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Review

Epithelioid angiomyolipoma: a pathological entity discovered in Verona with the endorsement of Doctor Rosai

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Summary
In this manuscript, we summarize the main features of angiomyolipoma highlighting the recognition of epithelioid angiomyolipoma and the discovery of immunohistochemical expression of HMB45 in a group of tumors that now are referred to as as PEComas. In this scenario, Dr. Rosai believed in our intuition, demonstrating his intellectual honesty and motivated us with his experience ("*when a tumor seems malignant it is malignant*") and enthusiasm for the new entities ("*in Verona, you use HMB45 instead of H&E*"). He really pushed the improvement of the knowledge in this field.

Key words: angiomyolipoma, epithelioid angiomyolipoma, PEComa, Rosai, tuberous sclerosis

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Conflict of interest
The Authors declare no conflict of interest.

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Historical review

"Angiomyolipomas constitute the most controversial of benign tumor and tumor-like lesions in the kidney" as Mostofi stated in 1965 in one of his seminal articles [1]. Although the term angiomyolipoma was first used in 1951 by Morgan et al. [2], the renal lesion which histologically corresponds to angiomyolipoma had been first described 40 years before by Fisher in association with tuberous sclerosis [3]. In the manuscripts published at that period, due to the multiplicity and bilaterality observed in a percentage of angiomyolipomas, the main issue was the relationship with tuberous sclerosis complex rather than the morphological features of the lesion. From a histological point of view, the characteristics were rather constant, with the tumors composed of admixture of mature adipose tissue, tangles of tortuous thick-walled blood vessel, and collarettes and sheets of smooth muscle fibers (Fig. 1). Another established topic was the hamartomatous nature of angiomyolipoma. Only in the 1990s was clonality detected demonstrating non-random inactivation of the X-chromosome [4]. Later, the loss of heterozygosity (LOH) of chromosome 16p (*TSC2*) [5] and the frequent presence of *TSC2* gene mutation observed in angiomyolipoma have confirmed its neoplastic nature [4].
In 1968, angiomyolipoma was considered uncommon with only 150 cases appeared in the literature [6] and not the most common renal mesenchymal tumor as we currently know based on the actual information. This discrepancy in frequency may be explained by the higher detection by imaging performed to evaluate other conditions [7]. On the other hand, in the past, predominantly lipomatous or predominantly leiomyomatous

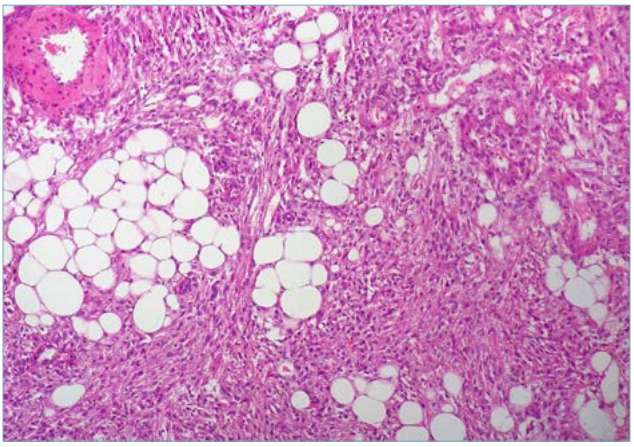

Figure 1. Classic angiomyolipoma showing mature adipocytes and thick-walled blood vessels intermixed with bundles of smooth muscle cells.

lesions were recorded under different headings such as lipoma, liposarcoma, leiomyoma, leiomyosarcoma, fibromyxolipoma, mesenchymoma, etc. However, until 1988 the consciousness of possible misdiagnoses was limited to mesenchymal tumors whereas a monophasic proliferation made up by atypical epithelioid smooth muscle component was not contemplated.
In summary, from 1951 to the 1990s, the attention on angiomyolipoma was mainly addressed to radiological (detection/recognition and embolization) and surgical (management/complication) aspects. The comprehension of its neoplastic nature, the discovery of epithelioid angiomyolipoma, and the identification of HMB45 as an immunohistochemical tool to reach this difficult diagnosis revived the pathological interest in angiomyolipoma.

