Primary Epithelial Neuroendocrine Tumors of the Retroperitoneum

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ABSTRACT

Neuroendocrine tumors are either epithelial or neural in origin. Neuroendocrine tumors of the retroperitoneum are mostly metastatic. Primary epithelial neuroendocrine tumors of the retroperitoneum are exceedingly rare. We describe a case of a retroperitoneal tumor that was discovered incidentally during exploratory laparotomy for small-bowel obstruction. Histopathologic and immunochemical analyses of the biopsied mass were consistent with an epithelial neuroendocrine tumor. The tumor was subsequently removed and final analyses confirmed the initial diagnosis. No evidence of lymph nodes or paraganglia were found within the tumor on histologic examination. Extensive evaluation did not reveal any other primary or metastatic lesions. Therefore, the diagnosis of primary epithelial neuroendocrine tumor of the retroperitoneum was made. The literature is reviewed and discussed. To date, this is only the fifth reported case of primary epithelial retroperitoneal neuroendocrine tumor. Although extremely rare, the possibility of such diagnosis should be included in the differential diagnosis of a retroperitoneal tumor.

INTRODUCTION

Primary retroperitoneal tumors account for 0.16% to 0.20% of all human neoplasms. The most frequent primary tumors of the retroperitoneum are lymphoproliferative disorders, soft-tissue neoplasms, and germ cell tumors.[1] Primary neuroendocrine tumors (NETs) arising in the abdominal cavity mainly originate from the gastrointestinal tract and pancreas. NETs found in the retroperitoneum are mainly metastatic.[2]

Tumors of the neuroendocrine system are commonly divided into two main groups on the basis of cytoskeleton filaments. The neural group, which includes paraganglioma, is characterized by the predominant expression of neuro-filaments; and the epithelial group, such as carcinoid, shows typically a cytoskeleton formed of keratins and occasionally neurofilaments.[3] Although neural tumors, particularly paraganglioma, are frequently reported in the literature,[1-3] epithelial NETs of the retroperitoneum are exceedingly rare.

We present a case of primary epithelial NET of the retroperitoneum that was discovered incidentally during exploratory laparotomy for small-bowel obstruction. We also present a comprehensive review of the literature and a summary of all reported cases.

CASE REPORT

A 65-year-old otherwise healthy woman presented to the emergency room with a 3 days of abdominal pain, constipation, and repeated emesis. She had no prior surgical operations. She was tachycardic and her abdomen was diffusely tender. Laboratory data was significant for a white cell count of 33,000/mm³. She was taken emergently to the operating room and underwent an exploratory laparotomy. She was found to have necrotic bowel caused by an adhesive band leading to a closed loop obstruction, ischemia, and gangrene. The necrotic segment was resected and viable bowel was re-anastomosed. Upon further exploration of the abdomen, the patient was noted to have an approximately 6 cm × 7 cm mass located to the left of midline adjacent to the left kidney, and anterior to the left ureter. The mass did not appear to originate from the aorta, kidney, or adrenal gland; was not related to the adhesive band; and was not involved in the intestinal obstruction. A decision was made to perform an intraoperative incisional biopsy; the biopsy specimen was sent for pathologic examination along with the resected bowel specimen. Computed tomography (CT) scan of the abdomen was performed after the surgery and showed a mass in the left retroperitoneum consistent with operative findings (Figure 1).
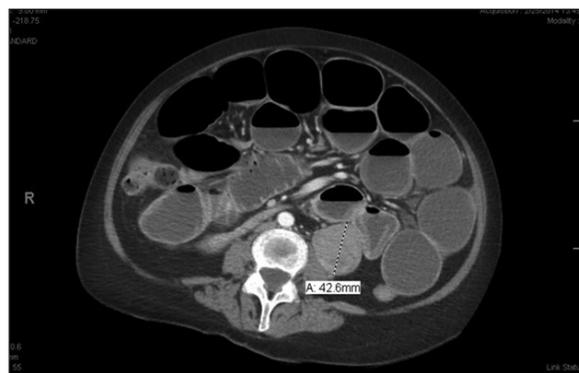

Figure 1. Computed tomography scan of the abdomen showing the left retroperitoneal mass.

