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Ultrastructural characteristics of primary renal epithelial tumours with granular oncocytic cytoplasm

Ultrastrukturne karakteristike primarnih epitelnih tumora bubrega sa granuliranom-onkocitnom citoplazmom

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Abstract

Background/Aim. Ultrastructural analysis of tumours has shown many common characteristics of certain neoplasms, as well as their specificities. Primary renal epithelial tumours with granular oncocytic cytoplasm is a very heterogeneous group in their histological origin and biological behaviour, which results in a difference in treatment and prognosis of the disease, making accurate morphological diagnosis necessary. The aim of this study was to determine ultrastructural similarities and differences among primary renal epithelial tumours with granular oncocytic cytoplasm. **Methods.** The analysis of archival and routine material in the archives of the Department of Pathology, University Hospital in Plzen, Czech Republic, as well as archival and routine material in the Centre for Pathology and Histology, Clinical Centre of Vojvodina in Novi Sad, discovered 346 primary renal epithelial tumours with granular oncocytic cytoplasm and divided them into 5 groups: 1) renal oncocytoma (RO) (234 tumours), 2) oncocytic papillary renal cell carcinoma (O-PRCC) (12 tumours), 3. sporadic renal hybrid oncocytic/chromophobe tumour (HOCT) without evidence of Birt Hogg Dubé syndrome (BHD) (14 tumours), 4) chromophobe renal cell carcinoma (ChRCC) (21 tumours) and 5) granular renal cell carcinoma (RCC) [64 tumours + 1 clear cell RCC (CRCC) with hyaline globules]. Ultrastructural analysis of tumour cells at the subcellular level was done using electron microscope (Philips electron microscope TEM 208) at the Department of Pathology, University Hospital in Plzen, Czech Republic. Cellular organelles and pigments were evaluated in 5 tumours from each group according to the simple random sample principle with a total of 30 analysed tumours. **Results.** In all analysed primary renal epithelial tumours with granular oncocytic, cytoplasm dominant organelles were mitochondria. Specific ultrastructural characteristics of RO were round mitochondria with lamellar cristae, whereas ChRCC had numerous typical cytoplasmic microvesicles 100–700 nm large and mitochondria with tubulovesicular, lamellar and circular cristae. Ultrastructural specificity of hybrid tumours were rare microvesicles and numerous mitochondria of O-PRCC mitochondria with lamellar cristae and small intracytoplasmic vesicles, 100–200 nm large, and of granular RCC, in addition to mitochondria, also glassy hyaline globules (GHG). **Conclusion.** Ultrastructural analysis indicates mitochondria as the dominant organelle in the analysed tumours. Electron microscopy showed specificities, i.e., differences in appearance of cristae, presence and size of vesicles as well as deposition of pigment in and out of cytoplasm and glassy hyaline globules.

Key words:
kidney neoplasms; microscopy, electron; diagnosis, differential; mitochondria; cytoplasmic granules.

Apstrakt

Uvod/Cilj. Ultrastrukturnom analizom tumora uočene su mnoge zajedničke osobine nekih neoplazmi, ali i specifičnosti. Primarni tumori bubrega sa granuliranom–onkocitnom citoplazmom su veoma heterogena grupa po svom histološkom poreklu i biološkom ponašanju, što rezultuje različitim u terapiji i prognozi bolesti, zbog čega je neohodna precizna morfološka dijagnostika. Cilj rada bio je određivanje ultrastrukturnih sličnosti i razlika između primarnih epitelnih tumora bubrega sa granuliranom-onkocitnom citoplazmom. **Metode.** Analizom arhivskog i rutinskog materijala arhive Departmana za patologiju, Fakultetske bolnice u Plzenu, Republika Češka i Centra za patologiju i histolo-

