

REVIEW



Renal oncocytoma with prominent xanthomatous reaction. A rare histopathological variant of oncocytoma

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Abstract

Renal oncocytoma (RO) is a distinctive neoplasm with a well-recognized gross and cytoarchitectural appearance. However, on some occasions, it may show uncommon, atypical, or worrisome gross and microscopic features potentially generating diagnostic difficulties. We herein review the oncocytoma variant characterized by a significant intraneoplastic xanthomatous reaction that produces a variegated macroscopic appearance. This feature may pose a genuine diagnostic problem with conventional (clear cell) renal cell carcinoma (RCC) because this reaction creates a departure from the typical uniform, tan-brown appearance of oncocytoma. The microscopic presence of foamy macrophages in RO may potentially lead to diagnostic difficulties with tumors exhibiting eosinophilic cells and significant infiltration for lipid-laden foamy macrophages such as cystic RCC, unclassified RCC rich in foamy macrophages, the solid variant of papillary RCC with oncocytic features, post-neuroblastoma RCC, succinate dehydrogenase-deficient RCC, mucinous-poor tubular and spindle cell carcinoma, and the oncocytic variant of the epithelioid angiomyolipoma. In conflictive cases, an immunohistochemical panel should help to solve the diagnostic problem. Therefore, the presence of abundant foamy macrophages should not dissuade the pathologist from establishing a diagnosis of RO. Prominent xanthomatous reaction despite its low frequency (4.3%) can be considered an additional feature of RO. Thus, RO should be added to the list of renal tumors that can show a significant reaction of lipid-laden foamy macrophages. Besides, Gamna–Gandy bodies can be present in this tumor.

Keywords: kidney, conventional renal cell carcinoma, Gamna–Gandy body, oncocytic neoplasia, oncocytoma, xanthomatous cells.

Introduction

Renal oncocytoma (RO) is a distinctive benign cortical neoplasm composed entirely of cells with abundant granular acidophilic cytoplasm, reflecting the presence of numerous mitochondria. The tumor was first described by Zippel [1]. However, this neoplasm was widely recognized since 1976 when Klein & Valensi [2] reported a series of 13 cases in a retrospective study at one institution.

Oncocytomas account for 6–7% of surgically resected adult epithelial, non-urothelial renal neoplasms [3, 4]. The majority occur in patients over age 50 (median age 63.5 years) with a reported age range of 36 to 91 years [5]. Men predominate over women in a ratio of 2–3 to 1 [5]. In about 82% the tumors are incidental findings [3]. These benign tumors show gross, microscopic, and ultrastructural characteristic features.

This renal neoplasm, however, may show uncommon, atypical [6] or worrisome gross and microscopic features potentially generating diagnostic dilemmas for the practicing pathologist. On the other hand, oncocytomas usually progress locally with a growth rate similar to that of renal cell carcinoma (RCC) [7, 8] and biopsy remains the mainstay of diagnosis. Thus, a challenge in the practice of surgical pathology is to face up to the different oncocytoma variants and establish the morphological limits for this entity.

Aim

This review aim was to present a detailed description of the RO with a significant reaction of lipid-laden foamy macrophages. This rare variant of oncocytoma with an unusual gross and microscopic appearance was briefly described by our group [9]. As this variant is not included in different reviews [10–12], authoritative monographs on urogenital pathology, or in standard surgical pathology books, we believe it merits a detailed description and consideration.

Typical renal oncocytoma

The tumor, situated in the renal parenchyma, is well-circumscribed, globoid in form, sometimes slightly lobulated or bosselated in contour and unencapsulated. The cut surface has been described as uniformly tan-brown, mahogany brown, dark brown, or reddish-brown, occasionally with a gray stellate central scar. Almost all ROs are solitary. Bilaterality occurs in about 4% [4] and multiple neoplasms in 11% [5] of cases.

