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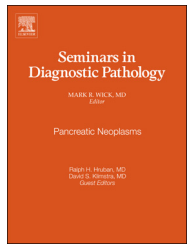

Mediastinal pathology and the contributions of Dr. Juan Rosai

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ABSTRACT

Dr. Juan Rosai is one of the most prolific contributors to the literature on mediastinal pathology, and he has added steadily to that body of work over a 50-year period. Rosai has written several landmark articles in this topical area, including articles on thymic epithelial lesions, mediastinal neuroendocrine tumors, mediastinal lymphoma and other hematopoietic lesions, thymolipoma, thymoliposarcoma, mediastinal solitary fibrous tumor, intrathymic langerhans-cell histiocytosis, mediastinal germ cell neoplasms, and multilocular thymic cyst. This review recounts his role as one of the principal figures in the surgical pathology of mediastinal diseases.

As late as the 1970s, considerable confusion and controversy accompanied concepts in pathology regarding thymic proliferations. In particular, the diagnosis of "thymoma" was commonly applied to a spectrum of tumors in the anterior mediastinum that manifested heterogeneous histologic appearances. A variety of modifying terms were appended, such that final interpretations included such designations as "granulomatous" thymoma, "seminomatous" thymoma, "cylindromatous" thymoma, "epidermoid" thymoma, "lymphoepithelioma-like" thymoma, "lymphosarcoma-like" thymoma, and others.[1] Thymic "carcinoma" was discussed conceptually in the literature of the time, but general opinion on that entity held that malignant behavior could not be predicted reliably by microscopic examination of a neoplasm in the thymus.

That situation began to change for the better after Drs. Juan Rosai (J.R.) and Gerald Levine (G.L.) became interested in the topic. They came from different backgrounds, with J.R. being of Italian descent, raised and educated in Argentina, and G.L. being a South African who emigrated to the United States for further education in pathology. The two of them met while they were fellowship trainees at Washington University Medical Center in St. Louis, MO, working with Dr. Lauren Ackerman.[2] Rosai and Levine were both skilled morphologists with an interest in the application of new techniques to problems in anatomic pathology. Systematically, they began to analyze the pertinent literature on thymic neoplasia, comparing it with their own experiences and observations. That collaboration resulted in the publication of several important articles on mediastinal tumors.[3–6] Furthermore, J.R. and G.L.[7] shared joint authorship of the fascicle on thymic lesions (FTL) in the second series of Tumor Atlases published by the Armed Forces Institute of Pathology. That was really the first book to present a logical construct for the classification and diagnosis of such neoplasms. Tragically, Dr. Levine died of non–Hodgkin lymphoma at age 43 only 5 years later, leaving Rosai to continue the study of thymic diseases.

This article reviews many contributions made by J.R. to mediastinal pathology as a discipline. His interests have been diverse in that area of study, encompassing thymic epithelial,

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neuroendocrine, mesenchymal, lymphoid, germ cell, and non-neoplastic proliferations.

Thymic "carcinoid" (neuroendocrine carcinoma)

Although mediastinal tumors with a microscopic similarity to "carcinoids" of the gut and lung had been reported sporadically in previous years,[1] Rosai and Higa[8] were the first to characterize such lesions properly and to separate them from true thymomas. In 1972, they reported 11 examples that were designated as "carcinoid tumors of the thymus" (CTT) (Fig. 1). The neuroendocrine nature of those lesions was supported by electron microscopic studies, and the authors linked CTT clinically to the multiple endocrine neoplasia syndrome, type I,[9] as well as ectopic Cushing's syndrome. In the past, the latter of those conditions was said to be associated with "cylindromatous thymoma," as described in an article by Scholz and Bahn.[10] Retrospectively, it was shown ultrastructurally that the three cases in that publication actually represented CTT,[11] as suggested by Rosai and Higa.

J.R. and G.L.[4] later described a spindle cell variant of CTT, associated with the syndrome of inappropriate production of antidiuretic hormone (SIADH). In addition, they extended the spectrum of neuroendocrine neoplasia of the thymus by describing cases of small cell neuroendocrine carcinoma arising in that gland[12] (Fig. 2).