Importance of the contribution of Dr. Rosai

In the autumn of 1988, the case of a young male, 16 years old, from Sicily, who suffered from hematuria, was observed in the Hospital of the University of Verona. Imaging analysis identified a large renal mass treated by nephrectomy. During surgery, the urologist identified numerous enlarged locoregional lymph nodes which were removed. In the Department of Pathology, the nephrectomy specimen revealed a 10 cm solid tan-brownish mass with hemorrhagic areas. After careful examination, in the extra-tumoral renal parenchyma, several yellow nodules ranging from millimeters to 1 cm were seen (Fig. 2A). Due to the unusual presentation, extensive sampling was performed including the large mass and the numerous small yellow nodules. Moreover, all the five lymph nodes removed were completely embedded. Based on our limited experience of pediatric renal tumors at that time, the first diagnostic hypothesis was Wilms tumor or other rare, strange tumors occurring in young patients. Surprisingly, the microscopic appearance was completely unexpected since none of the morphological features ascribable to Wilms tumor, mesoblastic nephroma, rhabdoid tumor, or clear cell sarcoma of the kidney were present. The principal mass was composed of medium and voluminous epithelioid cells mainly with clear cytoplasm often with feathery appearance arranged in sheets (Fig. 2B). Hemorrhagic areas were noted in which the neoplastic cells were dissociated “floating in a sea of red blood cells” as Dr. Rosai used to say. The large epithelioid cells showed frequently pleomorphic irregular nuclei, sometimes with nuclear pseudoinclusions. Considering all these characteristics together the cells were considered atypical. However, from the beginning, it was noted that the mitotic figures were rare and very difficult to find. For all these reasons, the first idea regarding the nature of the epithelioid cells was epithelial rather than mesenchymal and the tumor was considered an extremely unusual carcinoma arising in the kidney of a young boy. The slides of the case were shared among different pathologists of the department and the first impression was the same: an extraordinary uncommon renal carcinoma. The hypothesis of carcinoma was supported by the evidence of the same epithelioid neoplastic cells fulfilling the sinus of the lymph nodes, conceivably considered as metastasis (Fig. 2C). On the other hand, the occurrence of large anaplastic cells in the sinus was reminiscent for some of us to the recently recognized, and so-called at that time, Ki1 lymphoma. The cautious attention looking at the small nodules opened our minds. Some nodules were made up of epitheliod large cells as the main neoplastic mass, others were composed of the epithelioid cells and few adipocytes, and a minority of nodules were constituted of epithelioid cells, few adipocytes, and spindle cells (Fig. 3). The latter was reminiscent of angiomyolipoma even though the characteristic thick-walled vessels were absent. Moreover, intraglomerular lesions were observed. The case turned out to be even more complicated and the main idea of renal carcinoma became questionable because the evidence of these small nodules possibly linked to angiomyolipoma argued for the possibility that even the main mass could be related. But the question was: how can we consider the involvement of lymph nodes? In the liter-

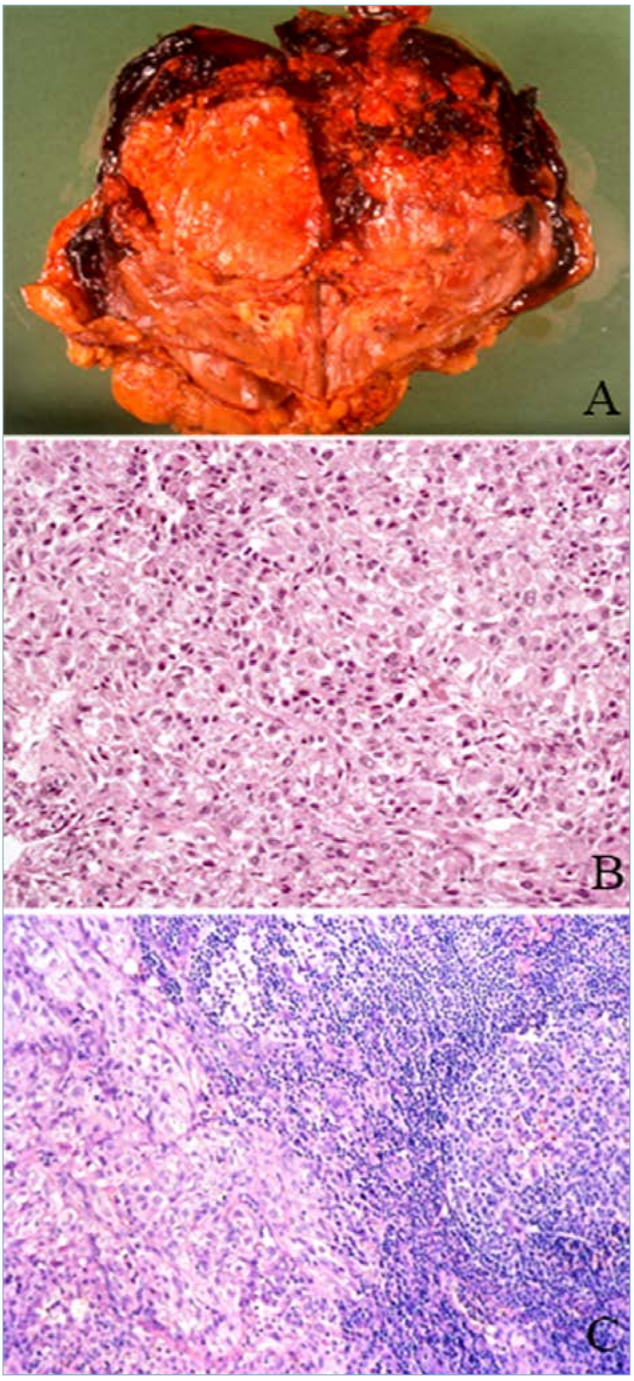

Figure 2. Original pictures from the case in 1988. (A) Gross appearance of the specimen with a large tan-brownish partially hemorrhagic renal mass and small satellite nodules in the surrounding parenchyma. (B) Microphotograph of the main tumor revealing sheets of medium-sized epithelioid clear to eosinophilic cells with nuclear atypia and sometimes prominent nucleoli. (C) High power magnification of a regional lymph node partially replaced by neoplastic cells, closely resembling those of the larger renal lesion, suspicious for a nodal metastasis.

