) Mediastinal lymphoma of clear cell type is a tumor corresponding to terminal steps of B cell differentiation. Blood 69:1087–1095
Möller P, Hofmann WJ, Mielke B, Otto HF (1989a) Das primäre mediastinale, hellzellige B-Zell-Lymphom ist ein epithelassoziiertes Thymuslymphom. Pathologe 10:234–239
Möller P, Matthaei-Maurer DU, Hofmann WJ, Dörken B, Moldenhauer G (1989b) Immunophenotypic similarities of mediastinal clear-cell lymphoma and sinusoidal (monocytoid) B cells. Int J Cancer 43:10–16
Momburg F, Herrmann B, Moldenhauer G, Möller P (1987) B-cell lymphomas of high-grade malignancy frequently lack HLA-DR, -DP, and -DQ antigens and associated invariant chain. Jnt J Caner 40:598–603
Müller-Hermelink HK (1986) The human thymus. Histophysiology and pathology. In: Berry CL, Grundmann E [eds] Current Topics in Pathology, Vol 75. Springer: Berlin, Heidelberg, New York, Tokyo
Müller-Hermelink HK, Marino M, Palestro G, Schumacher U, Kirchner Th (1985) Immunohistological evidences of cortical and medullary differentiation in thymoma. Virchows Arch [A] 408:143–161
Nathwani BN, Kim H, Rappaport H (1976) Malignant lymphoma, lymphoblastic. Cancer 38:964–983
Otto HF (1984) Pathologie des Thymus. In: Doerr W, Seifert G, Uehlinger E [eds] Spezielle pathologische Anatomie, Bd. 17. Springer: Berlin, Heidelberg, New York
Otto HF, Löning Th, Lachenmayer I, Janzen RWCh, Gürtler KF, Fischer K (1982) Thymolipoma in association with myasthenia gravis. Cancer 50:1623–1628
Pallesen G, Nielsen S, Celis JE (1987) Characterization of a monoclonal antibody (BG3C8) that reacts with basal cells of stratified epithelia. Histopathology 11:591–601
Perrone T, Frizzera G, Rosai J (1986) Mediastinal diffuse large-cell lymphoma with sclerosis. Am J Surg Pathol 10:176–191
Ritter MA, Haynes BF (1987) Summary of thymic epithelium workshop. In: McMichael AJ [eds] Leucocyte typing III. White cell differentiation antigens, Oxford University Press: Oxford, New York, Tokyo, pp 247–248
Rosai J, Higa E (1972) Mediastinal endocrine neoplasm of probale thymic origin, elated to carcinoid tumor. Clinico-pathologic study of 8 cases. Cancer 29:1061–1074
Rosai J, Levine GD, Weber RW, Higa E (1976) Carcinoid tumors and oat cell carcinomas of the thymus. Pathol Ann 11:201–226
Rosen PJ, Feinstein DI, Pattengale PK, Tindle BH, Williams AH, Cain MJ, Bonorris JB, Parker JW, Lukes RJ (1987) Convoluted lymphocytic lymphoma in adults. A clinicopathologic entity. Ann Intern Med 89:319–324
Salyer WR, Egglestone JC (1976) Thymoma. A clinical and pathological study of 65 cases. Cancer 37:229–24
Scarpa A, Bonette F, Menestrina F, Menegazzi M, Chilosi M, Lestani M, Bovolenta C, Zamboni G, Fiore-Donati L (1987) Mediastinal large-cell lymphoma with sclerosis. Virchows Arch [A] 412:17–21
Schuurman H-J, Ritter MA, Broekhuizen R, Ladyman H, Larché M (1987) The thymic epithelium panel of antibodies: immunohistologic analysis of human tissues. In: McMichael AL et al. [eds] Leucocyte typing III. White cell differentiation antigens. Oxford University Press: Oxford, New York, Tokyo, pp 259–262
Shimosato Y, Kameya T, Nagai K, Suemasu K (1977) Squamous cell carcinoma of the thymus. An analysis of eight cases. Am J Surg Pathol 1:109:121
Snover DC, Levine GD, Rosai J (1982) Thymic carcinoma: five distinct histological variants. Am J Surg Pathol 6:451–470
Sternberg C (1916) Leukosarkomatose und Myeloblastenleukämie. Beitr Pathol Anat 61:75–100
Takacs L, Savino W, Monostori E, Ando J, Bach JF, Dardenne M (1987) Cortical thymocyte differentiation in thymomas: an immunohistologic analysis of the pathologic microenvironment. J Immunol 138:687–698
Thomson AD, Thackray AC (1957) The histology of tumours of the thymus. Br J Cancer 11:348–357
Verley JM, Hollmann KH (1985) Thymoma. A comparative study of clinical stages, histologic features, and survival in 200 cases. Cancer 55:1074–1086
Wick MR, Carney J, Bernatz PE, Brown LR (1982) Primary mediastinal carcinoid tumors. Am J Surg Pathol 6:195–205
Wick MR, Rosai J (1988) Neuroendocrine neoplasms of the thymus. Path Res Pract 183:188–199
Wick MR, Scheithauer BW (1984) Thymic carcinoids. A histologic, immunohistochemical, and ultrastructural study of 12 cases. Cancer 53:475–484
Wick MR, Scott RE, Li CY, Carney JA (1980) Carcinoid tumor of the thymus. A clinicopathologic report of seven cases with a review of the literature. Mayo Clin Pro 55:246–254
Wick MR, Weiland LH, Scheithauer BW, Bernatz PE (1982) Primary thymic carcinomas. Am J Surg Pathol 6:613–630
Willcox N, Schluep M, Ritter MA, Schuurman HJ, Newsom-Davis J, Christensson B (1987) Myasthenic and nonmyasthenic thymoma. An expansion of a minor cortical epithelial cell subset? Am J Pathol 127:447–460