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giju, Kliničkog centra Vojvodine u Novom Sadu, pronađeno je 346 primarnih renalnih epitelnih tumora sa granuliranom-onkocitnom citoplazmom koji su razvrstani u 5 grupa: 1. renalni onkocitomi (RO) (234 tumora); 2. onkocitni papilarni karcinomi bubrega (O-PRCC) (12 tumora); 3. sporadični hibridni onkocitno/hromofobni tumori bubrega (HOCT) van Birt Hogg Dubé sindroma (BHD) (14 tumora); 4. hromofobni karcinomi bubrega (ChRCC) (21 tumor) i 5. granulirani karcinomi bubrega (RCC) [64 tumora + 1 *clear cell* RCC (CRCC) sa hijalinim globulama]. Vršena je ultrastrukturna analiza tumorskih ćelija, na subcelularnom nivou, elektronskim mikroskopom (Philips elektronski mikroskop TEM 208), Departmana za patologiju, Fakultetske bolnice u Plzenu, Republika Češka. **Rezultati.** U svim analiziranim primarnim epitelnim tumorima bubrega sa granuliranom-onkocitnom citoplazmom dominatne organele bile su mitohondrije. Specifične ultrastrukturne osobine za RO bile su okrugle mitohondrije sa lamelarnim kristama, za ChRCC brojne tipične, citoplazmatske mikrovezikule, veličine 100–700 nm i mitohondrije sa tubulovezikularnim, lamelarnim i cirkularnim kristama. Ultrastrukturna specifičnost za hibridne tumore bile su retke mikrovezikule i brojne mitohindrije, za O-PRCC mitohondrije sa lamelarnim kristama i male intracitoplazmatske vezikule veličine 100–200 nm, a za granulirane RCC pored mitohondrija i „glassy" hijaline globule (GHG). **Zaključak.** Ultrastrukturna analiza ukazuje na mitohondrije, kao dominatnu organelu u analiziranim tumorima. Elektronskom mikroskopijom uočene su i specifičnosti, odnosno razlike u izgledu krista, prisustvu i veličini vezikula, kao i deponovanje pigmenta u i van citoplazme, te "glassy" hijalinih globula.

Ključne reči:
bubreg, neoplazme; mikroskopija, elektronska; dijagnoza, diferencijalna; mitohondrije; citoplazmatske granule.

Introduction

In 1931 Ruske and Knoll constructed the first electron microscope which was used for ultrastructural analysis of different tissues [1]. The aim of ultrastructural tissue analysis is to detect the smallest cytological characteristics of tissue and characteristics at the subcellular level (presence and appearance of organelles). Normal cells of certain tissues as well as tumour cells of different neoplasm have their specificities, but also common characteristics [1, 2].

As a differential diagnostic problem in daily histopathological diagnostics of a uropathologist, a group of primary renal epithelial tumours with granular oncocytic cytoplasm stands out. This group is very heterogeneous in its histological origin and biological behaviour, which results in a difference in treatment and the prognosis of the disease. An accurate histopathological diagnosis of this group of tumours contributes significantly to the diagnostics and treatment of patients with the aforementioned types of tumours. In some cases, after standard pathohistological analysis, immunohistochemical staining, and molecular-genetic analyses, a definitive diagnosis of the type of renal epithelial tumours with granular oncocytic cytoplasm cannot be made. In that case, ultrastructural analysis of the tumour, by means of electron microscope, can provide substantial assistance, point out some ultrastructural tumour specifics and direct us towards the correct diagnosis.

Renal oncocytoma (RO) is a benign renal epithelial tumour, representing approximately 4%–9% of all renal tumours [3, 4]. Electron microscopy shows round nuclei and cytoplasm filled with mitochondria, generally exhibiting lamellar cristae [3, 4].

Renal hybrid oncocytic/chromophobe tumour (HOCT) appears in patients with the Birt Hogg Dubé (BHD) syndrome, or without evidence of it (sporadic). This tumour can be associated with renal oncocytosis, also within the aforementioned syndrome. HOCT without evidence of BHD syndrome, or renal oncocytosis is very rare. Ultrastructurally, as well as histologically, it can have characteristics of two components: chromophobe carcinoma and oncocytoma [3–10].

Papillary/chromophilic renal cell carcinoma (PRCC) is the second most frequent RCC with incidence of 11%–15%. Its five-year and ten-year survival rates are higher than in clear-cell RCC (CRCC), although some studies suggest that there is no difference between CRCC and PRCC. PRCC with oncocytic cytoplasm and low-grade nuclei are referred to as oncocytic, PRCC having a biological behaviour of type 1 PRCC. Ultrastructurally, beside mitochondria with glycogen granules, they have basal infoldings [5–7, 11–17].

Chromophobe renal cell carcinoma (ChRCC) is the third most common when talking about the subtypes of RCC. It was first published in 1985 by Thoenes et al. [16] and other authors [5–7, 17–19]. Its prognosis is much better than the one for CRCC, with indolent course of disease, and some studies give it even better prognosis than for PRCC [3, 4]. Electron microscopy shows cytoplasmic vesicles and abundance of mitochondria, often with tubulocystic cristae.