ature, it was well known the possible involvement of the lymph nodes by angiomyolipoma which was considered as multicentric lesion rather than metastasis. Although the epithelial appearance of the main tumor, this hypothesis was not completely to be discarded. The clock was running and the calls from urologists but also from a colleague of ours who moved to Sicily at that time became insistent. Although we convinced each other, day by day, that it was a strange tumor related to angiomyolipoma, we decided to send the slides to a renowned Italian Institution and a famous American pediatric pathologist. The following consultant diagnoses were obtained "*La neoplasia renale, da considerarsi biologicamente paragonabile a un carcinoma a cellule renali di grado terzo rappresenta verosimilmente una forma di dedifferenziazione adenocarcinomatosa di un tumore di Wilms. Metastasi a 5 linfonodi (uno di tipo subtotale e quattro di tipo parziale)*" and "*This is obviously not an easy case. On the basis of the four sections you sent me, I have the following comments. I believe there is a carcinoma which in one corner of one of the two H&E sections labelled as an area could well be a large clear cell type of renal cell carcinoma. Everywhere else what I consider a carcinoma is made of small poorly differentiated cells. These cells have metastasized to the regional lymph nodes*" (Fig. 4). Not completely persuaded to the idea of renal carcinoma and becoming more and more confident to deal with a renal tumor related to angiomyolipoma, we decided to send it to the most famous pathologist in the world: Dr. Juan Rosai. At that time, he was the chairman of the Department of Pathology of Yale University and quickly answered us with the following letter. "*I agree with your interpretation of this extraordinary case. I think that this is an example of the type of angiomyolipoma which is so cellular and atypical as to closely simulate a malignant epithelial tumor such as renal cell carcinoma. I also agree with you that this lesion is probably related histogenetically to the small "hamartomas" present elsewhere in the kidney, and that the lesion in the lymph node should be regarded as an expression of multicentricity*" (Fig. 5). He was excited about the extraordinary case because we had not only sent the hematoxylin and eosin slides of the tumor but also the immunohistochemical stains, in particular HMB45. During that period, we were studying HMB45 antibody, and we had been staining all the strange tumors encountered during routine practice, including this one. Not only the large mass but also the small nodules were patchy positive for HMB45. In the meanwhile, retrospective cases of classic angiomyolipoma with the typical triphasic appearance with different proportions of adipose tissue, spindle,

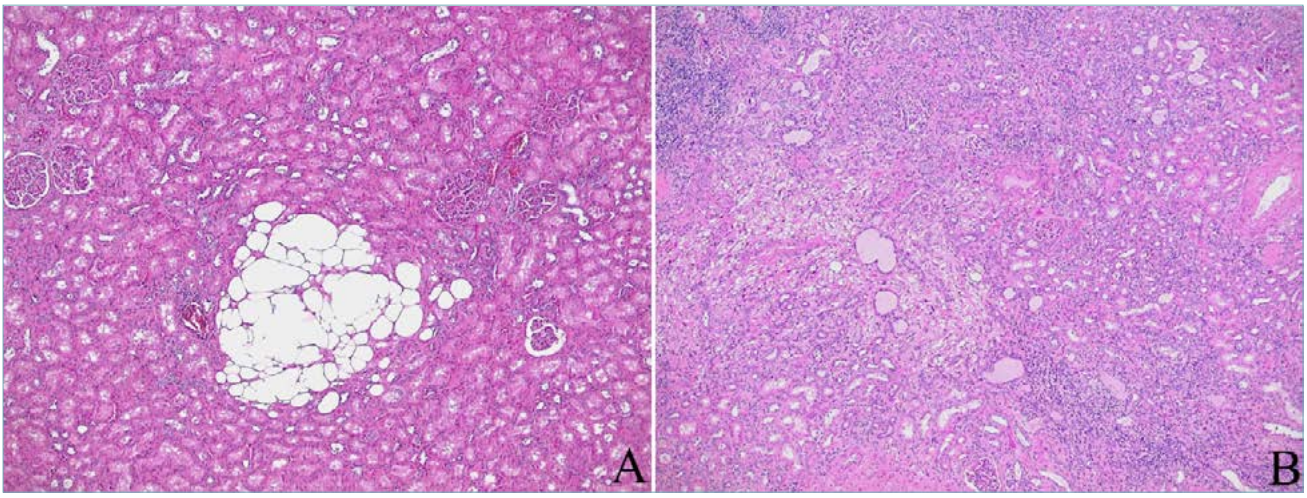

Figure 3. Small nodules in the renal parenchyma, variably made up of (A) mature adipocytes and (B) spindle cells surrounding blood vessels, with fewer adipocytes.

