PATHOLOGICA 2021;113:360-370;
DOI: 10.32074/1591-951X-539

Review

Juan Rosai as master of our comprehensive understanding of thymus and thymoma

Mirella Marino[1], Alexander Marx[2], Lucia Anemona[3], Libero Lauriola[4], Philipp Ströbel[5], Hans Konrad Müller-Hermelink[6]

[1] Department of Pathology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; [2] Institute of Pathology, University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany; [3] Department of Experimental Medicine, Faculty of Medicine, Tor Vergata University, Rome, Italy; [4] Department of Anatomic Pathology, Catholic University, Rome, Italy; [5] University Medical Center Göttingen, Göttingen, Germany; [6] Institute of Pathology, University of Würzburg, Germany

Summary

In this study, the authors report on the activity of Juan Rosai, one of the pathologists most engaged in the definition of cells, diseases and tumors occurring in the thymus and in the mediastinum during the last 60 years. With his morphological skills and tireless interest in clarification of disease patterns, he contributed extraordinarily to expand our knowledge of the mediastinal diseases and to improve our diagnostic approach. He determined extraordinary advances also in trasmission electron microscopy and in immunohistochemistry as powerful diagnostic tools. Moreover, he proposed and promoted, together with an international panel of Pathologists, the World Health Classification of Thymic tumors as a definite progress in our comprehension and diagnostics of thymic epithelial tumors (TET). Our purpose is to review J. Rosai's achievements in thymic normal structure, in TET and particularly in the entity now definied as "thymoma", in distinction from the thymic carcinoma. To do this, our narrative will also be based on personal memories, longstanding collaborations and/or friendship with J. Rosai.

Key words: thymus, thymoma, pathology, classification, mediastinum

Received and accepted: October 19, 2021

Correspondence
Mirella Marino
Department of Pathology, IRCCS Regina Elena National Cancer Institute, via Elio Chianesi 53, 0014 Rome, Italy
E-mail: mirella.marino@ifo.gov.it; mirellamarino@inwind.it

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Marino M, Marx A, Anemona L, et al. Juan Rosai as master of our comprehensive understanding of thymus and thymoma. Pathologica 2021;113:360-370. https://doi.org/10.32074/1591-951X-539

Introduction

Mediastinal neoplasms/diseases show a wide variety of morphological, biological and clinical behavior and functional activities, due to the anatomical complexity of organs and tissues and to the complex embryological development of this body area. The thymus is certainly the most relevant and enigmatic organ of that area, long debated in the past centuries. One of the pathologists most engaged in the definition of cells, diseases and tumors occurring in the thymus and in the mediastinum during the last 60 years period was Juan Rosai, born in Italy (Tuscany), grown up in Argentina, invited by Lauren Ackerman to the United States in 1965, professor and Chairman of Pathology in different Universities during his long career, following his mentors Eduardo Lescano in Mar de la Plata and L. Ackerman in St. Louis. With his morphological skills and tireless interest in clarification of disease patterns, he contributed extraordinarily to expand our knowledge of the mediastinal diseases and to improve our diagnostic approach. Our purpose is to review J. Rosai's achievements in thymic normal structure, in thymic epithelial tumors (TET) and particularly in the entity now definied as "thymoma", in distinction from thymic carcinomas. To do this, our narrative will also be based on personal memories, longstanding collaborations and/or friendship with J. Rosai.

In the past, until the 60s, the difficulties in understanding and classifying thymic tumors – according to J. Rosai – were largely related on the limited knowledge on thymic function. He just received in Buenos Aires his MD degree in 1961, when the Anglo-French-Australian immunologist Jacques FAP Miller began to publish his experiments on the role of the thymus in immunity. Miller showed that neonatal thymectomy – but not adult thymectomy – rendered mice unable to reject foreign skin grafts or to produce antibody to some antigens, induced a deficiency in lymphocytes and rendered the animals highly sensitive to intercurrent infections and prone to develop tumors. Therefore, J. Miller postulated that the thymus was the site responsible for the development of immunologically competent small lymphocytes, the place where self-tolerance develops and where the discrimination capability between self and nonself matures [1-3]. Moreover, few years before, Robert A. Good, from the University of Minnesota, Minneapolis, described a patient who had agammaglobulinemia and thymoma (Good's syndrome), therefore demonstrating the relationship between the thymus and immunodeficiency [4]. The time was ready for increasing the knowledge on thymus in normal and disease conditions.