Microscopically, it is a neoplasm composed exclusively of oncocytes. The tumor cells are regular, cuboid, or polygonal in shape. Their cytoplasm are eosinophilic and finely granular without perinuclear clearing. Nuclei are round, uniform, situated centrally, with coarse, mostly

peripherally located reticular heterochromatin and variably prominent nucleoli. There is no mitotic activity. The disposition of the cells is varying: solid sheets, nested or organoid arrangement, trabeculae, tubules, microcysts, and mixed pattern. The fibrous stroma is more abundant in the central scarred area and may show hyaline, edematous, or myxoid change. The tumor periphery is sharply defined [10].

Ultrastructural studies characteristically show abundant round to oval mitochondria filling the cytoplasm of the cells. These mitochondria have piled, long, lamellar cristae frequently arranged in parallel arrays. There is paucity of other organelles. Occasional matrical floccular woolly densities are also present [13, 14].

RO shows usually positive immunostaining for kidney-specific cadherin, cluster of differentiation (CD)117 (c-kit), antimitochondrial antibody, S100A1, discovered on gastrointestinal stromal tumor (GIST) 1 (DOG1), and cyclin D1 [12, 15, 16], and negative immunostaining for vimentin. Oncocytomas usually show minimal immunostaining for cytokeratin (CK)7 limited to individual cells or small cell groups. Carvalho *et al.* [17] proposed an immunohistochemical (IHC) panel composed of CK7, vimentin, S100A1, and CD117 in the differential diagnosis of RO from its mimics. CK7 is the most commonly used immunostaining technique for the diagnosis of oncocytoma. In a survey of urological pathologists, it was concluded that CK7 positivity of $\leq 5\%$ of tumor cells is supportive of oncocytoma [18]. Besides, the tumor cells around the central scar area may exhibit increased immunostaining for CK7 and positivity for vimentin [12]. Oncocytoma cells may show apical positivity for Hale's colloidal iron, but they do not show a cytoplasmic pattern.

Cytogenetically, oncocytomas may show either a diploid karyotype, loss of chromosomes Y, 1, 2, 8, 9, and 14, or translocations of 11q13. The breakpoint on chromosome 11q13 can have numerous partners including 6p21 and 9p23. An occasional translocation between chromosomes 6 and 9 has been reported [19]. However, no chromosome gains have been described [10]. Thus, oncocytomas are cytogenetically heterogeneous.

RO appears to be derived from type A intercalated cells of the cortical collecting duct system [20–22].

☞ Renal oncocytoma with uncommon, atypical, or worrisome features

RO is, in most circumstances, easily recognized based on the distinctive cytological and architectural features. However, since the seminal description of this neoplasm [2], distinct variants have been published. Diverse gross and microscopic pseudomalignant features, such as hemorrhage, small foci of necrosis, focal nuclear pleomorphism, sporadic mitotic figures, extension of tumor into perinephric fat or invasion of venous-type vessels, although of concern, are considered compatible with a diagnosis of oncocytoma, provided their extension is limited. Atypical features in oncocytoma were reported in variable percentages in different series [3–6]. Features typically associated with chromophobe RCC, such as binucleation, multinucleation, perinuclear clearing, or nuclear wrinkling are compatible with the diagnosis of oncocytoma depending on the

extension of these characteristics. Other features represent variants of the tumor. Table 1 includes a comprehensive list of the uncommon, atypical, or worrisome features that may be observed in RO [3–6, 9, 13, 18, 23–57].

Table 1 – Renal oncocytoma: unusual morphological features [Ref. #]