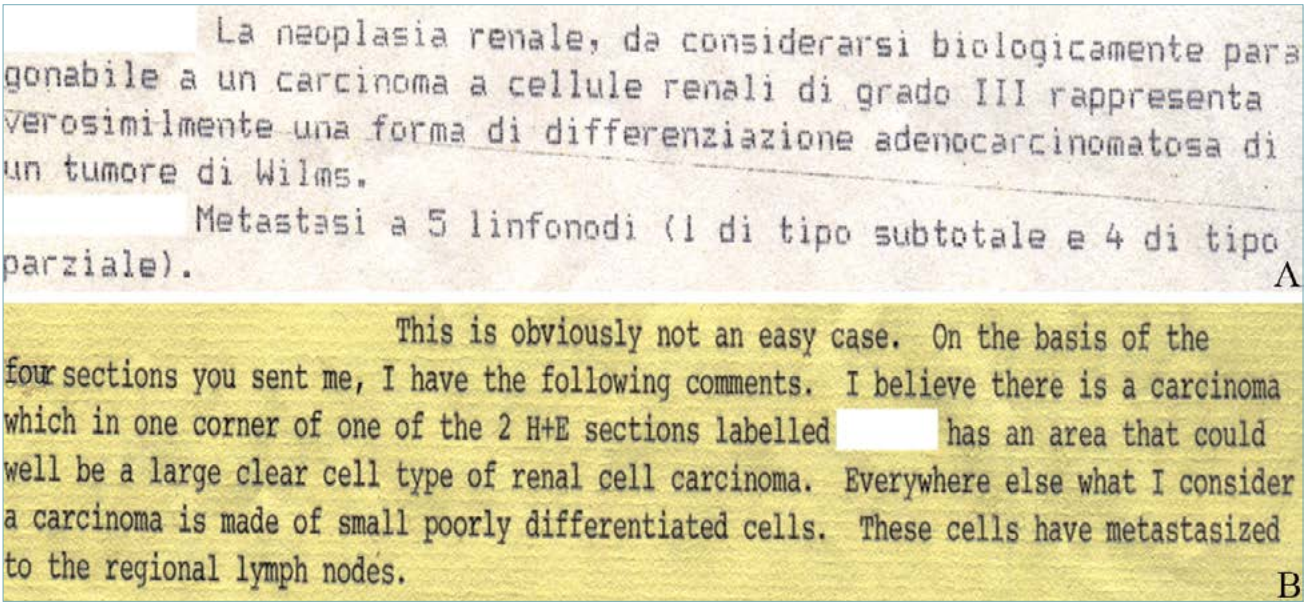

Figure 4. Consultation reports' from (A) Italian and (B) American pathologists.

and epithelioid smooth muscle, and thick-wall vessels were stained and variable labeling of HMB45 were seen (Fig. 6).

After three years from nephrectomy, the young boy suffered seizures, a CT scan was performed and calcifications around the third ventricle were observed. Due to this pathognomonic finding a final diagnosis of tuberous sclerosis was made, supporting after a few years the diagnosis of tumor strongly related to angiomyolipoma as suggested by Verona group and strengthened by Dr. Rosai. After the endorsement of Dr. Rosai who considered this a brilliant finding, we started collecting tumors with similar morphological and immunohistochemical features, some of them with oxyphilic appearance. In September 1993, one of us flew to the United States and went to Memorial Sloan Kettering Cancer Center in New York for a fellowship with Dr. Rosai who was the chairman of the Department of Pathology at that time. Showing the interesting cases collected in Verona, we tried

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Figure 5. Doctor Rosai's consultation regarding the case sent for second opinion.

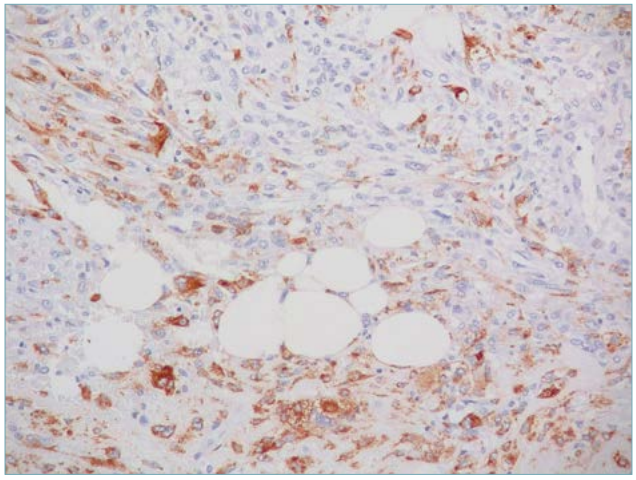

Figure 6. Patchy HMB45 immunohistochemical expression in classic angiomyolipoma, mainly labeling smooth muscle cells.