Rosai's studies on the normal thymic structure and thymic cell types

In the first part of his studies, J. Rosai investigated the thymus architecture by transmission electron microscopy (TEM), together with Hector Rodriguez. At that time they were both young surgical pathology trainees of L. Ackerman. They proposed TEM as a tool for the differential diagnosis of histologically similar neoplasms by recognizing subcellular structures or chemical functional group/s that could distinguish between different cell types and lineages [5,6]. In the normal thymus, J. Rosai demonstrated by TEM, for the first time, the presence of argyrophilic cells, suggesting an origin of the tumors called "carcinoid" from these cells. J. Rosai and Henrique Higa also described several of these tumors [7]. In 1976, J. Rosai was Director of the Anatomic Pathology at the University of Minnesota, Minneapolis. The collaboration of J. Rosai with Gerald D. Levine, from the Stanford University School of Medicine, Stanford, resulted in the second edition of the AFIP fascicle on thymic tumors [8]. J. Rosai and G.D. Levine first assessed that the knowledge of the normal structure of the thymus could solve histogenetic and semantic controversies about the thymus in disease. Specifically, they definitely stated the epithelial nature of the reticular framework of the thymus. At that time, only TEM could provide the evidence of the epithelial nature of the thymic reticular cells with their elongated processes, desmosomes and tonofilaments and of Hassall's corpuscles. They accurately defined different epithelial cell (EC) types in the cortex and in the medulla and stated that "these differences are reflected in the divergent appearance of thymomas". In the same period, they characterized the fine structure of thymoma [9]. The recent (at that time) immunological progresses and experimental studies in several animal species allowed Rosai and Levine to report that thymic lymphocytes are of extrathymic origin, namely the from bone marrow and that they enter the thymus, undergoing lymphocytopoiesis in the subcapsular cortex; later on lymphocytes exit the thymus with features of mature naive T cells [10,11]. All these concepts, debated for long at the beginning of the 20th century by J. Hammar [12], were clarified thanks to experimental immunology [11]. The morphological features of the thymus were then reviewed and updated in the paper by S. Suster and J. Rosai "Histology of normal thymus" [13] and later in the book of Histology for pathologists, third edition [14]. Concerning the finding of argyrophilic cells of supposed neuroendocrine nature in the human thymus, the possible occurrence of neuroendocrine differentiation was investigated in a series of a hundred of TET, also including carcinomas, by J. Rosai in collaboration with L. Lauriola from Rome, during a period that L. Lauriola spent at the Department of Pathology of Memorial Sloan-Kettering Cancer Center (NY) in 1997, where J. Rosai was Chairman in the period from 1991 to 1999. In fact, many papers in the 80s and 90s reported on the occasional evidence of neuroendocrine differentiation in human epithelial tumors from many sites. The cases were investigated by the then novel techniques of immunohistochemistry (IHC) and, in some cases, TEM. The study by Lauriola and Rosai showed in a proportion of thymic carcinomas the presence of a discrete neuroendocrine differentiation, as assessed by immunohistochemistry for Synaptophysin, chromogranin and neuron-specific enolase, sometimes confirmed by the presence of neuroendocrine granules by TEM. Therefore, the unreported finding of a neuroendocrine differentiation in the most malignant TET was described [15]. In the chapter on normal thymus already mentioned [14], years later, then J. Rosai expanded widely the part on IHC of normal thymus and on the immunological characteristics of thymic lymphocytes, making morphology and function indivisible. It is now well known that CD5, a hemato-lymphoid marker, might be a useful adjunct in the diagnosis of thymic carcinomas, being able to recognize non-lymphoid lesions that produced that marker in excess. Different clones, as stated by M.J. Kornstein and

J. Rosai, provided different staining characteristics [16]. Therefore, the role of IHC as a fundamental tool in the diagnostic work up of neoplasias of the thymus and of other neoplasias increased in relevant way. As pathologists we all know and appreciate the fundamental role of J. Rosai in changing the surgical pathology diagnostic procedure by immunohistochemistry [17].

A brief historical background on thymic tumors classification

Confusing concepts and nomenclature about thymoma and other tumors of the thymus were common in the first half of the 20th century [18]. Our purpose is to briefly mention here the "setting" in which the first contributes of Rosai developed. More detailed description of the historical topics discussed (nomenclature, classification and staging systems) could be found elsewhere [19-22]. At the beginning of the 20th century, confusion existed about the normal thymic cell types, and, accordingly, there was uncertainty about the distinction between tumor categories of the thymus. J. Paviot and E. Gerest in 1896 named "epithelioma" of the thymus a large mediastinal tumor metastatic to the kidney [23]. Later on, the term "thymoma" first introduced by F. Grandhomme in 1900 [24] was applied to all malignant thymic tumors. Already in 1906, however, E. T. Bell [25] first stated the epithelial origin of thymoma and described tumors of the thymus associated with myasthenia gravis (MG). However, he used the term "thymoma" to indicate non-malignant tumors. Therefore, at that time the term thymoma was variously applied to different categories of tumors.

