Thyroid-like follicular carcinoma of the kidney in a patient with nephrolithiasis and polycystic kidney disease: a case report

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Abstract
Thyroid-like follicular carcinoma of the kidney (TLFC), a rare neoplasm with low malignant potential, is histologically similar to primary thyroid follicular carcinoma, but characteristically lacks thyroid immunohistochemical markers. We report a case of 34-year old patient with nephrolithiasis. Ultrasound revealed hepatorenal cysts consistent with adult type polycystic kidney disease (ATPKD) and a cytologically confirmed left kidney tumor. Nephrectomy specimen contained sharply demarcated lesion of unusual morphology. Tubular and cystic structures lined by mostly cuboidal cells and filled with amorphous eosinophillic material, reminiscent of follicular carcinoma of the thyroid gland, were diagnostic for TLFC. Thyroid markers were negative. To our knowledge this is the first report of TLFC associated to ATPKD. Brief review of previously published TLFCs, possible relationship between entities and differential diagnosis are discussed.

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Background
Renal tumors which became unique clinico-pathologic entities with distinctive immunohistochemical, cytogenetic and molecular profiles have been successfully incorporated into the current WHO classification [1], which became the cornerstone of diagnostic work in the surgical pathology. Developments in the last decade have, however, led to description of additional entities with distinctive morphology [2], which are not yet covered in the current WHO classification. It is important to be aware of the existence of these new rare renal tumor entities because the description of further cases is needed in order to gain additional knowledge of their biological behaviour.

One of those new entities is the thyroid-like follicular renal cell carcinoma (TLFC) [2]. This rare neoplasm with low malignant potential is histologically similar to primary thyroid follicular carcinoma, but is characteristically negative for thyroid immunohistochemical markers. We describe a case of TLFC diagnosed in a patient with polycystic kidney disease.

Case presentation
Clinical history
A 34-year old patient has come to medical attention because of nephrolithiasis, proven by effective spontaneous stone elimination. Owing to persistence of the pain, the abdominal ultrasound (US) examination has been performed, revealing hepatorenal polycystic disease, consistent with adult type polycystic kidney disease (ATPKD) [3]. Patient had no familial history of ATPKD. Additionally, a hyperechogenic cyst has been discovered in his left kidney, measuring 4-5 cm in greatest diameter. US guided fine needle aspiration biopsy (US-FNAB) of the lesion confirmed a neoplasm and was followed by surgical removal of the left kidney. Systematic clinical examinations, including accurate imaging techniques, revealed no other tumors...
or disease changes. Renal function and blood pressure were normal and the results of urine laboratory examinations showed no abnormalities. Except for mild left lumbar pain persisting at the time of discharge from the hospital, the patient is well after 6 months, without any other signs of disease.

**Materials and methods**

**Ultrasound-guided fine needle aspiration biopsy (US-FNAB)**

Ultrasound-guided fine needle aspiration biopsy (US-FNAB) of atypical renal cyst was conducted by a radiologist using a 22-gauge needle attached to a 10-ml syringe. Direct smears were prepared on site, air dried and subsequently Giemsa stained. Few drops of blood stained fluid were submitted in the syringe. The material left in the syringe was suspended in short term storage cell medium. The cell suspension was used to prepare 10 cytopsins using a Shandon cytopsin 4 cytocentrifuge (Thermo Shandon Inc, USA). Cytopsins were immediately fixed in methanol. Test cytopsins were stained according to Papanicolau method. Immunostaining was performed in the automated immunostaining system NexES (Ventana Medical Systems Inc., USA). Bound primary antibodies were detected using an iView detection kit (Ventana Medical Systems Inc., USA). Immunocytochemical staining for RCC (renal cell carcinoma) marker (PN-15, Cell Marque), vimentin (clone V9, DAKO), CK7 (clone OV-TL 12/30, DAKO), P504S (α-methylacyl-CoA racemase-AMACR; clone 13H4, DAKO), CD 10 (clone 56C6, NCL) were performed.

**Nephrectomy**

The left nephrectomy specimen including perinephric fat weighted 720 g and measured 18×13 cm in greatest diameters, the kidney measured 13×7 cm. Renal parenchyma was for the most part polycystic, with cysts measuring up to 4 cm in greatest diameter. Cyst walls were smooth and glistening, the cysts were filled with clear watery fluid. The sharply circumscribed encapsulated solid grey tan tumor was present in the lower pole of the kidney, measuring 5.5×4.8 cm (Figure 1). Centrally it was partially haemorrhagic and cystically degenerated. Formalin fixed representative tissue specimens, sampled according to the current protocols [4] were routinely stained with hematoxylin and eosin (HE). Additional immunohistochemical stainings were performed in a Ventana XT apparatus (Ventana Medical Systems Inc., USA), with automated staining procedures. The panel of primary antibodies included (source, clone and solutions): CAM5.2 (BECT. DICK., RTU), CD10 (NCL, 56C6, 1:15), CD15 (NCL, BY87, 1:20), CD56 (NCL, 1B6, 1:25), CD117 (DAKO, rb, 1:40), CEA (DAKO, rb, 1:1000), CK7 (DAKO, OV-TL 12/30, 1:100), CK20 (DAKO, Ks20.8, 1:20), CK34βe12 (ENZO, 34βe12, 1:50), CK AE1/AE3 (DAKO, AE1/AE3, 1:50), EMA (DAKO, E29, 1:20), P504S (DAKO, 13H4, 1:20), RCC (VENTANA, ready to use-RTU), TFE3 (CELL MARQUE clone MRQ-37; 1:100), Thyroglobulin (DAKO, rb, 1:5000), TTF-1 (DAKO, 8g7g3/1, 1:20), vimentin (DAKO, V9, 1:300), WT-1 (DAKO, 6 F-H2, 1:40).