to convince Dr. Rosai that the tumors were indolent despite the atypical (carcinoma-like) morphology. His response was hasty but experienced: "*When a tumor seems malignant it is malignant*" (Fig. 7). Trying to prove this affirmation, we looked for similar cases in the personal archives of Dr. Rosai and the archives of the Department of Pathology of Memorial Sloan Kettering Cancer Center. A handful of cases were retrieved, mainly originally considered as carcinoma. All the tumors were characterized by epithelioid cells, some with clear feathery cytoplasm other with a more oxyphilic appearance, with a range of atypia particularly evident in a Brazilian case collected in Dr. Rosai's file (Fig. 8). Of 7 cases collected, four in men and three in women, two had tuberous sclerosis and, during follow-up, died of neoplastic disease. Although our initial hope of identifying a tumor with atypical features and indolent behavior, we acknowledged Dr. Rosai had the right intuition regarding the potential aggressiveness of this tumor. During a night of work discussing these cases, we summarized all the findings in a table, and we summarized the main common characteristics of this entity. All were localized in the renal parenchyma, made up of epithelioid cells, most of them with oxyphilic cytoplasm. Therefore, to describe this pleomorphic monophasic variant of angiomyolipoma, Dr. Rosai coined the term Renal Epithelioid Oxyphilic Neoplasm briefly called REON by using one of the acronyms which he liked to create [8]. All these tumors immunohistochemically expressed HMB45 and Dr. Rosai liked joking about this finding "*In Verona, you use HMB45 instead of H&E*" recognizing the experience of Verona group on this issue (Figs. 9, 10).

Figure 7. Doctor Rosai and his fellows in Memorial Sloan Kettering Cancer Center in New York in 1993.

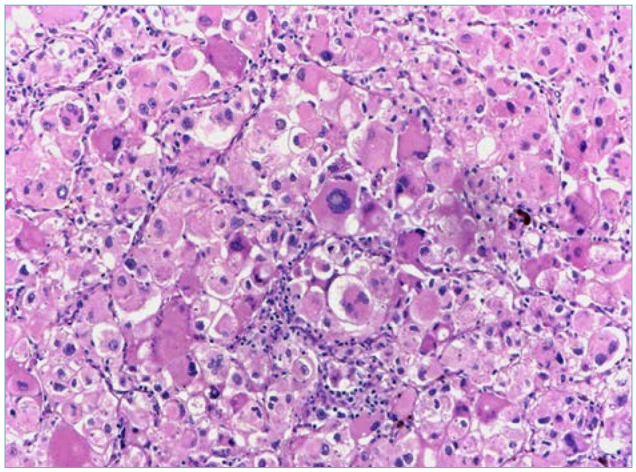

Figure 8. Renal tumor of a Brazilian patient from Doctor Rosai's personal collection, made up of large epithelioid cells with oncocytic cytoplasm and marked nuclear pleomorphism and atypia.

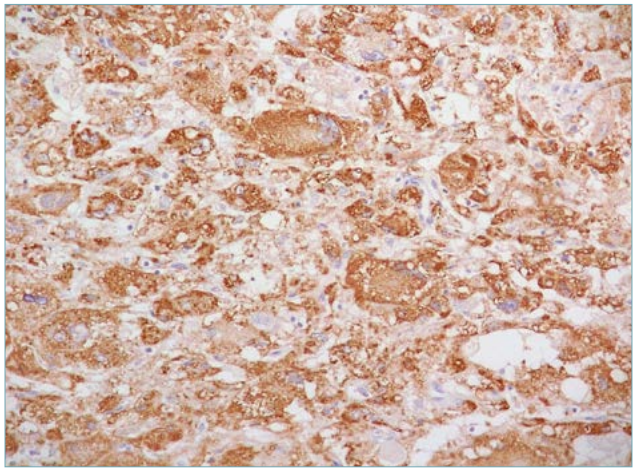

Figure 9. HMB45 immunohistochemical staining in epithelioid angiomyolipoma.

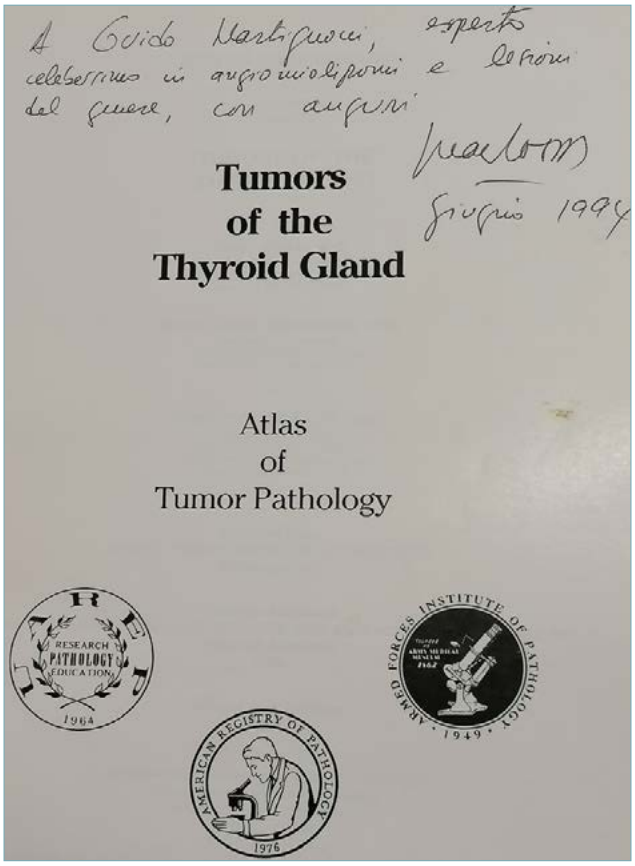

Figure 10. Doctor Rosai's personal dedication to the Verona group written on the AFIP book of Tumors of the Thyroid gland in 1994.