As authoritative opinion, James Stephen Ewing (1866-1943), Professor of pathology at the Cornell University, the Pathologist who discovered a form of malignant bone tumor, named Ewing's sarcoma, in 1928 proposed a classification of thymic tumors in**:** *A-Lymphosarcoma or thymoma*, therefore proposing an heterogeneous group of tumors, including thymoma as well as several types of lymphomas, particularly Hodgkin's Lymphoma, B-*Carcinoma* arising from reticulum cells, probably containing most of the tumors that are currently designated as such, C-*Spindle cell or myxosarcoma* - an heterogeneous group of tumors. Ewing in effect included under the same "umbrella" thymoma and lymphosarcoma and he believed that the so-called spindle-cell sarcomas and endotheliomas were varieties of thymoma [26]. It should be noted that the idea that thymic lymphocytes were of epithelial origin was widespread at that time, so that J. Ewing could be considered an "expression" of his time. It must be remembered, however, that in the same period Douglas Symmers, Professor of Pathology at New York University College of Medicine, wrote that "the practice of naming tumors after the organs in which they arise is a phylologic desecration" … "In order to formulate an intelligent conception of the origin and behavior of malignant tumors and tumor-like growths of the thymus and its remains, it is necessary to appreciate certain fundamental facts having to do with the embryogenesis and histologic structure of the thymus itself"… "Investigators are agreed that Hassall's corpuscles and the reticulum cells from which they spring are of epithelial origin". On this basis, D. Symmers formulated in 1932 his classification of Tumors of the Thymus: …"From *each of the histologic structures* enumerated, a particular sort of malignant tumor is capable of arising, the epithelioma from the epithelial reticulum and Hassall's corpuscles; lymphosarcoma from the lymphocytic elements, from the blood-vessels that variety of malignant growth known as perithelioma or as perithelial sarcoma and spindle-cell sarcoma from the supporting connective tissue" [27]. Several other classifications were proposed in the 60s-80s, based on the amount of lymphocytes, predominant cellular type (epithelial or lymphocytic) and their relative numbers [28] or, according to J. Verley and K. Hollman's schema [29], adding prognostic value to P.E. Bernatz's schema, classifying thymoma types from benign to potentially aggressive. Raffaele Lattes in 1962 then proposed a morphological classification later termed the "American classification", based on the EC type and lymphocytic content and together the reappraisal of the encapsulation or "non encapsulation" of the tumor and discussed the problem of thymoma malignancy. He was convinced that the microscopic aspects (thymoma subtyping) couldn't provide insights into the biological behavior [30].

Further developments in thymic epithelial tumors classification: Rosai and Levine and the "histogenetic" classifications

In the second part of the 20th century, after several classification schemes for TET had been proposed, Levine and Rosai, respectively at that time at the Stanford University, Stanford, and the University of Minnesota, Minneapolis, US, proposed in 1978 a very seminal work containing also the differential diagnostic points of several neoplasias occurring in the thymus. Moreover, they proposed a clinicopathological classification based on the histologic aspect of the tumors and their biological behavior as determined by the degree of invasion at surgery. They classified TET into 1) benign encapsulated thymoma, 2) malignant thymomas, including: a) type I malignant thymoma (in-

vasive thymoma), and b) type II malignant thymoma (thymic carcinoma) (Tab. I). The use of the term "thymoma" was restricted to thymic epithelial tumours with minimal or no cytological atypia, without subtyping them. A definite statement of the benign nature of lymphocytes in thymoma was made. Well-encapsulated non-invasive tumours were postulated to be benign, whereas tumours locally invasive or with lymphatic or hematogenous spread were classified as malignant thymoma. Tumors displaying obvious histological malignancy were definitely named thymic carcinomas [31]. This classification received wide consensus among pathologists in the years 70s and later on.

In 1985, the classification later on called "histogenetic"/"functional" (or "European", or "German") of TET was proposed from Hans-Konrad Müller-Hermelink, Professor and Chairman at the Würzburg Pathology Institute, Germany, and his collaborators, showing that TET reproduce the morphological and microenvironmental features of the normal thymic tissue, leading the authors to describe "cortical" and "medullary" epithelial features, as well as "mixed" features in thymoma. Even with the limited information available from the cases included in their retrospective study, including 71 cases, significant clinical correlations regarding invasion, association with myasthenia gravis (MG), and prognosis were found. In particular, the malignant invasive character as well as the occurrence of MG were found to be related to the neoplastic proliferation of the "cortical" EC, whereas in the usual mixed type of thymoma and the medullary type no gross invasion or metastases were noticed [32]. The study involved, as visiting scholar, M. Marino, coming from S. Giacomo Hospital/ Rome for short stages at the University; in 1983, she was recipient of a fellowship from the Deutscher Akademischer Austauschdienst (DAAD) at the Pathology Institute in Kiel.

Table I. Levine and Rosai Classification of Malignant Thymomas (from Levin and Rosai, 1978) [31].

Category I: Type I Malignant thymoma
1. Locally invasive
2. Thymoma with lymphatic or hematogenous spread
Category II: Type II Malignant thymoma (cytologically malignant) (thymic carcinoma)
1. Squamous cell carcinoma
2. Lymphoepithelioma-like
3. Clear cell carcinoma
4. Sarcomatoid (TEM often needed to distinguish from epithelial tumors)
5. Undifferentiated (TEM often needed to distinguish from histiocytic lymphoma and germ cell tumors)

Müller-Hermelink on the agreement with Rosai on the WHO classification – the value of cytoarchitectural features of TET

