"Large-cell Neuroendocrine Carcinoma of the Kidney: A Case Report and Review of the Literature"

SCHOOL OF MEDICINE
Department of Pathology
UNIVERSITY of COLORADO ANSCHUTZ MEDICAL CAMPUS

Department of Pathology
University of Colorado AMC
9th Annual Pathology Poster
April 07-09, 2022

Ellie Hong, MD, Allison H.H. Martin, MD, Francisco G. La Rosa, MD, FCAP

University of Colorado Anschutz Medical Campus, School of Medicine, Department of Pathology, Aurora CO 80045

ABSTRACT

Neuroendocrine carcinomas of the kidney are rare with ~166 cases reported since 1966, of which the large-cell variant (LCNEC) is exceedingly rare, with 6 definitive cases reported. These aggressive tumors are non-functional, and patients are usually asymptomatic. We report a new case of renal LCNEC in a previously healthy 45-year-old man who presented to the emergency room with 5-hours of acute onset epigastric and abdominal pain, nausea, vomiting, diarrhea, and chills. Computed tomography showed a large left renal mass with possible rupture and extravasation, 6mm left lung-nodule and enlarged left-external iliac lymph node. Emergency surgical procedure confirmed the renal mass with rupture through Gerota's fascia and associated retroperitoneal hematoma. A radical nephrectomy with retroperitoneal washing was successfully performed, and the post-op course was uneventful. Grossly, the kidney was largely replaced by a tan to yellow-orange, hemorrhagic, friable tumor (18x16x10cm) which extended to Gerota's fascia superiorly, inferiorly, and laterally, with tumor extrusion through the upper pole. Microscopically, the sections showed large tumor cells with high nuclear cytoplasmic ratio, vesicular-fine chromatin, prominent nucleoli and frequent mitoses at >30/10 HPF. These cells displayed organoid nesting, palisading, rosettes, trabeculae and solid growth patterns. Immunostains showed tumor cells with diffuse staining for pan-CK(AE1/E3) and CD56, scattered staining for CK7 and synaptophysin, and a high index of >60% of nuclei staining for Mib-1 (Ki-67). These features were consistent with a high-grade LCNEC of the kidney. The prognosis of LCNEC is still poor and management requires a multidisciplinary approach.

INTRODUCTION

- Neuroendocrine neoplasms (NENs) account for only 0.5% of all newly diagnosed malignancies[1]
- First case of a neuroendocrine neoplasm arising from the kidney was described in 1966, and only about 160 cases have been reported since then[2]
- The most frequent sites of involvement are the gastrointestinal tract, pancreas, and lung, where they are postulated to arise from native neuroendocrine cells[2]
- NENs can be roughly divided into
  - Low-grade and well-differentiated variants, such as neuroendocrine tumors
  - More aggressive and poorly differentiated variants, such as large cell neuroendocrine carcinomas.
- Furthermore, the aggressive large cell neuroendocrine carcinomas primary to structurally normal kidneys are exceeding rare, with fewer than 10 cases reported to date (Table 1)