Evolution of the knowledge and recent developments

Nowadays, epithelioid angiomyolipoma is a well-recognized entity, firstly accepted by World Health Organization (WHO) in 2004 [9] and defined as a rare variant of angiomyolipoma which consists of at least 80% epithelioid cells in 2016 WHO Classification [10].

Morphologically epithelioid angiomyolipoma may display two different patterns, one "carcinoma-like" as the first case identified in 1988 and the other "epithelioid and plump spindle cells in diffuse growth". The "carcinoma-like" is made up of atypical large eosinophilic cells with prominent nucleoli and frequent intranuclear inclusions (ganglion cell-like appearance), sometimes multinucleated, arranged in cohesive nests separated by thin vascular-rich septa (Fig. 11). Mitotic figures are present but difficult to find. Necrosis can be seen. The other pattern consists of epithelioid and plump spindle cells arranged in diffuse sheets with less atypia, and clearer cytoplasm in comparison with the carcinoma-like tumors [11-13]. Immunohistochemically, besides HMB45 staining, epithelioid angiomyolipoma expresses other melanocytic markers such as Melan-A and microphthalmia transcription factor (MiTF) and variably smooth muscle markers (smooth muscle actin, muscle-specific actin, and less common desmin). More recently the expression of cathepsin k (Fig. 12), CD68 (PG-M1), and STING has been described in epithelioid angiomyolipoma [14-17].

From a molecular point of view, loss of heterozygosity (LOH) of *TSC2* has been reported in occasional cas-

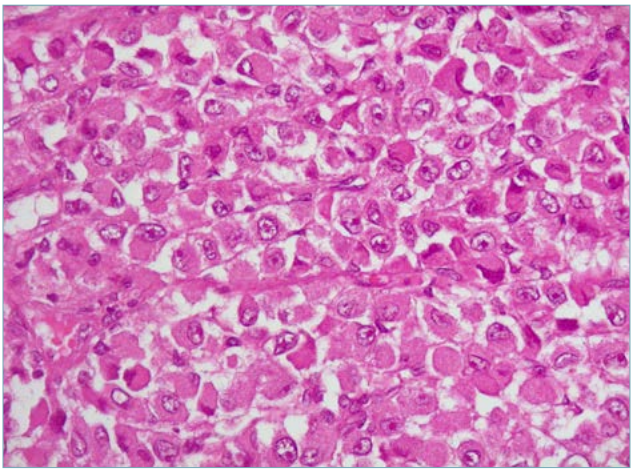

Figure 11. "Carcinoma-like" morphology of epithelioid angiomyolipoma: sheets and nests of plump and large epithelioid cells, with eosinophilic cytoplasm, voluminous and sometimes vesicular nuclei, and prominent nucleoli ("ganglion cell-like appearance").

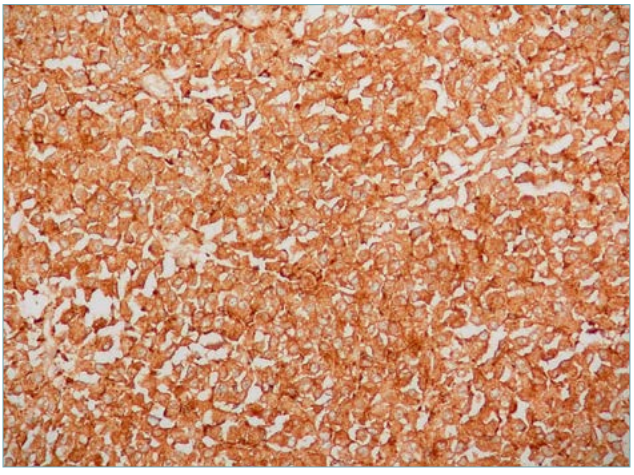

Figure 12. The same case of figure 11 strongly and diffusely immunolabeling for cathepsin K.

es of sporadic epithelioid angiomyolipomas as well as classic angiomyolipoma indicating clonality and its relationship with tuberous sclerosis as initially hypothesized. *TFE3* gene rearrangement has also been rarely described and, usually, the partner gene of such rearrangement is *SFPQ*/*PSF* [18].

As Dr. Rosai supposed, the potential aggressiveness of epithelioid angiomyolipoma is well-established. However, the clinicopathological features to predict the clinical behavior of each case managed in routine practice are still debatable. The main two prognostic systems were published by Brimo et al. in 2010 and Nese et al. in 2011 [19,20]. In the first, the prognostic criteria proposed are exclusive pathological based, whereas in the second combined clinical and pathological information was considered (Tab. I). Brimo et al. reported 40 atypical angiomyolipomas where the epithelioid component ranged from 5% to 90%, nine of which with aggressive behavior and suggest as criteria for malignancy the presence of three or more of the following histopathological parameters: ≥ 70% of atypical epithelioid cells, ≥ 2 mitotic figures per 10 HPF, atypical mitotic figures, and necrosis. In the other system, 41 cases of epithelioid angiomyolipomas (> 95% of epithelioid component) were evaluated for the presence of tuberous sclerosis and/or concurrent angiomyolipoma, tumor size (> 7 cm), carcinoma-like morphologic pattern, involvement of perinephric fat tissue and/or renal vein and presence of necrosis as associated with disease progression, recurrence, metastasis, or death due to disease. The authors provided a frequency of adverse prognostic parameters-based risk stratification model and divided tumors into low (0 to 1 parameter), intermediate (2 to 3 parameters), and high risk (4 or more parameters) for progression categories with 15%, 64%, and 100% risk for disease progression in each of the categories, respectively. Patients with 3 or more adverse parameters had disease progression in 80% of cases.