In this framework, with several classifications of TET proposed in the 80s and 90s and discussed all around the world, a new approach was needed. Pathologists should have reconsidered their original concepts and worked together to achieve a consensus. HK Müller-Hermelink, the proponent of the "histogenetic classification", had a longstanding interest on thymic cell types by morphology, electron microscopy, immunohistochemistry and experimental immunology [33-35], and on the classification of thymic tumors [32,36,37] and on the characterization of thymic B-cells in their microenvironment [38]. In the 80s, he was used to comment that "Thymic tumors, which are so rare, develop in greater number in the countries where the sun is more often shining", referring to the interest and scientific activity on thymus of several research groups in Italy. He shared with J. Rosai the responsibility of the 1999 WHO classification as a panelist of the WHO group, working to it at its first and then at its second publication (second and third edition, respectively, 1999 and 2004) [39,40]. He now tells us here the steps that finally resulted in the new proposal of the WHO classification of 1999. In the early 90s, Müller-Hermelink began a personal review of a large collection of "annotated" thymic tumors according to the "histogenetic classification", already well received by Pathologists [41,42], in order to validate its clinical relevance. He could examine the largest collection of thymic tumors since the "Castleman's era" in Boston, thanks to a good hematological relationship with Nancy Harris and the collaboration of Leticia Quintanilla-Martinez, who organized the review. In the same period, Müller-Hermelink met John K.C. Chan and Faith Ho, during his guest professorship at the Institute of Pathology, in Hong Kong. The prognostic significance of the organotypic or "European" classification was confirmed [43-45]. This setting gave to Müller-Hermelink the necessary international support for the relevance and impact of his diagnostic views on TET. In Würzburg he also organized a study group on this topic and Alexander Marx was responsible of this; also Philipp Ströbel joined the working group. Thymomatous and non-thymomatous MG became a further major topic of interest in Würzburg [46,47]. Moreover, in collaboration with Thomas Kirchner, at that time in Würzburg, the well differentiated thymic carcinoma (WDTC) was described [37]. This entity became a main terminological problem subsequently because the term carcinoma generally was reserved to the aggressive carcinomas lacking

Figure 1. A personal photo shared by Prof. Müller-Hermelink, from a European Society of Pathology (ESP) Innsbruck meeting in 1993: from the left to the right Nancy Harris, Y. Shimosato, M. Luisa Carcangiu, Juan Rosai, Thomas Kirchner, Leticia Quintanilla-Martinez, Falko Fend, Pauline M. Close, Hans-Konrad Müller-Hermelink.

specific thymus-related differentiation features. At that time, in the early 90s, Müller-Hermelink and Rosai met in New York, and discussed fruitfully about the classification of thymic tumors. Müller-Hermelink was requested to study Rosai's great collection of seminar cases and to classify them according to the histogenetic classification. They established an understanding and very positive contact, confirmed in subsequent years (Fig. 1). Later on, at a Meeting of the European Society of Pathology (ESP) in Nice in 1998, Rosai discussed the histogenetic classification, its terminology, and criticized the term "WDTC" occuring as "Composite Tumor" with cortical thymoma. In the discussion in plain audience, Müller-Hermelink made some comments and Rosai agreed on the histogenetic classification in principle. Both agreed that the terminology was not optimal and that a better classification with more specific designations should be sought. Subsequently Rosai proposed to forget about the traditional terms but use their meaning in large letters: "A" for "atrophic" medullary/spindle cell, "B" for "bioactive" cortical cells (with subtypes B1, B2 und B3, so that "chimeric" tumors could be termed B1/B2 or B2/B3), and "C" for "thymic carcinoma". Müller-Hermelink answered with a german proverb: "Namen sind Schall und Rauch" (meaning that "the names are not important if the scientific meaning of the "histogenetic classification" could be maintained and confirmed). And that's how it was decided! The WHO classification of 1999 was the result

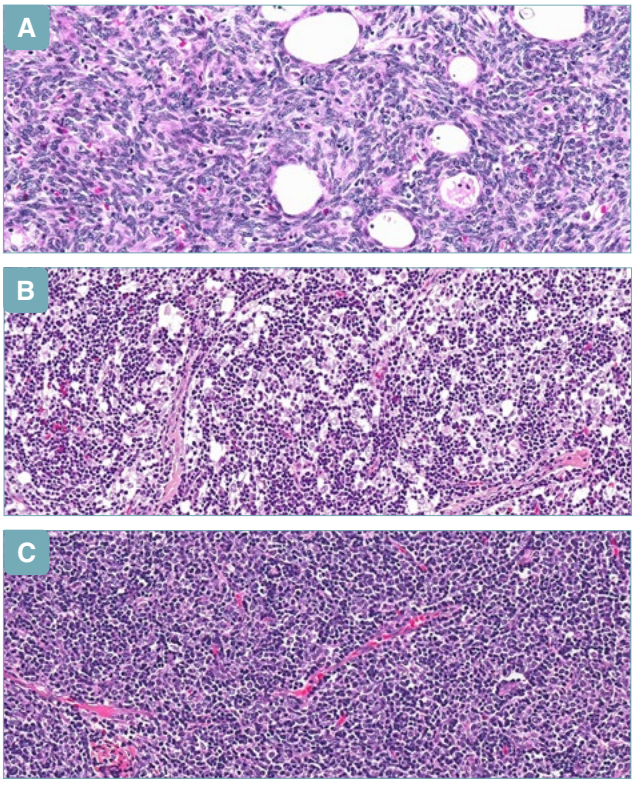

Figure 2. Epithelial cell types in thymomas: (A) "A" type cell, of spindle shape and nucleus; (B) "B" type cell, with plump epithelioid dendritic morphology, nucleus with distinct nucleolus; (C) In "AB" type thymomas a mixture of Epithelial cell types/patterns is seen. H&E, 200x. *Note: the cases shown here are the same shown in Figures 2A, 2D and 2B.*