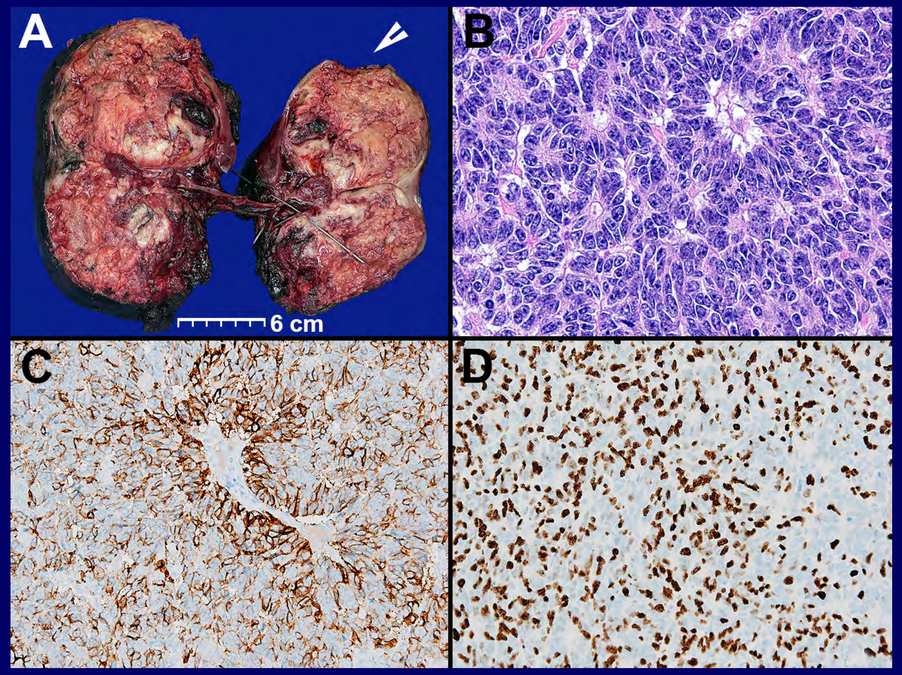

Figure 1. Grossly, the kidney was largely replaced by a tan to yellow-orange, hemorrhagic, friable tumor (18x16x10cm) which extended to Gerota's fascia superiorly, inferiorly, and laterally, with tumor extrusion through the upper pole (**A**, white arrow). Microscopically, the sections showed large tumor cells with high nuclear cytoplasmic ratio, vesicular-fine chromatin, prominent nucleoli and frequent mitoses at >30/10 HPF **(B, 400x)**. These cells displayed organoid nesting, palisading, rosettes, trabeculae and solid growth patterns. Immunostains showed tumor cells with diffuse staining for pan-CK(AE1/E3) and CD56 **(C, 200x)** , scattered staining for CK7 and synaptophysin, and a high index of >60% of nuclei staining for Mib-1 (Ki-67) **(D, 200x)**.

CASE PRESENTATION

A 45-year-old male presented to the Emergency Department with 5 hours of acute onset epigastric and left upper quadrant pain, with associated nausea, non-bloody emesis and diarrhea, and chills. He had no significant medical or family history and no prior abdominal surgeries. Computed tomography (CT) imaging showed a large left renal mass with focal rupture at the lower pole and suspected extravasation at the upper pole concerning for small volume retroperitoneal hemorrhage. As repeat CT showed no change and the patient was hemodynamically stable, he was taken to surgery the following day for a left radical nephrectomy. A large left renal mass displacing the left mesocolon, with rupture through Gerota's fascia and a hematoma in the left retroperitoneum were found. Grossly there were no intraperitoneal lesions and no enlarged lymph nodes.

The patient recovered appropriately from surgery and was discharged 4 days later. At post-op follow-up 2 weeks later, he was referred to oncology for chemotherapy treatment planning.

PATHOLOGY FINDINGS

Gross: Kidney largely replaced by a white to yellow-orange, hemorrhagic, friable tumor (18 x 16 x 10 cm) which extended to Gerota's fascia superiorly, inferiorly, and laterally, with tumor extrusion through the upper pole

- Tumor appeared to invade the renal sinus adipose tissue and hilar structures
- The sliver of remaining parenchyma was displaced but grossly unremarkable.

Microscopic: High-grade neoplasm with neuroendocrine architecture characterized by organoid nesting, palisading, rosettes, trabeculae and solid growth patterns

- Cells notable for large cell size, high nuclear to cytoplasmic ratio, vesicular / fine chromatin, and multiple prominent nucleoli
- Frequent mitoses at >30/10 HPF and
- IHC stains: tumor cells with diffuse staining for pan-CK (AE1/E3) and CD56 and scattered staining for CK7 and synaptophysin. Staining for Mib-1 (Ki-67) showed more than 90% of positive nuclei. No staining for chromogranin, CK34bE12, AMACR, RCC, CD45, CEA, OCT4, and TFE3.

Overall, consistent with a high-grade, large cell neuroendocrine carcinoma of the kidney.

