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Case Study

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WELL DIFFERENTIATED NEUROENDOCRINE TUMOR OF THE KIDNEY: CASE REPORT OF A RARE NEOPLASM AND REVIEW OF THE LITERATURE

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ABSTRACT

Primary renal neuroendocrine tumors are extremely rare. They exhibit a wide range of neuroendocrine differentiation and clinical behavior. Primary renal NETs include renal carcinoid tumor, atypical carcinoid, small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma. Well differentiated neuroendocrine tumors are slow growing whereas SCC and LCNEC are aggressive tumors with higher incidence of local recurrences and metastasis. We herein report a case of 37 year old male who presented with a large renal mass. Microscopic features suggested a well differentiated primary renal neuroendocrine tumor which was later on confirmed by immunohistochemistry. A little is known about the pathogenesis and parameters that may predict prognosis at diagnosis.

KEYWORDS: Kidney tumor, carcinoid, prognosis, synaptophysin, ki-67.

INTRODUCTION

Neuroendocrine tumors are heterogeneous tumors with diverse biologic and clinical behaviors that vary according to primary tumor origin, type of neuroendocrine cells and pathologic features.[1] NETs can arise from any organ including organs that do not contain neuroendocrine cells.[2] The most common location of NETs is gastrointestinal tract followed by respiratory tract.[3] NETs is an uncommon finding in genitourinary tract where it has been reported to occur in testes, kidney, ovary and prostate. A primary renal well differentiated neuroendocrine tumor arising from the renal parenchyma is extremely rare.[4] These tumors are slow growing, have indolent course and exhibit a wide range of neuroendocrine differentiation based on morphology and immunohistochemistry. NETs represent a spectrum of well-differentiated neuroendocrine tumors (carcinoid and atypical carcinoid) to high grade large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma.[5] Horseshoe kidney, a congenital condition is associated with an increased risk of renal neuroendocrine tumors.[6] With less than 100 cases reported in the literature, primary renal well differentiated NET represents an extremely rare group of neoplasm.[1-5] The rarity of these tumors poses a diagnostic, therapeutic and prognostic challenge. We herein report a rare case of well differentiated neuroendocrine tumor of kidney in a 37 year old male along with histopathological characteristics and immunohistochemical features.

CASE REPORT

A male of 37 year age presented with complain of swelling in the left upper abdomen associated with discomfort and weight loss of about 10kgs in past 3 months. The swelling was increasing rapidly in size. Patient later developed scrotal swelling. No other comorbidities were present. Per abdomen examination showed a solitary lump of about 30x30 cm extending from 2cm below the left costal margin superiorly and inferiorly up to the anterior superior iliac spine, extending medially till umbilicus and laterally till the flank. Swelling was hard, non-tender, bimanually palpable, and mobile in both axis and with dull note on percussion. Scrotum showed swelling in left side with superficial visible dilated veins with bag of worm appearance. Both testes were palpable separately.

USG abdomen showed a huge echogenic mass measuring 22x16.3 x 15.3 cm seen in the left flank region with cystic and calcified areas, extending up to epigastrium superiorly and anterior superior iliac spine inferiorly. Left kidney was not clearly visualized and appeared to be confluent with the mass. The differential diagnoses given were –Retroperitoneal mass/Left Renal mass /adrenal mass. USG of scrotum showed dilated veins suggestive of varicocele- Left scrotal region.

Laboratory investigations were done to rule out adrenal tumor, which includes serum cortisol, VMA, catecholamine, urinary metanephrons, DHEAS and other routine investigations were done, the results were unremarkable.

Later PET scan was done which revealed 23x18x18cm, heterogeneously enhancing, partially necrotic, relatively well encapsulated, hypermetabolic mass occupying whole of the left kidney with a thin rim of renal cortex along the upper border. Multiple small calcific foci are seen within the mass and an FDG avid focus was seen in left ischium. DTPA scan showed left kidney function was severely impaired.

Patient underwent Left Radical Nephrectomy, specimen was sent to our department in 10% formalin. Gross examination revealed a globular renal mass measuring 24 x 18 x 15cm seen. On serial sectioning, whole of the renal parenchyma was replaced by variegated tumor with areas of extensive hemorrhage and necrosis. The poles of the kidney could not be identified only a thin rim of preserved renal parenchyma was seen at the periphery.