of the work of a panel of 8 pathologists, coming from all around the world, coordinated by Rosai in order to reach a consensus-based classification (Tab. II) [39]. The 1999 WHO classification emphasized the value of classification of cytoarchitectural features of thymoma, independently of staging. TETs were classified according to the number and shape of EC (oval,

Table II. WHO Classification of Thymic Epithelial Tumors (from Rosai and Sobin, 1999) [39].

Type A (spindle cell, medullary)
Type AB (mixed)
Type B1 (lymphocyte-rich, lymphocytic, predominantly cortical, organoid)
Type B2 (cortical)
Type B3 (epithelial, atypical, squamoid, well-differentiated thymic carcinoma)
Thymic carcinoma (type C thymoma)

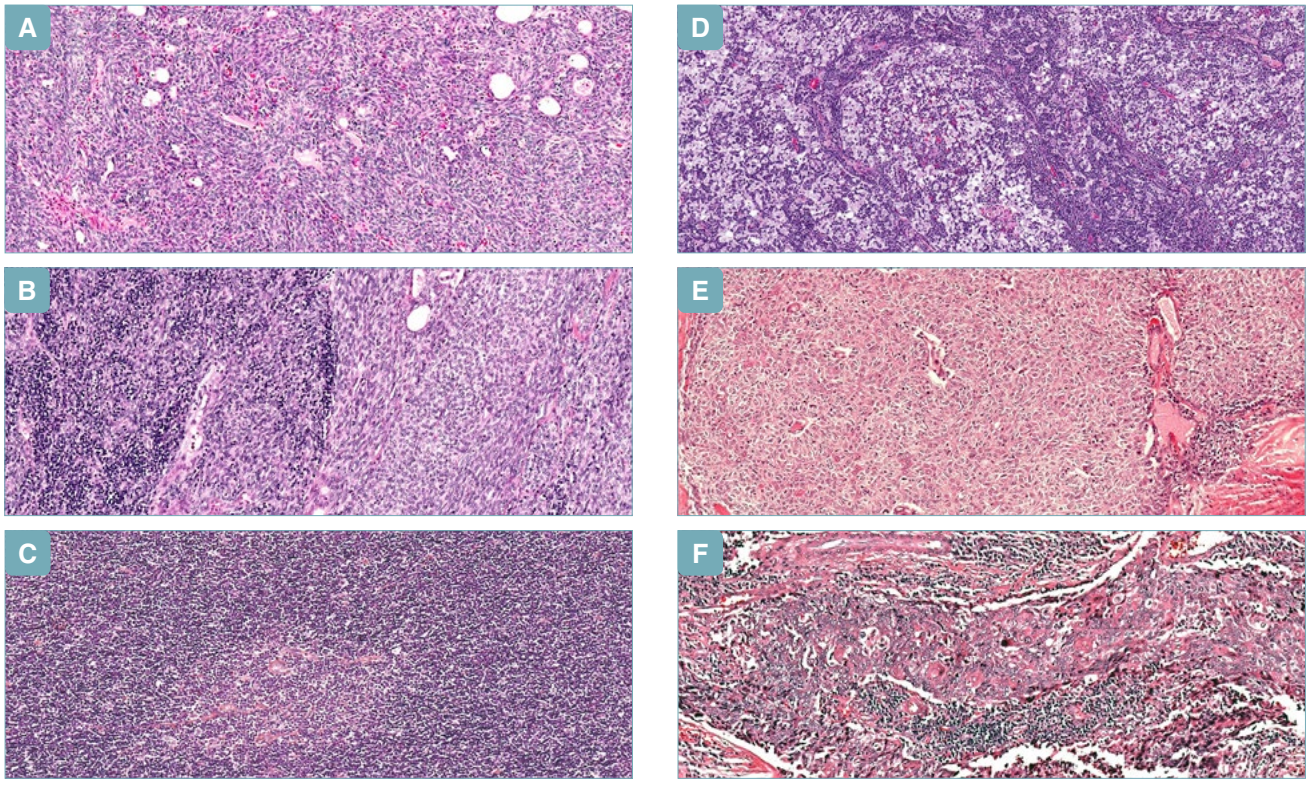

Figure 3. (A) Type A thymoma; (B) Type AB thymoma; (C) Type Type B1 thymoma; (D) Type B2 thymoma; (E) Type B3 Thymoma; (F) Thymic carcinoma (poorly differentiated thymic SCC), H&E, 100X. *Notes: Figures 2A and 2B were digitally acquired from cases presented in May 94 at the General Pathology California Tumor Registry Monthly sets; Figure 2C derived from slides presented at the HEM 1976, Series V congress Central Amer & Mex of Pathol; Figure 2D derived from a case presented at the California Tumor registry Seminars, Dec 99, San Francisco; Figure 2E derived from a case shown at California Tumor Tissue Registry, Huntington memorial Hospital-Protocol for Monthly Study Slides, Tumors of the Mediastinum, March 1990; Figure 2F derived from a case shown at the 107th Semi-Annual Seminar "Surgical Pathology of Tumors: What have we Learned In This Century?" moderator: Juan Rosai, M.D., December 5, 1999, - San Francisco, California. In these cases the original diagnosis were of Thymoma (A-E) (for "A" the diagnosis was Spindle cell thymoma) and now updated to the WHO classification; In Figure 2F the diagnosis made by Prof. Rosai was of Thymic carcinoma. All the slides were available at the site: https://digitalpathologyassociation.org/whole-slide-imaging-repository.*

spindle and so forth) and the number of lymphocytes in the tumor. The use of two alphabetic letters (A and B), as proposed by Rosai at the ESP Conference, made it possible to identify as "*A*", tumors with a component of spindle-oval EC without lymphocytes, and as "*B*", tumors with a component of large plump EC with dendritic (epithelioid) morphology, forming a lymphocyte attracting network. Tumours combining these two morphologies were designated as *type AB* (Fig. 2). "*Type B*" thymomas resemble the normal functional thymus, and were further subdivided into three subtypes on the basis of the proportional EC increase (in relation to the lymphocytes) and emergence of atypia of neoplastic EC, and respectively designated as B1, B2 and B3 (Fig. 3). Rosai himself found that the new classification corresponded with features of the "organotypic" classification [48]. Since then, the prognostic validity of the 1999 WHO classification has been confirmed in several studies [49,50]. In particular, a large-scale study reported that overall survival (OS) rates for patients with type A, AB, or B1 tumors were higher than those for patients with type B2 or B3 tumors, therefore pointing to the definition of "prognostic" groups [51]. Figure 4 reproduces a "historical" slide from Müller-Hermelink showing a comparison among the two classifications (the clinicopathological by Levine & Rosai and the "histogenetic" by Müller-Hermelink & coworkers) and the WHO classification 1999.

