Low-Grade Oncocytic Tumor of Kidney: A Distinct Emerging Entity in Renal Oncocytic Neoplasms with Diagnostic Challenge in An Old Female: A Case Report

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ABSTRACT

Low grade Oncocytic Tumor (LOT) is an emerging category in renal tumors having oncocytic morphology. It has overlapping features with Renal Oncocytoma and Eosinophilic variant of Chromophobe Renal Cell Carcinoma. LOT typically shows solid nests of cells with oncocytic cytoplasm and uniform round to oval nuclei with a CK7 positive/ CD117 negative immunophenotype. Pathogenesis is not well-understood, however, variations in mTOR pathway related genes have been described. The clinical course is indolent. Here, we present the case a 64-year-old female patient who presented with a solid enhancing mass in right kidney with the clinical impression of Renal cell carcinoma. Right radical nephrectomy was performed, and histologic features were consistent with LOT.

Keywords: Low Grade Oncocytic Tumor, Kidney, Emerging

Introduction

Oncocytic renal tumors is an evolving category and diagnosis is sometimes challenging when tumors are low grade. Renal Oncocytoma (RO) and Eosinophilic variant of Chromophobe Renal Cell Carcinoma (eChRCC) are the most common tumors in this group (Trpkov and Hes, 2019). Others include Eosinophilic Clear Cell RCC, Hybrid Oncocytic Tumours, Succinate Dehydrogenase (SDH) deficient RCC and Fumarate Hydratase (FH) deficient RCC (Kryvenko et al., 2014). However, recently, a distinct type of oncocytic tumor, Low-grade Oncocytic Tumor (LOT) has been described that shows oncocytic cells with low grade features. LOT usually affects old adults and elderly with female predominance. Multifocality is associated with Tuberous Sclerosis Complex and End-stage renal disease. LOT typically follows an indolent course without any reported recurrence or metastatic potential (Sharma et al., 2022).
Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) show circumscribed tumor with variable enhancement. Gross examination shows a well-circumscribed/ well-delineated tumor with non-infiltrative borders. Cut surface is grey white to tan brown. Cystic degeneration, gelatinous appearance and hemorrhage may be seen (Parkhi et al., 2022). Histologically, the tumor is characterized by cords and solid nests of monomorphic cells with abundant eosinophilic cytoplasm, round to oval nuclei and predominantly inconspicuous nucleoli. Perinuclear halos may be present, but raisinoid nuclei and high-grade nuclear features are absent. Dispersed single tumor cells, tubulocystic pattern, papillary pattern, cribriforming, nuclear irregularities and binucleation can be observed occasionally (Guo et al., 2021). Areas of hemorrhage and stromal edema may be seen. Necrosis is absent. Low-grade Oncocytic Tumor of kidney is the provisional name given to this entity and is yet to be included in the WHO classification of Renal Tumors (Siadat and Trpkov, 2020).

LOT shows strong diffuse expression of Cytokeratin 7 and is negative for cKIT/CD117.

E-cadherin shows diffuse membranous staining (Ishikawa et al., 2021). Other positive stains include BerEP4, PAX8, MTOR and Cyclin D1. Alpha-MethylAcy1-CoA Racemase (AMACR), CD10 and Vimentin can be negative or focal positive. Immunostain EMA shows focal apical staining. Negative stains include Cytokeratin 20, Synaptophysin, Chromogranin, CA9, TFE3, TFE B, HMB45, Melan-A and Cathepsin-K (Trpkov et al., 2019). Immunomarkers FH and SDH are retained. The proliferative index (Ki-67 index) is usually less than 5%. Special stain colloidal iron may show focal intense cytoplasmic staining in 15% cases. LOT is associated with genetic variations in the MTOR pathway related genes including TSC1, TSC2 and MTOR (Morini et al., 2022). Losses of loci 19p33.3 and 1p36.33 are present, suggestive of discrete molecular pathogenesis. Ultrastructural features of numerous mitochondria are seen in the cytoplasm of LOT (Kravtsov et al., 2021).

The aim of this study is to describe the clinicopathologic features of LOT, a distinct entity with emphasis on differential diagnoses. This case will be an addition to the group of low-grade eosinophilic tumors of kidney.

Case Report

A 64 year old female, known case of Chronic Kidney Disease and Renal transplant rejection 9 years back, presented with a renal mass involving the upper and middle poles of kidney. CT scan showed a circumscribed contrast-enhancing mass that measured 2.9 x 2 x 1 cm. The mass involved the upper and mid poles of kidney and clinical diagnosis of renal cell carcinoma was made. Patient underwent right radical nephrectomy. The specimen received was coded as “Right kidney” and
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comprised of an intact right radical nephrectomy specimen of 8.2 x 4.9 x 3.5 cm. Ureter measured 1.5 x 0.4 cm and the entire specimen weighed 95gms. Cut surface showed a well-circumscribed grey white solid cum cystic tumor involving the upper and middle poles of kidney. The tumor measured 2.8 x 1.9 x 0.9 cm and was limited to kidney. Adrenal gland and lymph nodes were not present in the specimen.

Microscopy showed a well-circumscribed neoplastic lesion composed of solid nests and small clusters of monomorphic population of polygonal cells (Fig. 1). Individual neoplastic cells had predominantly monotonous round vesicular nuclei with occasional atypia and binucleation. Cytoplasm was abundant, eosinophilic and granular and variable small conspicuous nucleoli were present (Fig. 2). Focal perinuclear halos were noticed, however, there were no nuclear irregularities or raisinoid nuclear appearance. Stromal edema and congestion were present. Upto 2 mitoses/10HPF were noted without any necrosis. Sarcomatoid and rhabdoid features were absent. Adjacent renal parenchyma showed patchy tubular atrophy and thyroidization (Fig. 1), mild chronic lymphoplasmacytic interstitial infiltrate and mild interstitial fibrosis. Intratubular calcifications were prominent at the periphery. Tumor was limited to kidney and ureteric, renal vein and Gerota’s fascia margins were tumor free.