CRCC is characterized by the von Hippel-Lindau gene mutation (3p25-26) or chromosome 3p loss. CRCC is the most aggressive and most common histologic type of carcinoma, with five and the ten-year survival rates of 75%, and 62% respectively. Eosinophilic variant of clear cell renal cell carcinoma/granular cell RCC occurs as part of conventional CRCC, as larger and smaller areas of cells with eosinophilic cytoplasm, or in a pure form. Differentiating granular RCC from ChRCC and RO is one of the most difficult differential diagnostic problems in renal pathology. Unlike chromophobe cell carcinoma, which is an indolent, and RO, which is a benign tumour, granular RCC is a very aggressive neoplasm. Electron microscopy shows mitochondria as the dominant organelle and a fewer number of microvesicles [16, 17, 20–23].

Methods

The study was retrospective and prospective. It included the patients with primary renal epithelial tumours with granular oncocytic cytoplasm, after partial, or total nephrectomy. Routine and archival materials were used, lo-

cated in the computerised archives of the Department of Pathology of the University Hospital in Plzen, Czech Republic, as well as archival and routine materials of the Centre for Pathology and Histology, Clinical Centre of Vojvodina in Novi Sad, Republic of Serbia.

In the period from January 2010 to December 2015, after examination of both archives and daily routine diagnostics, the study included 346 primary renal epithelial tumours with granular oncocytic cytoplasm that were classified into 5 groups: 1) RO (234 tumours), 2) oncocytic PRCC (O-PRCC) (12 tumours), 3) sporodic HOCT (14 tumours), 4) ChRCC (21 tumours), and 5) granular RCC (64 tumours + 1 CRCC with glassyhyaline globules).

The ultrastructural analysis of tumour cells at the subcellular level was done using electron microscope (Philips electron microscope TEM 208), at the Department of Pathology, University Hospital in Plzen, Czech Republic, with cellular organelles and pigments evaluated in 5 tumours from each group according to the simple random sample principle, with the total of 30 tumours.

The small pieces of wet and formalin-fixed tissue of about 1 mm² were cut into drops of fixative into small pieces and then transferred to the fixative (4% solution of glutaraldehyde in 0.1M Na-cacodylate buffer pH 7.3) where they were held for two hours at a temperature of 4°C. After two to three rapid changes in Na-cacodylate buffer, the material was postfixed in 1% solution of OsO4 in 0.1M Na-cacodylate buffer at 4°C, for 2 hours. This was followed by two to three rapid changes in Na-cacodylate buffer and the samples were stored overnight in a 4% uranyl acetate solution, in order to increase the contrast of the material. The segments were then put through a series of alcohols (25%, 50%, 70%, 80%, 90% and 100%), followed by dehydration and "illumination" by keeping them in propylene oxide two times for 10 minutes. The sampling in resin was done at room temperature, through three different mixes of propylene oxide and Epon resin (3:1, 1:1, 1:3). This way, samples were put into pure Epon resin and held in it overnight at room temperature. After embedding in the plastic pellets, the resin was polymerized at 60°C for three days. After completed polymerization samples were cut on LKB ultramicrotome III, with the glass and diamond knives. Sections up to 1 micron thick- semi-fine sections were cut first. The sections were transferred to glass slides and stained with aqueous toluidine blue and borax solution, over a flame, at a temperature of 80°C. The molds were cut with a diamond knife on a LKB ultramicrotome III, to the thickness of the section of 30–50 nm, placed on the copper-meshes coated with paraffin. Subsequently, they were positively stained for 20 minutes with 5% uranyl acetate solution, and then washed with redistilled water, and air-dried. Dry sections were stained with Reynolds lead citrate solution for 10 minutes, then washed and dried again.

The analysis of stained sections was performed using the Philips electron microscope TEM 208, at the Department of Pathology, University Hospital in Plzen, Czech Republic.

Results

After the histopathological evaluation using the standard hematoxylin and eosin (HE) staining, immunohistochemical staining and molecular genetic analyses, tumours were classified into 5 groups and ultrastructurally analysed.

Using electron microscope, the ultrastructure of RO was analysed, with some having small cell components and/or pseudorosettes. Figure 1A shows the ultrastructure of small cell variant of RO. Classical oncocyte had typical cytoplasm packed with numerous round mitochondria, with lamellar cristae. Mitochondria were also the most common organelles in small cells, but in considerably smaller number compared to classical tumour component. Microvilli and plasmalemma elements could not be observed in either cell types. The ultrastructural analysis of the two RO with vascular invasion showed oval nuclei with small nucleoli. Cytoplasm of tumour cells was packed with predominantly lamellar mitochondria. Cytoplasmic lumens, covered with short microvilli could be observed in some places. Luminal surface of oncocytic cells was also coated with microvilli.