Classification of Thymic Epithelial Tumors (TET)

Clinicopathological Classification (Levine&Rosai, 1975)	Histological Classification of Thymic Epithelial Tumors (TET)	
	WHO Type 1999	Histological Terminology
Benign thymoma		Organotypic TET
	A	Medullary thymoma[1]
	AB	Mixed thymoma
Malignant thymomas, Category I	B1	Predominantly cortical (organoid) thymoma[2]
	B2	Cortical thymoma[3]
	B3	Well differentiated thymic carcinoma[4]
Malignant thymomas, Category II	C	Non-organotypic TET

[1]spindle cell thymoma [2]lymphocyte-rich thymoma; lymphocytic thymoma
[3]mixed lymphocytic and epithelial thymoma [4]epithelial; squamoid hymoma

Figure 4. Comparison of thymic epithelial tumors classifications: On the left the clinicopathological classification of Levine and Rosai, in the middle the 1999 WHO classification and on the right the "histogenetic" classification of Muller-Hermelink and coworkers. (Kindly shared by Prof. Müller-Hermelink who frequently used this slide for his lectures).

An uphill struggle for the 1999 WHO Thymic Epithelial Tumors classification

In the same year, 1999, a classification schema was proposed by C. Moran and S. Suster. They proposed the increasing cellular atypia, and the identification of the organotypical features as the basis of their proposal. Three diagnostic categories were proposed: thymoma, atypical thymoma, and thymic carcinoma, which lumped together – in effect- types A-AB, B1 and B2 of the WHO classification in the "thymoma" group, leaving only the B3 type in the "atypical thymoma" group [52]. Further discussions followed [53-55] after the publication of the 1999 WHO classification. In spite of the critique, however, the WHO classification gained worldwide acceptance not least due to its prognostic significance [50,56]. The definition of prognostic groups by histotypes (A-AB-B1 versus B2-B3 versus TC) was confirmed by analyses of long term outcome [57].

Thereafter, Rosai comments on Rosai's WHO 1999 classification

During the period 2000-2005, Prof. Rosai was chairman of the Pathology Department at the National Cancer Institute (INT) in Milan, Italy. He enjoyed the near mountains surroundings Como's lake and the collaboration with italian pathologists (Fig. 5). In that period he contributed to the proposal of a TNM-based staging system based on the examination of clinicopathological data of 149 patients, treated at the INT during the period 1972-1995. This stage grouping proposal, based on Masaoka's stages as translated into a TNM system by Yamakawa et al. [58], was oriented around the treatment approach: (1) locally restricted disease, which permits complete resection (for stages T1 and T2); (2) locally advanced disease, sometimes responsive to primary surgery but often requiring an extended resection (for stages T3-T4) and (3) systemic disease, including any T and positive lymph nodes [59].