Focal or massive hemorrhage [3–6, 23]
Central cystic degeneration [24, 25]
Multicystic (multilocular) or tubulocystic pattern [26–28]
Focal cellular pleomorphism with mitoses absent or very rare [3–6, 13]
Vascular (venous) invasion [4–6, 29, 30]
Intra-neoplastic adipocytes [9, 31]
Calcification, including psammoma bodies [4, 5, 32]
Intranuclear inclusions [33]
Nuclear holes [3]
Binucleation [5]
Multinucleation [18]
Vacuolated cells [33]
Focal cytoplasmic clearing [3]
Focal nuclear wrinkling [18]
Osseous and myeloid metaplasia [4]
Isolated papillary formations into dilated tubules without true fibrovascular cores [3–5]
Small foci of necrosis [5, 6]
Extension into perinephric fat [3–6, 30] or sinus fat invasion [34]
Cilindromatous changes [35]
Oncocytoma with obliterative renal fibrosis [36]
Involvement by metastatic tumor [37, 38]
Multicentricity with growth in multiple nodules (oncocytomatosis or oncocytosis) [39–41]
Entrapped normal renal tubules at the oncocytoma periphery without desmoplastic response [3, 5]
Oncocytoma with focal chromophobe-like histology [5]
Hybrid oncocytoma/chromophobe renal cell carcinoma [42, 43]
Primary collision renal oncocytoma/other renal neoplasms [6, 44–50]
Presence of Gama–Gandy bodies [9]
Prominent xanthomatous reaction [3, 9]
Mucin-producing oncocytoma [51]
Small cell (oncoblastic) oncocytoma [52]
Small cell oncocytoma with pseudorosettes [53]
Oncocytoma with glassy hyaline globules [54]
Oncocytoma with prominent intracytoplasmic lumina [21, 55, 56]
Telangiectatic oncocytoma [57]

The following features are incompatible with the diagnosis of RO: grossly visible or extensive microscopic necrosis, gross involvement of the renal vein, prominent papillary architecture, conspicuous groups of clear cells, presence of spindled (or sarcomatoid) cellular transformation, readily found mitotic activity, or presence of any atypical mitotic figure [3, 5, 12, 18].

☞ Renal oncocytoma with prominent xanthomatous reaction

The presence of foamy macrophages in RO was only briefly mentioned in a reappraisal of 80 cases of oncocytoma previously published [3]. The authors observed foam cells in six (7.5%) cases, but a formal study was not performed. In 2010, we published a microscopic study of a series of three oncocytomas with intense xanthomatous reaction [9].

Currently, we have collected four cases of xanthomatous oncocytoma, including the three ones previously published, in a surgical pathology series of 93 ROs in 92 patients. Thus, significant lipid-laden foamy macrophages were observed in 4.3% of the ROs.

The clinicopathological features of the four cases are included in Table 2. The mean patient age was 51 years (range, 37–66 years), with male/female ratio of 3:1. The laterality right/left ratio was 3:1. Associated lesions were multiple homolateral papillary adenomas (one case), homolateral angiomyolipoma (one case), and contralateral typical RO (one case). Mean tumor size was 2.9 cm (range, 0.8–6.0 cm). Macroscopically, all the tumors were well circumscribed but unencapsulated. No central scar was seen. These tumors were dark brown with prominent mixed yellow areas. The yellow areas were scattered (Figure 1A) or relatively localized (Figure 1B), but always striking. Thus, RO rich in lipid-laden foam (xanthomatous) cells may have mixed yellow areas similar to the clear cell RCC. This variegated appearance may pose a significant diagnostic problem because it creates a departure from the typical uniform appearance of this neoplasm.

Table 2 – Clinicopathological features of renal oncocytomas with xanthomatous cells

Case No.	Age [years]/gender	Laterality	Size [cm]	Macroscopic yellow areas	Predominant histological pattern	Other renal lesions
1.	66/F	Right	0.8	Disseminated	Microcystic	Angiomyolipoma (4.5 cm), right papillary adenomas
2.	60/M	Right	2.0	Disseminated	Microcystic	None
3.	37/M	Right	2.3	Disseminated	Microcystic	Left typical oncocytoma (3.7 cm), right papillary adenomas
4.	41/M	Left	6.5	Located	Mixed, tubular, microcystic, and trabecular	None

F: Female; M: Male.