The findings were consistent in all cases of renal hybrid oncocytic-chromophobe tumour analysed using the electron microscope. Neoplastic cells had numerous mitochondria, of different sizes. Rare microvesicles with amorphous lamellar content were also detected. Tumour cells with abundant microvesicles in their cytoplasm were not noticeable. Nuclei were mostly round and with hardly noticeable nucleoli. Small intracytoplasmic tubules covered in microvilli were observed in one case.

The ultrastructural analysis of O-PRCC showed cytoplasm filled with numerous mitochondria with lamellar cristae (Figure 1B). Other organelles were present separately. Intracytoplasmic vesicles were 100 to 200 nm in diameter and granular endoplasmic reticulum was rarely noticeable.

Tumour cells of renal chromophobe carcinoma showed weaker bond-forming in outer lamina. Two main intracellular components were detected: typical cytoplasmic vesicles, commonly observed in ChRCC, 100–700 nm in size (Figure 1C), and mitochondria with tubulovesicular, lamellar and circular cristae.

In addition to preserved mitochondria, there were also the degenerated ones with alternately oriented internal cristae. Some tumour cells contained dark, electronically dense pigment pellets, that corresponded to the brown pigment observed under the light microscope. The aforementioned pigment pellets were round to polygonal (Figure 1D).

In addition, some tumours had vesicles containing tiny beads of the same dark, electronically dense material as the granules. This material melted and built larger pigment pellets. Melanosomes and neurosecretory pellets in neoplastic cells could not be observed in any of the analyzed cases.

Mitochondria were also dominant organelles in granular CRCC. Ultrastructurally smallest GHG was like an amorphous secretion within a cisterna of granular endoplasmic reticulum (Figure 1E). Ultrastructurally larger GHG were in the form of globules, filled with amorphous material, inside cytoplasm or extracellularly.