Whereas presenting/discussing this staging system, Rosai commented also on the recently published WHO classification (source: draft of a conference given by Prof. Rosai "The clinical significance of the new WHO classification of thymoma", date undefinied, Milan - source M. Marino).

During this conference, Rosai commented that, considering the several conflicting classifications existing on TET, the WHO office in charge of the International His-

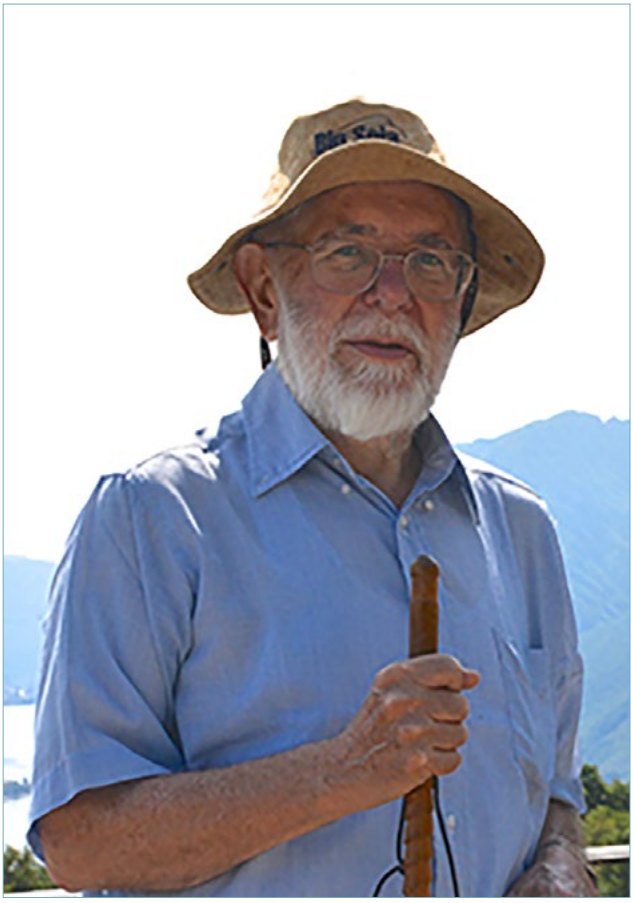

Figure 5. Juan Rosai on the mountains near Lake Como in the "Italian period" of his activity (personal photo shared by Libero Lauriola).

tological classification of tumors, headed by Leslie Sobin, set up as a goal the production of a classification taking the best from the existing classification schema and reaching consensus among the pathologists in the panel. The system, based on letters and numbers, was internationally accepted. Moreover, Rosai suggested that the letters were chosen to describe important functional features of the thymic EC so named: he reaffirmed the functional relevance of, "*A*", which stands for *atrophic* (i.e., the *effete* thymic EC of adult life), of "*B*" which stands for *bioactive* (i.e., the epithelioid, *biologically active* organ of the fetus and infant) and type "C" is the Cytologically malignant tumor". The classification, according to Rosai, proved to be easy to teach and easy to use and shortly reached wide consensus. Moreover, he commented that there is no question that there is a correlation between histological subtypes and patterns of growth/stage and that type A and AB are usually encapsulated and/or minimally invasive, and that type B3 and C are usually widely invasive, and B1 and B2 are usually intermediate in behavior.

The 3rd and 4th editions of the WHO classification and related controversies. The input from scientific societies and the Consensus workshops

The discussions on the WHO classification continued after the publication of the 3rd edition of the WHO in 2004, which provided important improvements including imaging and clinical data [40,60]. Some studies, reviewed by Detterbeck, gave conflicting results: the concordance in reproducibility of the WHO system among different pathologists appeared to be relatively good. However, there was some inconsistency in classification of the B subtypes. Moreover, by reviewing the literature, there was a marked variability in clinical characteristics of patients with WHO subtypes out than thymic carcinoma [61]. Verghese et al. reported a moderate agreement on the WHO-based diagnoses in a multicenter study [62]. The need of studies based on a large number of patients to obtain significant prognostic information in all the disease's stages and the adoption of more stringent diagnostic criteria to reduce diagnostic discrepancies, as well as the establishment of diagnostic reference centers [63,64] were proposed. Interestingly, a digital pathology study on the WHO classification reproducibility demonstrated results comparable to glass slides-based studies [65]. Nevertheless, not digital but two face-to-face workshops were organized before the 2015 (4th) edition of the WHO classification to discuss and improve diagnostic criteria: In New York City in 2011, with major input from the International Thymic Malignancy Interest Group (ITMIG) [66], and in Mannheim, Germany, in 2011, with the joint support from ITMIG and the European Society of Pathology (ESP). Rosai was invited to both Workshops and provided his sapient, brilliant and friendly support. The Consensus workshop in Mannheim refined definitions, updated histological criteria and provided rules for reporting [67], anticipating the 2015 classification [68]. Practical insights and differential diagnostic features in support of the classification were provided [69]. Moreover, the prognostic data for the 2015 classification were provided by the ITMIG retrospective database, based on more than 10,000 TET cases from all around the world [70]. The impact of thymoma histotyping was also analyzed in 4221 cases deriving from the ITMIG retrospective database: stage was lower in type A (90% in stages I-II) and AB than B1-B3 thymomas (38% of type B3 in stage III). In univariate analysis, recurrence was significantly less frequent among stage I/II tumors, in type A and AB (recurrence rates 1-2%) than B1-B3 thymomas (2-7%) [71]. It appears that the 4th edition of the WHO classification was well received and used all around the world. Digital pathology consultations on the reproducibility of the classification gave positive results; training and discussions among pathologists and specific expertise in rare thoracic tumors provided a relevant increase in reproducibility [72].