Microscopic examination showed uniform population of tumor cells arranged in sheets, nests, ribbons, trabeculae and rosette formation (Figure 1). The cells were small round with stippled chromatin, inconspicuous nucleoli and thin rim of eosiniphilic cytoplasm. Mitosis was seen occasionally.

The surrounding stroma showed necrosis, calcification and hemorrhage. The capsular invasion was seen with tumor extending into perinephric fat. Angioinvasion was seen. No perineural invasion was seen. Distal surgically resected end of ureter was also involved by the tumor. Microscopic features were suggestive of Well Differentiated Neuroendocrine tumor. IHC was done for CD99, NSE, synaptophysin, which showed strong positivity in all tumor cells and Ki67 was 1%, hence confirmed the diagnosis of Well Differentiated Neuroendocrine Tumor of Left Kidney (Figure 2).

DISCUSSION

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasm with varying degrees of neuroendocrine differentiation and clinical behavior. They can arise throughout the human body including the organs that do not normally contain neuroendocrine cells.[2] Organs of gastrointestinal tract like small intestine, large intestine, stomach and pancreas are most commonly involved by these tumors.[1] Respiratory tract is second most common site with majority of tumors localized in bronchopulmonary segments.[7] NETs of gastrointestinal tract accounts for 73.7% while NETs occurring in respiratory tract accounts for 25.1% of carcinoid tumors.[8] NETs in genitourinary tract constitute less than 1% of all carcinoid tumors and have been reported to occur in testis, ovary, kidney, and prostate.[4] Primary neuroendocrine tumor of kidney is rare with only less than 100 cases reported in the literature.[1-5,9] These tumors can arise anywhere in the kidney including renal parenchyma and renal pelvis.[10] NETs of kidney have predilection for both gender equally and occur in adults with age ranging from 21 to 87 years.[5] WHO has classified renal neuroendocrine tumors into well differentiated neuroendocrine tumor and neuroendocrine carcinoma. Well differentiated neuroendocrine tumor includes typical and atypical carcinoid while neuroendocrine carcinoma includes small cell and large cell neuroendocrine carcinoma.[10] Neuroendocrine carcinoma have more mitotic activity, more necrosis and aggressive clinical course than well differentiated NET of kidney. Regional lymph node metastasis is a common finding in patients with well differentiated NET.

Intrinsic neuroendocrine cells in normal renal parenchyma have not been reported and pathogenesis of primary NETs occurring in kidney is still controversial. Several attempts have been made to describe the origin of neuroendocrine tumor in the kidney. *Guy et al* suggest their origin from unrecognized intrinsic neuroendocrine cells representing either minute endocrine paracrine component or entrapped or misplaced progenitor cells of the dispersed neuroendocrine system during embryogenesis.[11] Another theory suggest their derivation from interspersed neuroendocrine cells as a result of intestinal metaplasia of pelvicalyceal urothelium due to chronic pyelonephritis.[6] *Romero et al* noted that these findings were not common in neuroendocrine tumor.[12] Several studies concluded that NETs arise from primitive multipotent stem cells that subsequently differentiate into NE direction due to neoplastic activation of gene sequences.[13] *El-Naggar et al* noted a loss of heterozygosity at one locus on chromosome 3p21 in one case and suggested that 3p abnormality constitute a preliminary event in the development of renal neoplasms including renal carcinoids.[14] Other mechanisms of origin includes association of neuroendocrine tumor with congenital anomalies such as horseshoe kidney or renal teratoma and metastasis from an occult primary site to the kidney.[15] The risk of development of primary renal carcinoid in adults with polycystic kidney disease is very low.[13]

Clinically, most of the primary renal NETs present with abdominal or flank pain followed by hematuria, constipation, urinary frequency, epigastric discomfort and abdominal mass. Serotonin related symptoms of carcinoid syndrome like flushing, sweating, edema and diarrhea is reported in less than 10% patients of primary renal NET. Since clinical symptoms are similar to those with other renal neoplasms a diagnosis of primary renal carcinoid is rarely made before surgery. Approximately 25-30% cases of primary renal NET is reported to be diagnosed as an incidental finding.[16] Clinical behavior of NETs is heterogeneous and unpredictable.