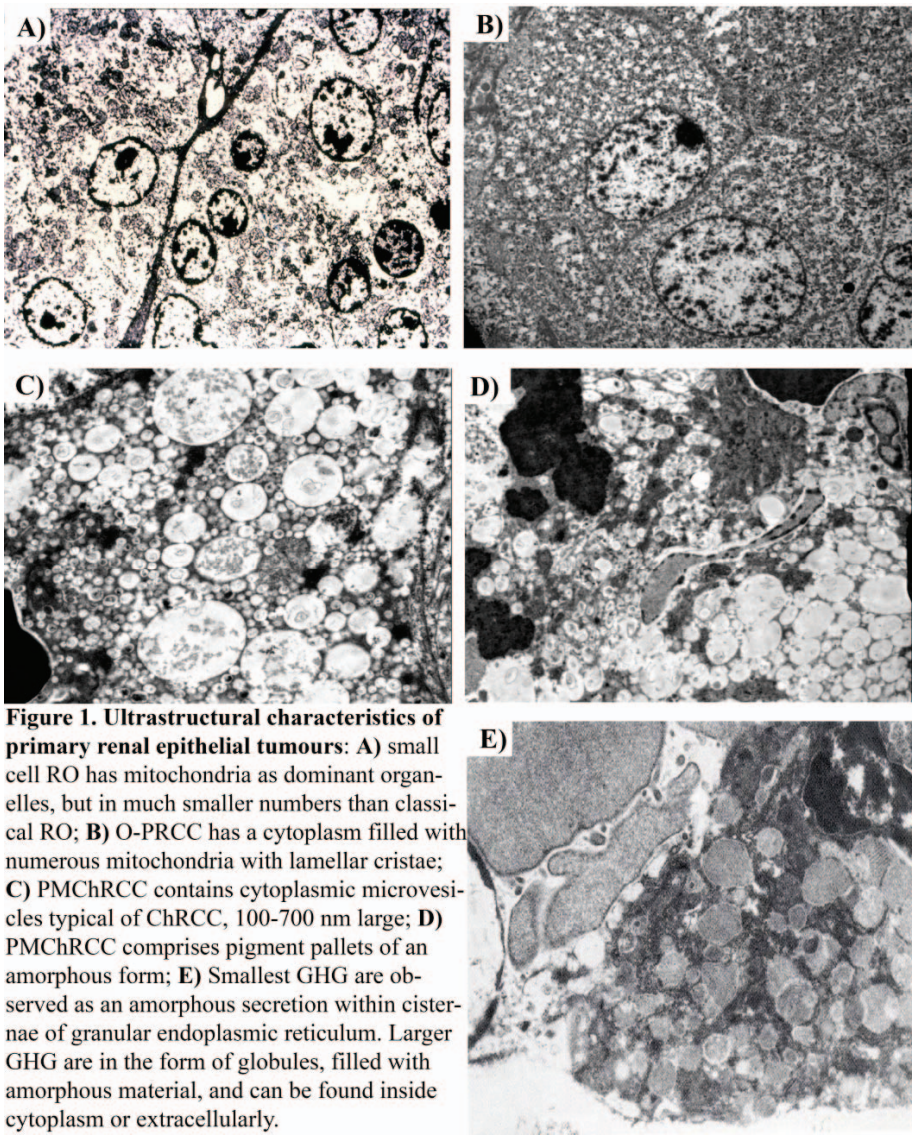

Figure 1. Ultrastructural characteristics of primary renal epithelial tumours: **A)** small cell RO has mitochondria as dominant organelles, but in much smaller numbers than classical RO; **B)** O-PRCC has a cytoplasm filled with numerous mitochondria with lamellar cristae; **C)** PMChRCC contains cytoplasmic microvesicles typical of ChRCC, 100-700 nm large; **D)** PMChRCC comprises pigment pallets of an amorphous form; **E)** Smallest GHG are observed as an amorphous secretion within cisternae of granular endoplasmic reticulum. Larger GHG are in the form of globules, filled with amorphous material, and can be found inside cytoplasm or extracellularly.

RO – renal oncocytoma; O-PRCC – oncocytic papillary renal cell carcinoma; PMChRCC – psammoma chromophobe renal cell carcinoma; GHG – glassy hyaline globules.

Discussion

Under the electron microscope, classical oncocytoma showed typical picture of small nuclei with nucleoli and cytoplasm, with densely packed round mitochondria with lamellar cristae, which is in accordance with other literature references [24–27]. In small cells, mitochondria were also the most prevalent organelles, although the number of mitochondria was significantly lower than in the traditional components. Ultrastructurally, microvesicles with amorphous lamellar content were barely present. These structures were typically abundantly present in neoplastic cells of the conventional ChRCC, however, they were often damaged due to inadequate fixation. Microvesicles that can be seen in almost all chromophobe RCC and are rarely described in RO, were not detected in our cases [28].

Ultrastructurally, cytoplasm of renal hybrid oncocytic-chromophobe tumour also had numerous mitochondria of different sizes, with rare microvesicles with amorphous lamellar content, and it could differentiate it from ChRCC, with which it had the greatest morphological similarity [29]. Nuclei were mostly round, with very rarely observed nucleoli, and the presence of small intracytoplasmic tubules covered with microvilli, in one case, could also facilitate the diagnosis and indicated this rare type of tumour with granular oncocytic cytoplasm.

The cytoplasm of O-PRCC tumour cells was packed with large mitochondria that had lamellar cristae, such as those seen in RO. This finding has already been described by Erlandson et al. [27], in the example of two cases of papillary RCC.

In terms of differential diagnosis, psammoma ChRCC (PMRCC) is a challenging tumour. Considering its more indolent behavior compared to other renal cell carcinomas, it is important to distinguish ChRCC from RO, which is sometimes very difficult. In general RO shows a wide spectrum of

morphological images. RO polygonal tumour cells are typically uniform, usually with abundant eosinophilic cytoplasm filled with mitochondria, but without vesicles whose diameter is, in case of ChRCC, 100–700 nm [20, 27, 30]. The psammoma bodies and calcifications are often present in both RO and PMChRCC. Dark brown pigment and architectural features we listed as well as its morphological diagnostic characteristics should be helpful in diagnosing PMChRCC.

Glassy hyaline globules can occasionally be seen in tumours of several organs, brain, liver, breast, lung, adrenal gland [31–33] and gonads (tumours of germ cell and non-germ cell origin). Even if hyaline globules in these organs have similar appearance, they probably represent heterogeneous structures with different histogenesis. Our experience is that GHG is rarely seen in low-grade papillary RCC. These tumours are practically easily confused with granular RCC. GHG of similar appearance to those that we described in our study have previously been described in RCC [34, 35]. Datta [36] published a case of RCC with globules of ultrastructural appearance similar to the appearance of structures with osmiophilic, dense aggregates, i.e., fine granules without the membrane, which were closely arranged in relation to the strips of granular endoplasmic reticulum. In other paper, describing hyaline globules in RCC, Jagirdar et al. [35] made a parallel between them and Mallory bodies in the liver. We do not know of any systemic study that described the extent of GHG in different types of renal carcinoma. In our work, it was observed that GHG were specifically present in granular and mixed type of clear/granural cells of RCC. Globules were not detected in cases of ChRCC and RO. This finding may potentially be significant, for it is sometimes very difficult to distinguish between the two types of tumour, ChRCC and RO. It is believed that in general, the so-called metastasising RO represents probably misdiagnosed granular RCC, or chromophobe RCC [36, 37].