When needed, appropriate positive and negative controls have been used.

**Results**

**US-FNAB** smear was highly cellular, the predominant morphological pattern were three-dimensional tissue fragments. Rounded papillary-like structures and nuclear pallisading was noted surrounding the edge of many fragments, while some exhibited cribriform-like pattern. In all, numerous deep pink stained globules of different sizes were seen (Figure 2). Calcifications were noted on
the top of some particles. Cells were rather uniform, medium sized, mainly organized around pink globules. Nuclei were oval with slight variation in size, bland chromatin, with small nucleoli, some exhibiting grooves (Figure 3). The cytoplasm was moderate or more abundant, vacuolated, cell borders could be appreciated in Papanicolaou stained cytopins (Figure 3). Single cells were very rare, however some round naked nuclei were found. In the background there was abundant granulated pink material in addition to numerous macrophages and erythrocytes (Figure 2). Tumor cells were negative for RCC and CD10. They were positive for P504S, vimentin and CK7.

The proposed **cytological diagnosis** was papillary renal cell neoplasm, morphologically corresponding to MiTF/TFE family translocation-associated renal carcinoma. **Histologically**, the encapsulated tumor consisted of tubular and cystic structures reminiscent of follicular carcinoma of the thyroid gland. The structures lined by mostly cuboidal cells were filled with amorphous eosinophilic/basophilic material (partially colloid-like, partially mucoid; Figure 4). In some areas, the material extravasated out of the follicles into the stroma. The follicles varied in size, the nuclei were round to oval, the nucleoli only focally inconspicuous, the chromatin was evenly distributed. Occasionally, nucleoli were more prominent, with nuclear features corresponding mostly to Fuhrman grade 2, focally even grade 3. Similarly to FNAB nuclear grooves could be detected in some areas, but there were no calcifications. Invasion into the capsule (Figure 5), resembling incipient but, since the tumor did not extend across the whole thickness of the capsule, not diagnostic capsular invasion of follicular thyroid carcinoma, was obvious on multiple locations at the periphery of the tumor. There was no mitotic activity. In some areas the tumor showed some papillary growth, focally it was even more solid (Figure 6). Those solid areas contained cells with higher nuclear grade comparing to macrofollicular areas.

In the nonneoplastic kidney, simple cysts were irregularly distributed, with focal signs of mild primary urine stasis in the Bowman capsular space of the adjacent glomeruli. No other obvious chronic glomerular, vascular, or tubulointerstitial changes of the renal parenchyma could be seen, which is in accordance with clinically normal renal function. The only renal pathology, worth mentioning, was the presence of rare birefringent calcium oxalate crystals with small foci of adjacent mild chronic inflammatory infiltrate, confirming clinical picture of nephrocalculosis.
According to morphology and results of immunohistochemistry (Table 1), the histological diagnosis of TFLC was made.

**Discussion**

Thyroidization of the kidney is a well known phenomenon, where dilated tubular structures with atrophic epithelium containing colloid-like material imitate the usual structure of the thyroid gland. Usually, thyroidization occurs as a process secondary to chronic pyelonephritis and is a habitual characteristic of an end stage kidney disease. But the similarities between the kidney and the thyroid gland do not end up here. In the last years, a unique tumor type, primary to the kidney, but essentially looking as a thyroid lesion has been described, being named TLFC of the kidney. The first and by now the only real series consisted of 6 cases [5], 4 of those tumors being described for the second time by the same author. The well circumscribed neoplasms histologically resembling follicular carcinoma of the thyroid gland, but lacking typical thyroid markers, were reported to have favorable prognosis. Only one of the patients from that series, with tumors measuring up to 11.8 cm in greatest diameter, developed a metastasis in the renal hilar lymph node. The other patients were disease free in the follow up period from 7 to 84 months [5].