Currently, it is well understood that CTT and thymoma are unrelated lesions. Furthermore, CTT are clearly regarded as more aggressive neoplasms than thymomas, with distant metastasis and tumor-related mortality in as many as 75% of cases in some series.[13]

Thymic epithelial neoplasms

As discussed above, the basic definition of "thymoma" was in doubt for many years, and that fact alone interfered with its proper recognition and classification. After the advent of electron microscopy, J.R. and G.L.[3] used that method to firmly establish the fact that thymomas were epithelial tumors (Fig. 3) that resembled squamous proliferations in other sites. Those tumors were found to contain cytoplasmic tonofibrils, and the lesional cells were joined by well-formed desmosomes. The ultrastructural features of thymomas were shown, in comparative studies, to differ from those of lymphoid, germ cell, and mesenchymal neoplasms.[14–19]

Once thymoma and its morphological variants could be confidently recognized, construction of a logical system for classifying them was possible. The preferred nosological model that was used throughout the 1960s and early 1970s was the Bernatz scheme[20]; it divided thymomas into predominantly lymphocytic, predominantly epithelial, mixed lymphocytic and epithelial, and spindle cell tumors predicated on the microscopic appearance of the lesions. J.R. and G.L.[7] essentially adopted that system with some modifications, but, in the FTL, they also stressed the importance of the biological nature of thymomas. Thus, such lesions were not only classified histologically, but by their behaviors, yielding the categories of "encapsulated" thymoma; malignant thymoma, type I (locally invasive thymoma); and malignant thymoma, type II (metastasizing thymoma)[5,7] (Fig. 4). Thymic carcinomas were also defined well for the first time in the FTL, with emphasis on their cytological aberrancy and microscopic resemblance to epithelial malignancies in other topographic locations.[7]

That approach was embraced and generally applied until 1985, when an alternate nosological system was introduced by Marino and Muller-Hermelink (M.M.H.).[21] It was based on histological resemblances between thymoma variants and microanatomic zones in the normal thymus. Hence, the principal categories in the MMH system were "cortical" thymoma and "medullary" thymoma, with admixtures of the two also being recognized. "Medullary" thymoma was largely synonymous with "spindle-cell" thymoma in the Bernatz scheme.

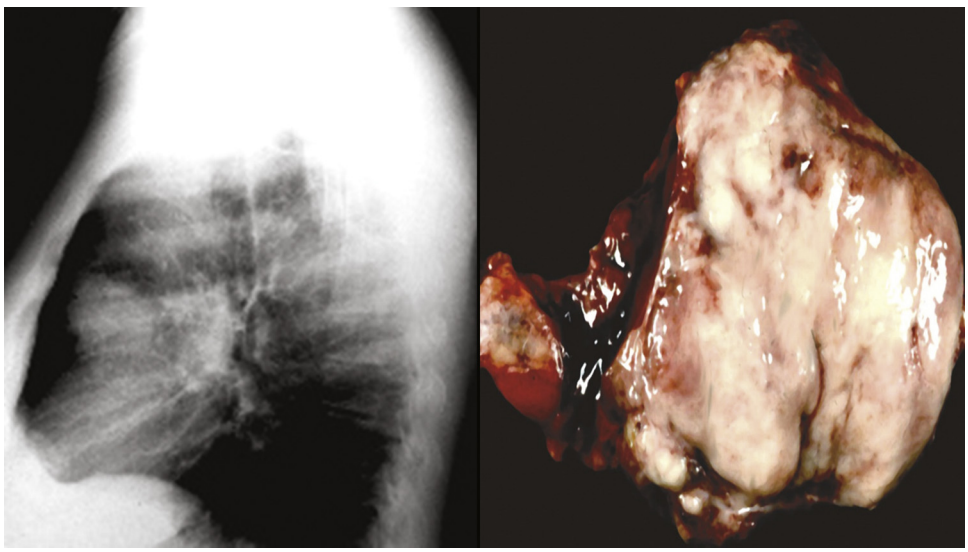

Fig. 1 – This lateral chest film (left) shows an anterior mediastinal mass in a middle-aged man. The excision specimen on the right proved to be a carcinoid tumor of the thymus (thymic neuroendocrine carcinoma).