

History of Pathology Society**Boston, March 8 , 2009, 3:30 PM****TUMORS OF SELECTED ORGANS AND WHO WROTE ABOUT THEM****THE THYMUS****Juan Rosai, M.D.****Centro Diagnostico Italiano, Milan, Italy
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The most important advances that have been made during the past 50 years concerning the neoplastic pathology of the mediastinum are the following:

- The realization that thymoma is a specific tumor of the thymic epithelial cells;
- The realization that the lymphocytic component which is often present in thymomas and that sometimes dominates the microscopic feature is of non-neoplastic and immature T-cell nature;
- The realization that there is a range of differentiation in thymomas, which embraces thymic carcinoma;
- The reaching of an international agreement on the histologic classification of thymomas using a letter-number system, which has been sanctioned by the WHO;
- The confirmation of the fact that the most accurate prognostic indicator of thymoma is the clinical/surgical staging using the Masaoka system or any of its modifications;
- The confirmation of the fact that the histologic typing of thymomas correlates closely with prognosis, but that this correlation loses much of its significance when evaluated within the confines of a given clinical stage;
- The realization that, despite their rarity, there is a marked morphologic variation among the cytologically malignant thymomas, i.e., those tumors traditionally known as thymic carcinomas and designated as type C thymomas in the previous version of the WHO classification,
- The realization that the tumor originally described as granulomatous thymoma by James Ewing and further elaborated by Elizabeth Lowenhaupt represents Hodgkin's lymphoma of the thymus, and that this is nearly always of the classic type, nodular sclerosis subtype;
- The documentation of the fact that the tumor formerly diagnosed as "compartmentalizing large cell tumor of the thymus" is a large B-cell lymphoma of this organ, and that it has distinctive clinical, immunophenotypic and genotypic characteristics which suggest a specific origin from thymic B-cells. Fibrosis is a conspicuous feature of this tumor. Some B-cell markers such as CD19 and CD20 are consistently present, but Ig and HLA class I and II molecules are frequently expressed only incompletely or not at all. CD10 and CD5 are also absent, whereas there may be a weak expression of CD30. At the genetic level, Ig rearrangements are present. The karyotype is hyperdiploid, often with gains in 9p,

amplification of the REL gene, and overexpression of the MAL gene. There are no BCL2, BCL6 or MYC rearrangements.

- The documentation of the fact that the old Sternberg's sarcoma, which then became Lukes' convoluted cell lymphoma, is a precursor T-lymphoblastic lymphoma, an entity closely related to T-lymphoblastic leukemia. This tumor has been stratified into different stages of intrathymic differentiation according to the number and sequence of antigens expressed;
- The realization that the thymus is yet another place where so-called MALT-type lymphoma can develop;
- The realization that there is a whole gamut of thymic tumors exhibiting neuroendocrine differentiation in the thymus, from the well-differentiated thymic carcinoid to the highly malignant small cell neuroendocrine carcinoma, and that their classification scheme mirrors that of the corresponding neuroendocrine neoplasms of the lung. It has also been ascertained that a high proportion of thymic carcinomas (type C thymomas) exhibit some degree of neuroendocrine differentiation, whereas this is almost never the case for types A and B thymomas;
- The documentation of the fact that the old germinomatous thymoma is a seminoma of the thymus. The close anatomic connection of this tumor type with the thymus (the relationship being much more specific than that usually implied when stating "mediastinal" or "midline" location) and its almost exclusive occurrence in males are two intriguing facts in search for a biologic explanation;
- The realization that a certain morphologically distinctive type of mediastinal tumor formerly thought to be a subtype of spindle (type A) thymoma is actually the mediastinal counterpart of the pleural lesion once known as solitary fibrous mesothelioma and now designated as solitary fibrous tumor;
- The acceptance of the fact that multilocular thymic cyst is the thymic expression of a theme which repeats itself at several places in the head and neck region, and which is characterized by proliferation and cystic dilatation of epithelial branchial pouch-derived structures as a result of stimulation by a reactive lymphocytic component. In the thymus, these lymphocytes may be the expression of an idiopathic "thymitis", HIV-infection, or congenital syphilis, or may be accompanying Hodgkin's lymphoma, seminoma, and other tumors of the thymus;
- The documentation of the fact that tumors arising from thymic and related branchial pouch derivatives can occur at several locations in the neck (often in close anatomic relationship with the thyroid gland), some of them having a distinctive appearance not seen at the thymic orthotopic site, as in the case of ectopic hamartomatous thymoma and so-called SETTLE (spindle epithelial tumor with thymic-like elements).

As one looks back at this list of developments, one cannot help but concluding that some real progress has been made. Among the many people responsible for this achievements, I would like to single out the following (listed in alphabetical order, and leaving out those from the current generation): Benjamin Castleman, Raffaele Lattes, Robert Lukes, Gerald Levine, Akira Masaoka, and Hans K. Müller-Hermelink.