Currently, there is no well-defined grading system for renal NET. However, based on mitotic activity and proliferative index (ki-67 index), WHO has graded neuroendocrine tumors of gastrointestinal tract, pancreas, lung and thymus into low, intermediate and high grade. Macroscopically the tumor exhibit hemorrhage and necrosis. Histologically, trabecular or ribbon like pattern

of cells with stippled chromatin occurs. Sheet-like and nested patterns can also be seen. Well differentiated tumors usually lack necrosis and have low mitotic activity (<4 per 10HPF). Neuroendocrine carcinoma including small cell and large cell carcinomas exhibit larger tumor size, prominent mitotic activity and necrosis. Renal NETs are consistently immunoreactive for markers of neuroendocrine differentiation including chromogranin, synaptophysin, neuron-specific enolase and CD56/NCAM. CD99 expression can also be seen. Frequent sites of metastasis include region lymph nodes and liver.

Hansel et al examined 21 cases of primary renal carcinoid tumor, it was found that most of the patient presented at younger age (below 50 yrs.). Four patients had horseshoe kidney. One case with highest mitotic rate (>4/10 HPF) exhibited liver and bone metastases at initial diagnosis and died of the disease 8 months after surgery.[17] *Raslan et al* suggested three pathologic parameters important for predicting prognosis which includes tumor stage, number of mitoses and cellular atypia.[18]

Romero et al published an extensive review of 56 cases of renal carcinoid. Median age of the patient was 49 years. An incidental diagnosis of renal carcinoid was made in 28.6% cases. Horseshoe kidney was present in 10 patients while teratoma was present in 8 patients. Carcinoid syndrome was observed in 4 cases. Tumor size was more than 4cm in 73.6% cases. Half of the patients presented with metastasis and almost 60% cases with tumor size more than 4cm demonstrated metastasis. The adverse prognostic factors suggested by this study includes age >40 years, tumor size >4 cm, purely solid tumors on the cut surface, mitotic rate higher than 1/10 HPF, metastasis at initial diagnosis and tumors extending throughout the renal capsule. Tumors measuring less than 4cm in size and tumors limited to renal parenchyma are associated with a lower rate of metastasis and better prognosis.[12]

Clinical course of the disease is not predictable due to rarity of the condition and heterogeneous behavior. However, most of the patients have an indolent and prolonged clinical course. Regional lymph node metastasis is a common finding in primary renal well differentiated NET with frequency of metastatic disease ranging from 50-60% cases.[13]

The standard management in renal NET is radical nephrectomy with lymph node dissection for optimal staging. Partial nephrectomy is performed when the tumor size is small. Some cases of metastatic renal carcinoids are noted to be resistant to chemotherapy. Primary and metastatic renal carcinoids have high affinity receptors for somatostatin, which is also known as cytostatic agent to neoplastic cells.[13] Octreotide, a somatostatin analogue plays an important role in decreasing the symptoms of hormonal excess and considered as first line anti-neoplastic agent in patients with positive octreoscan. PROMID, a double-blind, randomized, controlled trial comparing octreotide with placebo showed that it significantly improved time to progression.[19]

Liver metastasis can be treated with open resection or with minimally invasive ablative procedures. The mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib are two newer drugs reported to be used in renal carcinoids. Long term follow-up is essential due to prolonged clinical course of renal carcinoids.