The most commonly diagnostic methods employed to find differences between renal tumours with granular-oncocytic cytoplasm, the standard HE staining, histochemical, immunohistochemical and sometimes molecular genetics, often do not provide enough criteria to give additional information in establishing the diagnosis. It seems that the most effective one is electron microscopy, but it is still a quite expensive and time-consuming method. Correct diagnosis is very important, as the prognoses for these three types of tumours are significantly, dramatically different. Chromophobe RCC is a relatively indolent type of carcinoma, RO is a benign neoplasm [21, 23], and granular RCC is an aggressive type of tumour [16, 21–23]. Identification of GHG in granular RCC can serve as a potentially valuable and reliable morphological finding in distinguishing these tumours. Identification of GHG is easy and reproducible. It can be used to diagnostically separate granular and mixed type of clear/granular cell RCC from chromophobe renal cell carcinoma and renal oncocytomas.

Bonsib et al. [38] described globular filamentous bodies in RO that should not be identified as, or mistaken for GHGs. He detected these globules in 16 out of 20 cases of RO, but they were not observed in 35 renal cell carcinomas (clear cell, granular cell, papillary and chromophobe RCC) [39, 40]. The aforementioned globular filamentous bodies differ significantly from GHGs that we described. Ultrastructurally, they look like discreet round to oval cytoplasmic foci, poor of mitochondria, containing collections of intermediate filaments, occasionally mixed with lipid drops, lysosomes, mitochondria, smooth endoplasmic reticulum or lamellae of Golgi apparatus. The described structures probably belong to the family of similar bodies seen in a variety of tumours, named after globular filamentous bodies, by Ghadially [39]. Under the light microscope, unlike GHG in granulated RCC, they are easily detectable and in our opinion should not be morphologically mistaken for GHG.

Another type of hyaline globules in RCC and oncocytoma was described by Gatalica et al. [40]. They cite the PAS-positive spherical accumulations of amorphous materials with extracellular localisation. Ultrastructurally, hyaline globules in their case were constructed of materials of the basal membrane. GHG differ from the aforementioned hyaline globules (HG), in that they are frequently intracellularly localised, and ultrastructurally, they originate from cisternae of granular endoplasmic reticulum, such as the amorphous secretion [39–41].

Pathohistological classification of renal tumours with granular-oncocytic cytoplasm is not always simple and routine, because in such cases the diagnosis should include standard pathohistological analysis, immunohistochemical stainings, molecular genetics i.e., cytogenetics and ultrastructural analysis, as was cited and done by other authors in their studies [26, 42–47].

Conclusion

In RO mitochondria represent the most prevalent organelles, although the number of mitochondria is significantly lower in oncoblasts, the small cell components, than in a traditional, i.e., oncocytes. Ultrastructurally, small cell RO with pseudorosettes also have numerous mitochondria of different sizes. O-PRCC contains numerous large mitochondria with lamellar cristae, just like renal oncocytomas. PMChRCC contains cytoplasmic vesicles typical of ChRCC, and mitochondria with tubulovesicular, lamellar and circular cristae. The presence of GHG in granular RCC can serve as a potentially valuable and reliable morphological finding in distinguishing this tumour from chromophobe RCC and RO. GHG are present in "pure"granular RCC and the mixed type of clear/granular cell RCC and are related to the poor differentiation, necrosis and bleeding. GHG are not specific for RCC, but can be useful when we encounter metastatic carcinoma of unknown origin, since the presence of GHG in the background of eosinophil cells, granular cytoplasm, or metastatic carcinoma always cause suspicion of renal carcinoma. Electron microscopy, as an expensive and time-consuming method, is the last resort in diagnosis of renal epithelial tumours with granular oncocytic cytoplasm. It provides considerable assistance when a definitive diagnosis cannot be made after the standard histopathological diagnosis, immunohistochemistry and molecular genetic analyses, hence it should not be *a priori* dismissed as part of diagnostic procedure.

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