Histopathologically, the tumors were composed of round to polygonal cells arranged predominantly in microcysts in three cases and tubules, microcysts, and trabeculae in another case. The cytoplasm was dense, granular, and acidophilic. The nuclei were regular, round, with dispersed finely granular chromatin. Nucleoli were centrally placed but small, occasionally prominent. No mitoses were present. Zones of recent interstitial or microcystic intraluminal hemorrhage were common (Figure 2A). Groups of macrophages with hemosiderin granules were observed in the vicinity of those areas (Figure 2B). One tumor showed large Gamna–Gandy (fibrosiderotic) bodies (Figure 3A). Scattered dystrophic small, calcification foci (calcospherites) were also seen (Figure 3B). Commonly, the lumen of dilated tubules, microcysts, and stroma were filled with aggregates of lipid-laden foamy macrophages along with the tumors. The size of the foamy aggregates varied from large areas (Figure 4A) to small groups in the dilated tumor tubules (Figure 4B). Isolated xanthomatous cells were also scattered among the tubules or microcysts. Sometimes, Touton giant cells and cholesterol clefts were seen distributed with the foam cell aggregates (Figure 5A). Infrequent pseudopapillae projecting into the lumina were observed in one tumor (Figure 5B). Dispersed small groups of lymphocytes were observed infiltrating the stroma in two tumors (Figure 6A). Necrosis or mitoses were not seen.

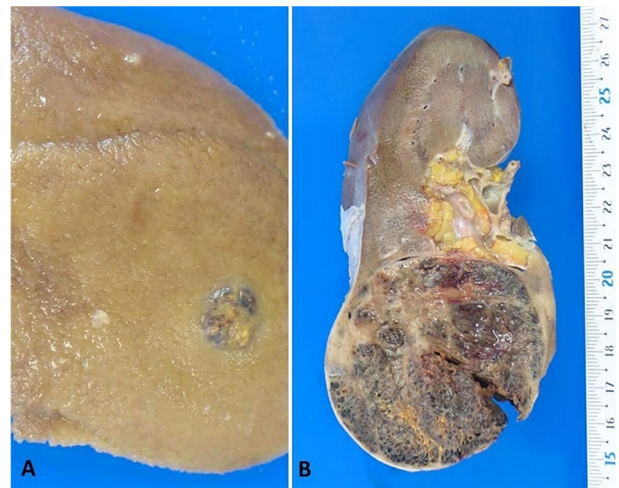


Figure 1 – Gross features of the renal oncocytoma rich in xanthomatous cells. Tumors are dark brown with prominent mixed yellow areas: (A) Lower pole variegated oncocytoma 0.8 cm in diameter with scattered yellow areas; there are associated papillary adenomas (from Case No. 1); (B) Lower pole oncocytoma 6.5 cm in diameter with prominent localized yellow areas (from Case No. 4).

In one case, there was bone metaplasia, and adipose tissue in the stroma (Figure 6B).

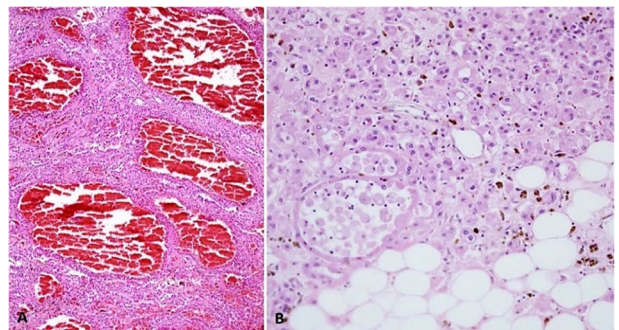


Figure 2 – Histopathology of the xanthomatous oncocytoma: (A) Recent hemorrhagic areas (from Case No. 4); (B) Presence of hemosiderophages (from Case No. 2). Hematoxylin–Eosin (HE) staining: (A) ×100; (B) ×200.

The immunostaining for vimentin, CD10, alpha-methyl-coenzyme A racemase (AMACR), and transcription factor E3 (TFE3) was negative in tumor cells. Hale's colloidal iron did not show a cytoplasmic pattern. Scant scattered cells showed positive immunostaining for CK7 (Figure 7). Neoplastic cells displayed strong diffuse positivity for the antimitochondrial antibody (Figure 8A). Positivity for c-kit (CD117) was observed in three tumors. The lipid-laden foamy macrophages showed intense positivity for CD68 (Figure 8B).