Additional case reports appeared in the literature [6-10], all but one describing tumors with follicular morphology, composed of cells with moderate amphophilic to slightly eosinophilic cytoplasm creating macro and microfollicles containing inspissated colloid-like material, with only small amount of packed follicles devoid of secretions. One of two cases described by Alessandrini et al. [9], however showed focal papillary architecture, without nuclear grooving or optical clearing. In our case, nuclear grooves have been visible in both specimens. In FNAB, focal calcifications were additionally noted on top of some fragments, which was not the case in histological samples, where they were absent. Analogous to our case, nuclear grooves in FNAB of TLFC have been noted by Dhillon et al. [11]. The authors retrospectively described FNAB results after already publishing histologic and clinical characteristics of the same TLFC, unique for the presence of lung and retroperitoneal lymph nodes metastases [8]. This was also the only case of TLFC with distant metastases, as these tumors generally have low malignant potential [12].

Concerning the tumor growth pattern in our case, although predominantly macrofollicular in HE slides, the papillary tumor growth could be observed focally in the histology, as well as in FNAB. This, in addition to calcifications present in FNAB, has led to the cytological diagnosis of papillary renal cell neoplasm, morphologically corresponding to MiTF/TFE family translocation-associated renal carcinoma, which was subsequently excluded by morphology of the nephrectomy specimen and negative TFE3 immunohistochemistry.

Marked lymphocytic infiltration may be present in cases of TLFC, mostly as prominent intratumoral collections, but sometimes it is seen at the periphery, surrounding the tumor. These collections may occasionally contain lymphoid follicles with reactive germinal centers [12]. Our case was devoid of inflammation. Due to the presence of calcium oxalate crystals, only mild lymphocytic infiltrate was present around focally disrupted tubuli in the medulla.

Immunohistochemically, the TFLCs described in the literature showed variable, although relatively consistent
negativity for Pax-2, RCC, CD10, WT-1, P504S, vimentin, CD56 and CD57 [12], and typical (but not obligate) negativity for CK7. For the diagnosis of TFLC all cases should be negative for thyroid markers such as TTF-1, thyroglobulin and galectin-3. In one reported case [13] the tumor was thyroglobulin positive, but the authors did not test TTF-1 or galectin-3. The exclusion of a metastasizing thyroid carcinoma was carried out merely with clinical methods therefore one can argue, that the kidney tumor was a metastasis. However, the uneventful follow up of 18 months is a strong argument against a metastasizing thyroid carcinoma.

Although very rare, metastases to the kidney from the thyroid have been reported. Due to typical follicular morphology of the FTCL the metastasis of follicular thyroid carcinoma should be excluded in the first place. Metastatic follicular and papillary thyroid carcinoma in the kidney usually occur in patients with disseminated disease [14,15], sometimes even long after the primary tumor has been treated [16,17]. Another possible origin of a TTF-1 positive follicular tumor metastasis is struma ovarii, which is a very remote possibility, as are other follicular neoplasms, entering differential diagnosis such as serous and small cell carcinoma of the ovary, intrahepatic cholangiocarcinoma or breast tumors with follicular morphology [5,9]. Other rare primary tumors of the kidney with follicular growth pattern include carcinoma (trisomy 3q, 7, 8, 12, 16, 17 and loss of Y chromosome) but completely unspecific aberrations (loss of chromosomes 1, 3, 7, 9p21, 12, 17, and X). Genetic profiling of RCCs generally helps defining renal cell tumor subtypes in cases with inconclusive morphology, as shown in a report of synchronous clear cell RCC and tubulocystic carcinoma [18]. However, more data on genetic changes in a report of synchronous clear cell RCC and tubulocystic subtypes in cases with inconclusive morphology, as shown in a report of synchronous clear cell RCC and tubulocystic carcinoma [18]. However, more data on genetic changes in a report of synchronous clear cell RCC and tubulocystic carcinoma [18]. However, more data on genetic changes in a report of synchronous clear cell RCC and tubulocystic carcinoma [18]. However, more data on genetic changes in a report of synchronous clear cell RCC and tubulocystic carcinoma [18]. However, more data on genetic changes in
the immunostaining patterns. Thyroid like kidney tumors with both, follicular and papillary features have been described also by other authors [24-26].

Conclusions

In conclusion, this is the first case of TFLC associated with ADPKD. The possible correlation to cystic kidney disease has already been confirmed for RCC and other renal tumors, but should be further elucidated for TFLC. Moreover it seems, that the predominant pattern of thyroid like renal cancer is follicular indeed, but papillary features can be encountered as well. Future investigations are needed to verify whether this tumor is a true new nosologic entity or only a variant of one of the conventional RCCs.

Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of Written consent is available for review by the Editor-in-Chief of this Journal.

Competing interests

The authors declare they have no competing interests.

Authors’ contributions

MV carried out the morphological analyses and wrote the manuscript. MSF is Head of Department of Uropathology, Faculty of Medicine, University of Innsbruck, AUSTRIA and a former Chair of the Department of Cytopathology, both Institute of Pathology, Faculty of Medicine, University of Innsbruck, AUSTRIA, and MV is Head of the Department of Uropathology, Faculty of Medicine, University of Innsbruck, AUSTRIA. All authors read and approved the final manuscript.

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