Currently, the term used for epithelioid angiomyolipo-

Table I. Prognostic stratification models to predict clinical behavior of epithelioid angiomyolipoma.

Study	Classification	Criteria
Brimo et al.[18]	Benign epithelioid angiomyolipoma with atypia (≤ 2 adverse parameters)	1) ≥ 70% atypical epithelioid cells
		2) ≥ 2 mitotic figures per 10 HPF
	Malignant epithelioid angiomyolipoma with atypia (≥ 3 adverse parameters)	3) Atypical mitoses
		4) Detection of necrosis
Nese et al.[19]	Low-risk group (0-1 worrisome features)	1) Evidence of TSC and/or concurrent angiomyolipoma
		2) Large tumor size (> 7 cm)
	Intermediate-risk group (2-3 worrisome features)	3) Histological pattern A
		4) Extrarenal extension and/or involvement of renal vein
	High-risk group (4-5 worrisome features)	5) Detection of necrosis

Abbreviations: HPF: high power field; TSC: Tuberous Sclerosis Complex.

ma is pure epithelioid PEComa [10]. This term derives from the perivascular epithelioid cell (PEC) [21] which is a cell type characterized by distinctive features: i) an epithelioid appearance with a clear to granular cytoplasm, a round to oval, centrally located nucleus, and an inconspicuous nucleolus; ii) a typical perivascular location; iii) expression of myogenic and melanocytic markers (HMB45, Melan-A, microphthalmia transcription factor); iv) modulation in morphology and immunophenotype. PEC may show muscular features with a spindle shape and a stronger positivity for actin than for HMB45 or it can have an epithelioid feature with strong positivity for HMB45 and a mild, if any, reaction for actin. Supporting this idea of plasticity in morphology, the ultrastructural analysis demonstrated the presence of cells both with transition features between smooth muscle and adipocytic cells [22,23] and with granules and crystalloids in the cytoplasm. Those granules have been variably considered over the years as renin granules or premelanosomes [24-27]. At present, PEC has no known normal counterpart. This unique cell is constantly present in a group of tumors, named PEComas which include angiomyolipoma, considered the prototype of this group of tumors, clear cell "sugar" tumor of the lung and extrapulmonary sites, lymphangioleiomyomatosis, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres and rare clear-cell tumors of other anatomical sites [4,23,28].

The discovery of PEC and its immunohistochemical expression of HMB45 and more recently cathepsin K shed light on heterogeneous tumors arising in different sites and give an important diagnostic tool to pathologists.

Author's contributions

Conceptualization: G.M.; methodology: A.C. and G.M. data curation: G.M.; writing-original draft preparation: A.C. and G.M.; writing-review and editing: S.M., M.B., G.Z., M.P. and F.B.; artwork managing and editing: S.M.; supervision: G.M.

Ethical consideration

No ethical issue was raised by this work.

References

1 Price EB Jr, Mostofi FK. Symptomatic angiomyolipoma of the kidney. Cancer 1965;18:761-774. https://doi.org/10.1002/1097-0142(196506)18:6<761::aid-cncr2820180614>3.0.co;2-a

2 Morgan GS, Straumfjord JV, Hall EJ. Angiomyolipoma of the kidney. J Urol 1951;65:525-527. https://doi.org/10.1016/s0022-5347(17)68515-x.

3 Fisher W. Dienierenturomorenbei der Tuberosen Hirsklerose Zeigler Beite. Z Path Anat UZ allg Path 1911;50:235-282.

4 Caliò A, Brunelli M, Segala D, et al. Angiomyolipoma of the kidney: from simple hamartoma to complex tumour. Pathology 2021;53:129-140. Epub 2020 Oct 31. https://doi.org/10.1016/j.pathol.2020.08.008

5 Carbonara C, Longa L, Grosso E, et al. Apparent preferential loss of heterozygosity at TSC2 over TSC1 chromosomal region in tuberous sclerosis hamartomas. Genes Chromosomes Cancer 1996;15:18-25. https://doi.org/10.1002/(SICI)1098-2264(199601)15:1<18::AID-GCC3>3.0.CO;2-7

6 Farrow GM, Harrison EG Jr, Utz DC, et al. Renal angiomyolipoma. A clinicopathologic study of 32 cases. Cancer 1968;22:564-570. https://doi.org/10.1002/1097-0142(196809)22:3<564::aid-cncr2820220311>3.0.co;2-p

7 Fujii Y, Ajima J, Oka K, et al. Benign renal tumors detected among healthy adults by abdominal ultrasonography. Eur Urol 1995;27;124-127. https://doi.org/10.1159/000475142

8 Martignoni G, Pea, M, Bonetti, F, et al. Renal epithelioid oxyphilic neoplasm (REON), a pleomorphic variant of renal angiomyolipoma (Abstract). J Surg Pathol 1995;S:539.