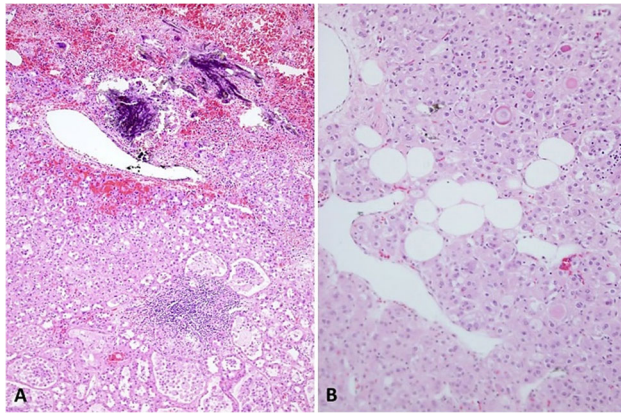


Figure 3 – Histopathology of the xanthomatous oncocytoma: (A) Large Gamna-Gandy (fibrosiderotic body or “tobacco flecks”) in relation to a bleeding area (from Case No. 2); (B) Scattered concentric laminated bodies (psammoma bodies or calcospherites) (from Case No. 2). HE staining: (A) $\times 100$; (B) $\times 200$.

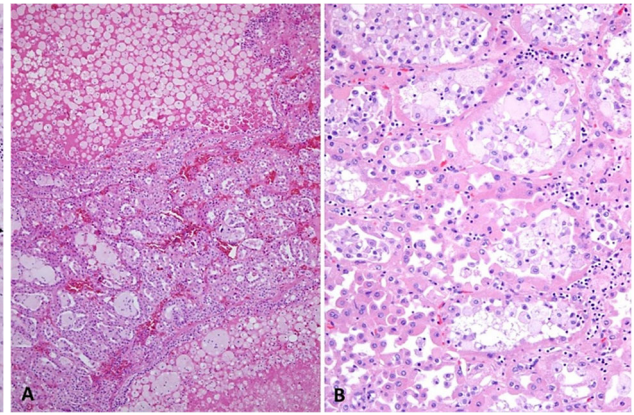


Figure 4 – Histopathology of the xanthomatous oncocytoma: (A) Large tumor areas are occupied by foamy macrophage aggregates (from Case No. 4); (B) Microcystic growth pattern of the oncocytoma; the lumina of dilated tubules are filled with collections of foamy macrophages (from Case No. 2). HE staining: (A) $\times 100$; (B) $\times 200$.

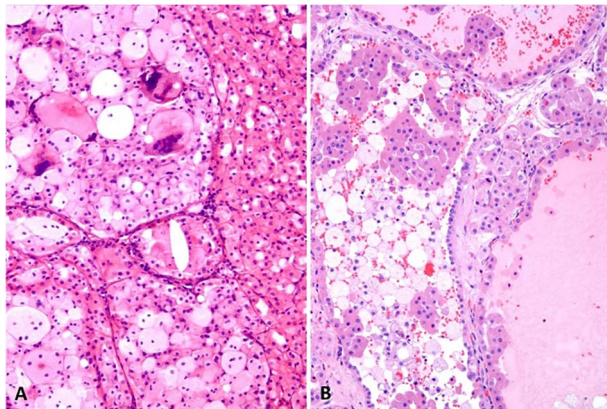


Figure 5 – Histopathology of the xanthomatous oncocytoma: (A) Touton giant cells and cholesterol clefts can be seen interspersed with the collections of foamy macrophages (from Case No. 1); (B) Pseudopapillae formations with absence of true fibrovascular cores are projecting into dilated tubules (from Case No. 1). HE staining: (A and B) $\times 200$.

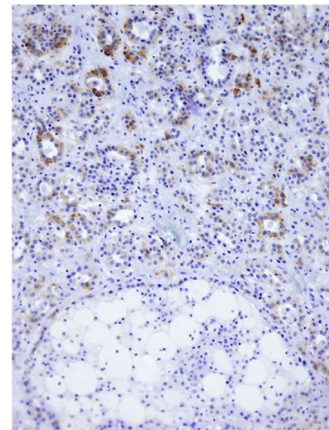


Figure 7 – Immunohistochemistry ($\times 200$): focal positivity for cytokeratin 7 in a small number of tumor cells (from Case No. 4).