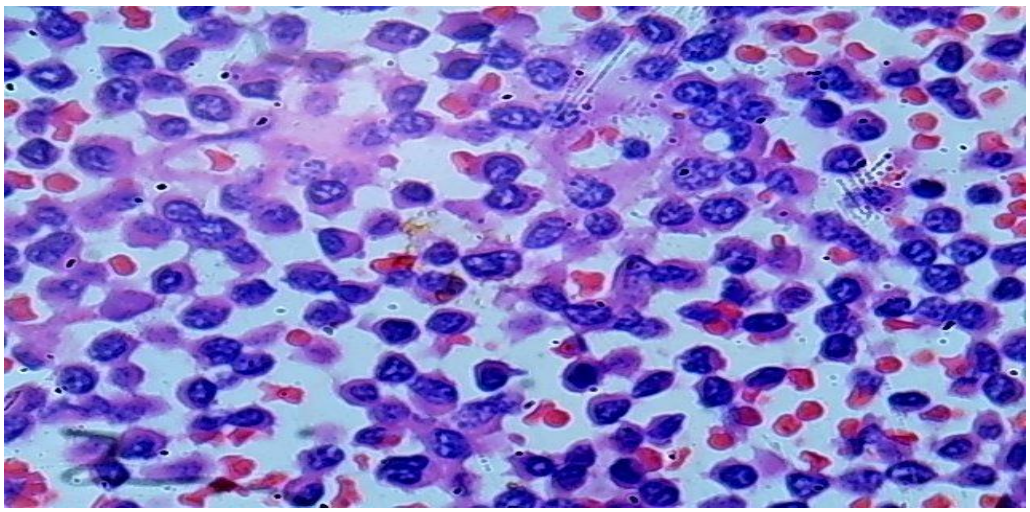

Figure 1: Round tumor cells with stippled chromatin, inconspicuous nucleoli and a thin rim of eosiniphilic cytoplasm.

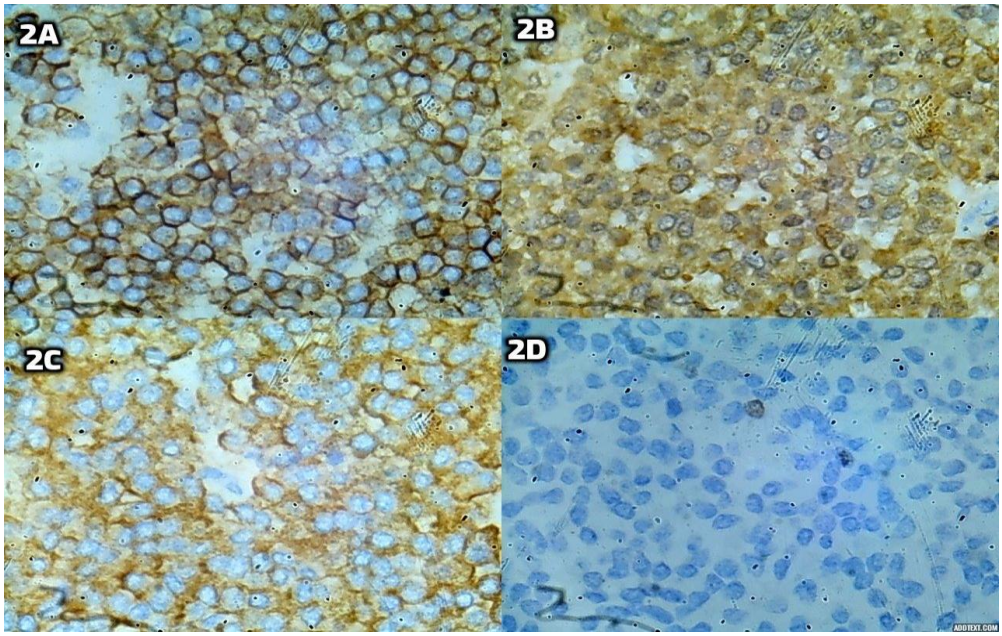

Figure 2: On immunohistochemical analysis the tumor cells demonstrate positivity for A)CD-99, B)NSE, C)Synaptophysin, D)Low ki-67.

CONCLUSION

Well differentiated neuroendocrine tumor of kidney is a rare entity with prolonged clinical course. Most of the patient present with abdominal or flank pain. Regional lymph node metastasis is common finding at the time of surgery. Surgical resection with lymph node dissection is the standard treatment. Age, tumor stage, tumor size, mitotic rate, metastasis at diagnosis and renal capsular extension are important prognostic factors. Immunohistochemical markers for neuroendocrine differentiation are essential to confirm the diagnosis as the management guidelines may differ from other renal neoplasms.

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