9 Eble JN, Sauter G, Epstein JI, et al. Pathology and genetics. Tumors of the urinary system and male genital organs. Lyon: IARC Pres, 2004.

10 Moch H, Humphrey PA, Ulbright TM. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press 2016.

11 Martignoni G, Pea M, Bonetti F, et al. Carcinomalike monotypic epithelioid angiomyolipoma in patients without evidence of tuberous sclerosis: a clinicopathologic and genetic study. Am J Surg Pathol 1998;22:663-672. https://doi.org/10.1097/00000478-199806000-00003

12 Pea M, Bonetti F, Martignoni G, et al. Apparent renal cell carcinomas in tuberous sclerosis are heterogeneous: the identification of malignant epithelioid angiomyolipoma. Am J Surg Pathol . 1998;22:180-187. https://doi.org/10.1097/00000478-199802000-00005

13 Martignoni G, Pea M, Bonetti F, et al. Oncocytoma-like angiomyolipoma. A clinicopathologic and immunohistochemical study of 2 cases. Arch Pathol Lab Med 2002;126:610-612. https://doi.org/10.5858/2002-126-0610-OLA

14 Martignoni G, Bonetti F, Chilosi M, et al. Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. Mod Pathol 2012;25:100-111. Epub 2011 Aug 26. https://doi.org/10.1038/modpathol.2011.136

15 Caliò A, Brunelli M, Segala D, et al. t(6;11) renal cell carcinoma: a study of seven cases including two with aggressive behavior, and utility of CD68 (PG-M1) in the differential diagnosis with pure epithelioid PEComa/epithelioid angiomyolipoma. Mod Pathol 2018;31:474-487. Epub 2017 Oct 20. https://doi.org/10.1038/modpathol.2017.144

16 Caliò A, Brunelli M, Gobbo S, et al. Stimulator of interferon genes (STING) immunohistochemical expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. Pathology 2021;53:579-585. Epub 2021 Jan 16. https://doi.org/10.1016/j.pathol.2020.09.025

17 Caliò A, Brunelli M, Gobbo S, et al. Cathepsin K: A Novel Diagnostic and Predictive Biomarker for Renal Tumors. Cancers (Basel) 2021 18;13(10):2441. https://doi.org/10.3390/cancers13102441

[18] Argani P, Zhong M, Reuter VE, et al. TFE3-Fusion variant analysis defines specific clinicopathologic associations among Xp11 translocation cancers. Am J Surg Pathol 2016;40:723-737. https://doi.org/10.1097/PAS.0000000000000631

[19] Brimo F, Robinson B, Guo C, et al. Renal epithelioid angiomyolipoma with atypia: a series of 40 cases with emphasis on clinicopathologic prognostic indicators of malignancy. Am J Surg Pathol 2010;34:715-722. https://doi.org/10.1097/PAS.0b013e3181d90370

[20] Nese N, Martignoni G, Fletcher CD, et al. Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: a clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. Am J Surg Pathol 2011;35:161-176. https://doi.org/10.1097/PAS.0b013e318206f2a9

[21] Bonetti, F, Pea M, Martignoni G, et al. Clear cell ("sugar") tumor of the lung is a lesion strictly related to angiomyolipoma--the concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC). Pathology 1994;26:230-236. https://doi.org/10.1080/00313029400169561

[22] Zamboni G, Pea M, Martignoni G, et al. Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells. Am J Surg Pathol 1996;20:722-730. https://doi.org/10.1097/00000478-199606000-00010

[23] Martignoni G, Pea M, Reghellin D, et al. PEComas: the past, the present and the future. Virchows Arch 2008;452:119-132. Epub 2007 Dec 14. https://doi.org/10.1007/s00428-007-0509-1

[24] Holm-Nielsen, P. & Sørensen, F. B. Renal angiomyolipoma: an ultrastructural investigation of three cases with histogenetic considerations. APMIS 1988;4:37-47.

[25] Perez-Atayde AR, Iwaya S, Lack EE. Angiomyolipomas and polycystic renal disease in tuberous sclerosis. Ultrastructural observations. Urology 1981;17:607-610. https://doi.org/10.1016/0090-4295(81)90089-3

[26] Weeks DA, Malott RL, Arnesen M, et al. Hepatic angiomyolipoma with striated granules and positivity with melanoma--specific antibody (HMB-45): a report of two cases. Ultrastruct Pathol 1991;15(4-5):563-71. https://doi.org/10.3109/01913129109016264

[27] Gaffey MJ, Mills SE, Zarbo RJ, et al. Clear cell tumor of the lung. Immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644-653. https://doi.org/10.1097/00000478-199107000-00005

[28] Martignoni G, Pea M, Zampini C, et al. PEComas of the kidney and of the genitourinary tract. Semin Diagn Pathol 2015;32:140-159. https://doi.org/10.1053/j.semdp.2015.02.006