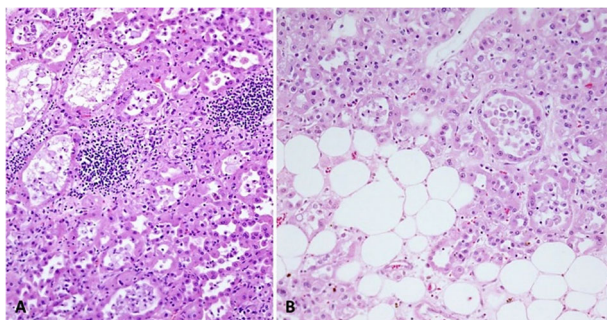


Figure 6 – Histopathology of the xanthomatous oncocytoma: (A) Dispersed small groups of lymphocytes can be seen infiltrating the stroma (from Case No. 3); (B) Stromal infiltration by adipose tissue (from Case No. 3). HE staining: (A and B) $\times 200$.

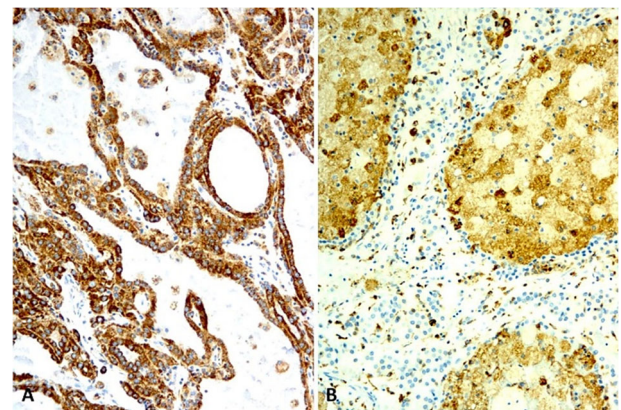


Figure 8 – Immunohistochemistry ($\times 200$): (A) Strong positivity in tumor cells for antimitochondrial antibody (from Case No. 4); (B) Numerous CD68-positive macrophages can be seen filling the microcysts and scattered in the stroma (from Case No. 4).

The list of renal tumors with significant infiltration by foamy macrophages includes tubulo-papillary adenoma [58], papillary RCC [59], papillary renal neoplasm with reverse polarity [60], oncocytic papillary RCC [61], oncocytic papillary RCC with solid architecture [62],

oncocytoid RCC after neuroblastoma [63], cystic RCC [64], unclassified RCC [65], succinate dehydrogenase (SDH)-deficient RCC, mucinous tubular and spindle cell carcinoma (SpCC) [66], and epithelioid angiomyolipoma [67].

According to our description, RO should be added to the list of renal tumors that can show a significant reaction of lipid-laden foamy macrophages.

We estimate that the formation of lipid-laden foamy macrophages is secondary to damage to cells, including tumor cells and intraneoplastic erythrocytes. The presence, in one case, of large Gamna–Gandy bodies or nodules, which represent post-hemorrhage organization and fibrosis with thick collagen fibers encrusted with iron and calcium salts, and the association with bone metaplasia and adipose tissue in the stroma, may indicate a longer duration of the tumor. Gamna–Gandy bodies have also been reported in clear cell RCC [68].

☞ Main differential diagnosis of the xanthomatous oncocytoma

The present review, illustrating an uncommon change, expands the morphological spectrum of oncocytoma of the kidney. The presence of abundant foamy macrophages can potentially mask the customary appearance of this tumor and may lead to confusion with other neoplasms of the kidney. RO rich in foamy macrophages should be differentiated from conventional (clear cell) RCC, cystic RCC, unclassified RCC rich in lipid-laden foamy macrophages, eosinophilic variant of chromophobe RCC, solid variant of papillary RCC with oncocytic features, oncocytoid RCC after neuroblastoma, SDH-deficient RCC, mucinous tubular and SpCC, epithelioid angiomyolipoma, and oncocytic angiomyolipoma [69, 70].