The 5th edition of the WHO classification: continuity and changes

Recently, a new (the 5th edition) of the WHO classification of thymic tumors was published in a fascicle entitled "WHO classification of Thoracic Tumors" [73]. Here, we would like to highlight both the "continuity and changes" of this new classification of TETs.

As to continuity, the new edition is largely a revision of the 4th edition. The "type A, AB, B1-B3 thymoma" nomenclature, introduced by Rosai in the 1999 edition, was retained, as was the integration of clinical, radiological, pathological and genetic data in the same book. Also, there was no change in the reporting of histologically heterogeneous thymomas that remains based on the prevalence of the different thymoma components. By contrast, detailed recommendations are now given for the labeling of the various combinations of thymic carcinomas, neuroendocrine neoplasms and thymomas, taking aggressiveness of the various components into account.

Of course, scientific advances had an impact on the 5th edition: an example is the introduction of the TNM-based system published by the UICC (International Union against Cancer) in 2017 [74] on the basis of joint retrospective data from the International As-

sociation for the Study of Lung Cancer (IASLC) and the ITMIG [70]. The use of the new TNM staging is now considered mandatory, whereas the Masaoka-Koga should be optional [75]. Moreover, the multiomics The Cancer Genome Atlas (TCGA) study was published, based on the analysis of 117 cases of thymoma and thymic carcinoma [76]. In the TCGA study and an antecedent multiomics study [77], TET were found to exhibit very few targetable mutations. In the TCGA four molecular subtypes were identified, which corresponded to the main WHO histological subtypes, demonstrating that A/AB and type B thymomas as well as thymic carcinomas are distinct biological entities and do not represent a continuum of diseases [76].

Moreover, following the publication of the 4th edition classification in 2015, several diagnostic, molecular and conceptual advances were reported in thymomas. Metaplastic thymomas were found to bear the apparently unique *YAP1-MAML2* translocation [78], while 6% of heavily pretreated type B2 and B3 thymomas (but not de novo thymic carcinomas) harbored novel *KMT2A-MAML2* translocations [79]. Both these translocations appear to be oncogenic drivers.

Conclusions

An increasing knowledge of TET, on morphological, genetic, immunological and clinical levels, has become available to researchers and clinicians involved in tumor diagnosis and treatment. We do not know how far this exploration of TET will proceed, due to their rarity and to their peculiar biological behavior. Very recently, other multiomics-based studies have been performed, pointing to the occurrence in TET of more molecular subgroups than those described in the TCGA [80]. Such complexity should not be surprising, because evidence from experimental immunology indicate wide immunophenotypic and functional heterogeneity in thymic EC [81,82]. The progress and the interest in the diagnosis and treatment of these rare tumors are increasing. The European Reference Networks (ERN)-EURACAN, the network for rare solid tumors of adults (https://webgate.ec.europa.eu/ern), included as first TET among the rare thoracic tumors to be considered, both clinically and in molecular genetic studies. Citing the words of Rosai himself, at a conference at the History of Pathology Society, on March 8, 2009 (https://hps.wisc.edu/past-meetings/),"one cannot help but conclude that some real progress has been made" in the past 50 years concerning the neoplastic pathology of the mediastinum. For these achievements we are indebted to several great personalities, among whom Juan Rosai has made a unique and outstanding contribution due to his originality, wit and visionary power.

Acknowledgements

The authors want to thank the International Thymic Malignancy Interest Group (ITMIG) which always encouraged the multidisciplinary discussion on pathological topics in Thymic epithelial tumors. Moreover, this work is generated in the framework of transnational collaboration promoted by the European Reference Network (ERN)-EURACAN.

Author's contributions

M.M.: conceptualization, original draft preparation, data curation, visualization, reviewing and editing; A.M.: conceptualization, original draft preparation, reviewing and editing; L.A.: Visualization, reviewing and editing; L.L.: original draft preparation, visualization, reviewing and editing; P.S.: reviewing and editing; H.K.M.H.:supervision, original draft preparation, visualization, reviewing and editing.

All Authors read and approved the manuscript.

Ethical consideration

The authors ensure that all procedures reported in the manuscript concerning human subjects were performed in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee(s) have approved them, and that informed consent was obtained for experimentation with human subjects.

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