Based on these histologic features, differential diagnoses included Oncocytoma, LOT and eChRCC. The latter was excluded based on absence of raisinoid nuclei and CD117 negativity. CK7 showed diffuse positivity in the neoplastic cells with moderate intensity in the middle and strong at the periphery of tumor (Fig. 3), excluding Oncocytoma. E-Cadherin was strong diffuse positive and immunohistochemical stains AMACR, CD10, Vimentin, RCC and TFE3 were negative. Hence, the tumor was best diagnosed as LOT.

Figure 1: Circumscribed tumor composed of nests of polygonal cells (); native renal tubules exhibiting thyroidization (towards the left). (H&E, 40X).
Figure 2: Monomorphic population of polygonal cells with abundant, eosinophilic and granular cytoplasm, round vesicular nuclei and variable small conspicuous nucleoli. (H&E, 200X).

Figure 3: Diffuse CK7 positivity in tumor cells: weak in the middle, strong at periphery. (Immunostain, 100X).

Discussion

Low grade oncocytic neoplasms are an emerging new category in the family of renal cell tumors. Only few case series have been published in the literature in the recent years. These tumors have overlapping features with Chromophobe Renal Cell Carcinoma (ChRCC) and RO that makes them a diagnostic challenge for pathologists (Ishikawa et al., 2021). The distinct histologic features and immunohistochemical profile makes LOT a distinct entity (Kravtsov et al., 2021).

Oncocytoma and LOT share many similar histologic and cytologic features. Both tumors contain polygonal cells arranged in nests, trabeculae, cysts, tubules and solid sheets (Trpkov et al., 2019). The
neoplastic cells contain small round or oval-shaped nuclei, finely dispersed chromatin and variable conspicuous nucleoli. Mitotic count is typically low, and stroma may show congestion in both tumors. These morphologic features may lead to the diagnosis of RO if immunohistochemistry is not performed. LOT shows diffuse positivity for CK7, and immunostain CD117 is negative (Trpkov et al., 2021). However, RO is usually Cytokeratin 7 negative and CD117 can be negative or focal weak positive (Wu, 2017).

Trpkov et al. recently published a series of 28 cases of low grade oncocytic tumors of kidney from 4 major institutions with characteristic low grade morphology and typical CK7 positive/CD117 negative immunoprofile, and designated such tumors as LOT after detailed histomorphological and array comparative genomic hybridization (aCGH) findings. The tumors had indolent behavior and no syndromic association/metastasis was reported (Trpkov et al., 2019). The karyotypic abnormalities found included Del 1q, 19p and 19q, Del 1, 14 and 11q13 rearrangements and t (5;11). Morini, et al. (2022) recently identified a somatic mTOR mutation in low-grade oncocytic tumors, previously classified as chromophobe renal cell carcinomas.

Eosinophilic variant of Chromophobe Renal Cell Carcinoma (eChRCC) is also a differential that typically shows nests and sheets of polygonal cells. These cells show abundant eosinophilic cytoplasm with raisinoid nuclei and perinuclear halo (Williamson et al., 2017). Stroma is vascular and mitotic activity is usually scant. The distinguishing feature remains the presence of raisinoid nuclei, which may be focal as well. Hence, thorough sampling should be done to find such areas. Immunostain CK7 will be diffusely positive as in LOT, and CD117 will be positive as well (Guo et al., 2021). Diagnosis of eChRCC is highly important owing to its potential for sarcomatoid differentiation.

Hybrid oncocytic tumors (HOCTs) is another group of oncocytic tumor that shares overlapping features with RO and ChRCC. According to Delongchamps, HOCTs comprise approximately 10% of renal tumors (Delongchamps et al., 2009). The 2016 WHO classification of renal tumors has briefly outlined this group. These tumors have been reported in patients with Birt-Hogg Dube syndrome, renal oncocytosis, but some tumors occurred sporadically as individual tumors in non-syndromic setting (Petersson et al., 2010). HOCTs grossly appear as non-encapsulated and circumscribed tumors. Cut surface is gray white to tan homogenous. Histology shows solid and alveolar pattern of cells with abundant eosinophilic cytoplasm and round to oval mildly atypical nuclei. Perinuclear halo and binucleated cells are often present, but raisinoid nuclei, peculiar to ChRCC, are typically absent. Perinuclear cytoplasmic clearing can also be observed as in ChRCC. These tumors are positive for Pancytokeratin. CK7 expression is also present with a varied proportion of positive cells and positivity
for CD117 is diffuse strong. Shuji Mikami et al. emphasized on the features and behaviour of HOCTs, including a recently published paper by Ruiz-Cordero, et al. (2019), where they recommended HOCTs as clinicopathologically and biologically distinct tumors in comparison to ROs and ChRCCs (Mikami et al., 2019).

Late discovery of LOT is also attributed to delayed clinical presentation of patients along with similar histologic features to other oncocytic tumors. Patients with LOT are usually asymptomatic and the renal mass is usually discovered incidently (Wu, 2017). Moreover, only surgical excision and close followup of these patients is sufficient and neoadjuvant chemoradiation is not required (Kravtsov et al., 2021).

**Conclusion**

Therefore, LOT should be kept in the differential diagnoses of renal cell tumors with eosinophilic cytological features. The difference in the clinical outcome makes this even more important. Although difficult on a core biopsy, a confident diagnosis can be made in most surgically resected cases by careful assessment of cytomorphological features with appropriate use of immunohistochemical studies.

**References**


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