Macroscopically, oncocytomas rich in foamy macrophages are tan-brown with yellow areas similar to conventional RCCs. However, these last tumors show a sinusoidal vascular network, and they are positive for vimentin, CD10, carbonic anhydrase 9 (CA9), and RCC marker. Nuclei are centrally located and more rounded in oncocytoma than in conventional RCC. Nevertheless, it is necessary to stand out that there is a risk of missing the diagnosis of an RCC when lipid-rich foamy macrophages are in abundance [65]. A cystic RCC may also contain numerous xanthomatous cells and scant clusters of clear cells in the fibrous wall of the cyst [64].

Perinuclear haloes, raisinoid nuclei, frequent binucleation (koilocytoid atypia) [71], and prominent cell membranes (“cobblestone or vegetable cells”) are commonly seen in the eosinophilic variant of chromophobe RCC [72]. Atypical cells in this tumor are evenly distributed, not in clusters as they are in oncocytoma [72]. Chromophobe RCC shows diffuse positivity for CK7. As far as we are aware foamy macrophages have not been reported in this neoplasm [72]. The diagnosis of the oncocytic variant of chromophobe RCC requires immunostaining for CK7 and cytogenetic study demonstrating monosomies or gains of chromosomes [73].

Papillary RCC with oncocytic cells shows a diffuse expression of CK7, CD10, and AMACR. Vimentin and RCC marker can also be expressed. On the other hand, if there are obvious papillary projections the tumor is unlikely to be an oncocytoma. The solid variant of the papillary RCC with oncocytic cells [62] poses a differential diagnosis problem with RO because both may show diffuse growth pattern, occasional papillae, venous or adipose tissue

invasion, and foamy macrophages. The IHC panel helps to solve the problem.

The mean age at the time of diagnosis of post-neuroblastoma RCC is about nine years (range 5–13 years) [63]. The tumor shows oncocytoid cells arranged in papillary and solid growth patterns. Some cells may show a reticular cytoplasm. Tumor cells are reactive for CK8 and CK18. Some cases are positive for CK20 [63]. One case in a 40-year-old woman showed cells with voluminous cytoplasm depicting the typical stippling seen in the eosinophilic solid and cystic RCC. The tumor displayed prominent foam cells and demonstrated two tuberous sclerosis complex 2 (*TSC2*) mutations [74].

SDH-deficient RCC is characterized by medium-sized oncocytic cells with prominent pale cytoplasmic vacuoles or inclusions of flocculent material, and loss of SDH-B expression by immunohistochemistry. Xanthomatous cells can be observed within the lumina of microcystic structures. Interstitial mast cells are conspicuous [75].

Mucinous tubular carcinoma and SpCC may show a classical morphology or diverse variants including cases with tubular predominance without mucinous matrix. Unusual cases present prominent oncocytic tubules, papillations, focal clear cells, necrosis, and foamy macrophages [66]. Tumor cells are usually reactive for claudin-7, CK7, and AMACR.

Oncocytic angiomyolipoma lacks the atypical features of the epithelioid variant of angiomyolipoma. It is composed of solid sheets of epithelioid, eosinophilic cells with abundant cytoplasm and polygonal contours. Nuclei are single with central nucleoli and occasional cytoplasmic pseudoinclusions. Glandular architecture is not observed [68]. The tumor shows positivity for human melanoma black 45 (HMB45), Mart-1/Melan-A, and smooth muscle actin, and negativity for the epithelial markers.

☞ Conclusions

RO ordinarily does not offer diagnostic difficulties. However, the presence of a prominent intraneoplastic xanthomatous reaction produces a variegated macroscopic appearance that may pose a significant diagnostic problem with conventional RCC, because this reaction creates a departure from the typical uniform, tan-brown appearance of oncocytoma. The microscopic presence of foamy macrophages in RO may potentially lead to diagnostic difficulties with tumors exhibiting eosinophilic cells and significant infiltration for lipid-laden foamy macrophages. In conflictive cases, an IHC panel should help to solve the diagnostic problem. Therefore, the presence of abundant foamy macrophages should not dissuade the pathologist from establishing a diagnosis of RO. Prominent xanthomatous reaction despite its low frequency (4.3%) can be considered an additional feature of RO. Besides, Gamna–Gandy bodies can be present in this tumor. Awareness of these changes should allow for improved recognition of RO.

Conflict of interests

The authors declare that they have no conflict of interests.

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