DISCUSSION

- Primary renal neuroendocrine tumors likely arise from stem cells that acquire neuroendocrine differentiation, as there are no native neuroendocrine cells in the kidney parenchyma[2]
- The paucity of renal large cell neuroendocrine carcinomas could be partially attributed to inconsistent and changing nomenclature over the past 30 years[3]
- Historically, the terms carcinoid, atypical carcinoid, and small- and large-cell neuroendocrine carcinoma have been used for tumors of increasing aggressiveness with worse prognoses
  - Currently, this nomenclature is retained for neuroendocrine neoplasms in the lung, with grading into the distinct categories based on morphology, number of mitoses, and presence of necrosis
  - In the GI tract, "carcinoid" and "atypical carcinoid" have been replaced by the term "well-differentiated neuroendocrine tumor," which is graded from 1 to 3 based on mitotic rate and Ki-67 index. GI neuroendocrine carcinomas are still categorized as either small cell or large cell
- The most current classification proposed by the International Agency for Research on Cancer (IARC) and World Health Organization (WHO) in 2018 categorized renal neuroendocrine neoplasms into the following: well-differentiated neuroendocrine tumors (NET), large cell neuroendocrine carcinoma (LC-NEC), small cell neuroendocrine carcinoma (SC-NEC), and pheochromocytoma[4]. Due to their rarity, there are no precise criteria for placement into these categories unlike in the GI tract or lung.
- In the largest study of renal neuroendocrine neoplasms gathered from the Surveillance, Epidemiology, and End Results database over 4 decades, there were 55 cases of small cell neuroendocrine carcinoma, 2 cases of large cell neuroendocrine carcinoma, and 51 cases of neuroendocrine carcinoma, not otherwise specified[2]
  - Based on overall survival and disease specific survival curves, it is possible that a subset of the "not otherwise specified" cases would now be reclassified as large cell neuroendocrine carcinomas
- Most renal neuroendocrine neoplasms are not biochemically active, especially more poorly differentiated types such as LCNECs
  - The majority of patients ultimately diagnosed with LCNECs are asymptomatic or minimally symptomatic
  - Unlike our case where the patient presented in acute distress due to tumor rupture
- Previous cases of primary renal large cell neuroendocrine carcinomas have been grossly described as lobulated firm lesions, grey to white in color
- The architecture ranged from trabeculae, nests, papillae, to pseudo-rosettes with some having necrosis
- The cells were medium to large with characteristic neuroendocrine nuclear features such as a vesicular, or open, chromatin
- IHC: universally positive for synaptophysin, chromogranin (except for one) and CD56 (when performed), with variable positivity for vimentin and various cytokeratins
- Mitosis were reported as >20 to 74 per 10 HPF and the Ki-67 index ranged from 15-80%
  - Our case recapitulates these previous features, with the exception of an even higher Ki-67 index at 90%
- Patients with renal LCNEC were ultimately diagnosed with stage T2 and above. Those patients that expired did so on average 5 months after initial diagnosis; the longest period of disease-free follow-up is 1 year.

Case Studies	# Cases	# LCNEC	Symptoms? Met?	Greatest Dimension	Synapto Chromo	CD56	Vimentin	CK/ pan-CK/ HMW CK	Other IHC	Ki67/ Mitoses	Architecture and cytology
Shimbori et al., 2017	1	1	+ +	11.6 cm	+ +	+				15-20%	Solid nests, central necrosis High N:C ratio
Ratnagiri et al. 2009	1	1	-		+	+	-	+	+ NSE	>20/10 HPF	Trabeculae, pseudorosettes & strands Med-Lg cells, mod. eosinophilic C, vesicular N, fine chromatin, prominent nucleoli
Badiu et al., 2016	1	1	+ +	8 cm	+ +	+	+		Partial EMA, CD10, CK7	74/10 HPF	High anaplastic with monstrous nuclear proliferation
Palumbo et al., 2014	1	1	-	3 cm	+ +	+		-		80%	
Wann et al., 2014	1	1	+	10 cm	+ +		+	+	(-) EMA, CD10, CK7	>20% in poor diff. areas	Gyriform patterning w/ anastomosing trabeculae and papillae. Tall columnar cells, pleomorphic oval N w/ coarse chromatin, mod. eosinophilic cytoplasm
Lane et al., 2007	9	1	+ +	18 cm	+	-				50/HPF	
Amin et al. 2021	8	≤ 3									
This Case	1	1	+	18 cm	+	-	+	+		90%, >30/HPF	Nesting, palisading, rosettes, trabeculae and solid growth Lg cells, high N:C ratio, vesicular/fine chromatin, prominent nucleoli

Table 1 – Previous Renal NECs in the Literature
A comprehensive search of the literature through PubMed and Google Scholar reveals 5 single-case studies and 2 small case studies with an additional 2-4 LCNECs (Amin 2021 lists 3 renal NEC tumors without distinguishing between Large and Small Cell variants). This case is then the 8th or 10th reported LCNEC in the literature.

REFERENCES