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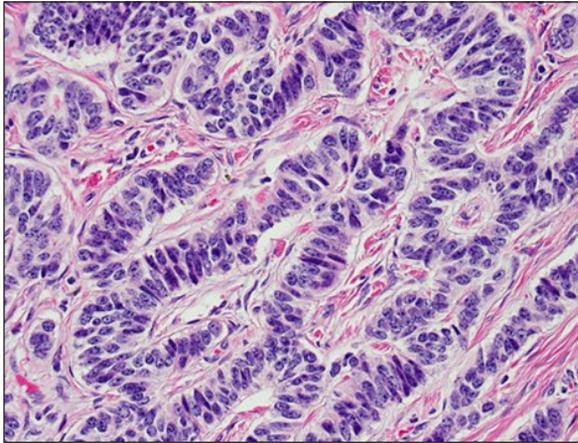
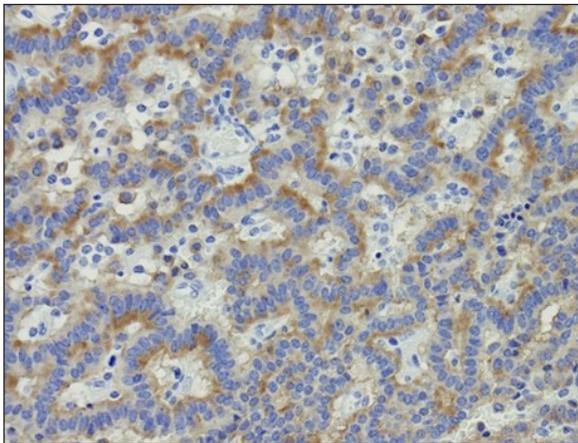Figure 2. Tumor cells arranged in a trabecular pattern.

Figure 3. Tumor cells show diffuse positivity for synaptophysin stain.

The postoperative course was uneventful and the patient was discharged to home 3 days after surgery in good condition. Histopathologic examination of the resected intestine revealed findings consistent with ischemia secondary to obstruction with no evidence of malignancy. Histologic examination of the incisional biopsy specimen of the mass showed oval and round tumor cells arranged in a trabecular pattern with less than 1 mitosis/10 high-power fields and 2% Ki-67 proliferation rate. Tumor cells were positive for cytokeratin, chromogranin, and synaptophysin (Figures 2 and 3). The diagnosis of low-grade, well-differentiated epithelial NET was made. The patient was seen in the clinic 2 weeks after surgery; further questioning revealed no recent history of flushing, diarrhea, breathing difficulty, or weight loss.

Octreotide scan at that time showed a somatostatin-avid tumor in the left abdomen consistent with the previously noted mass (Figure 4). The remainder of the full-body octreotide scan was unremarkable. CT scan of the chest was negative for any metastatic disease. Biochemical evaluation, including urine 5-hydroxyindoleacetic acid and chromogranin, were within

normal limits. The patient was then referred to gastroenterology for upper and lower gastrointestinal tract endoscopical examination. Colonoscopy was normal except for a 3 mm polyp in the sigmoid colon that was removed. Histopathologic examination was consistent with mucosal prolapse without evidence of malignancy. Esophagogastroduodenoscopy with endoscopic ultrasonographic examination was completely normal except for a small area, less than 1 cm, of mucosa in the second portion of the duodenum that was mildly nodular. Multiple biopsies were performed and found to be negative for malignancy. The patient was seen in the clinic one month after the surgery; further surgical resection was recommended but the patient declined surgery at that time.

Six months later, the patient returned to the clinic and wanted to proceed with surgery. Repeat CT imaging showed the mass stable in size with no new lesions elsewhere in the body, and the decision was made to proceed with surgery. Considering the proximity of the mass to the left kidney and ureter, a left ureteral stent was placed preoperatively by urology. Upon abdominal exploration, the peritoneum, liver, pancreas, intestines, uterus, and ovaries were examined. No evidence of tumor was seen. We then proceeded with resection of the mass. The left colon was mobilized laterally to medially along the white line of Toldt, and the colon was reflected medially. The left ureter was identified. The stent was palpated and dissection was carried inferosuperiorly to the level of the mass. The mass was noted to lay anteriomedially to the ureter, with a distinct plane between the two. Using both sharp and blunt dissection, the mass was carefully dissected off the surrounding structures of the retroperitoneum. The resected mass was solid, ovoid, and approximately 7.5 cm in diameter (Figure 5). Cross-sectioning revealed a tan-red, focally hemorrhagic, and necrotic cut surface. In addition to the removal of the mass, the grossly normal appendix was removed in a standard open fashion to rule out the possibility of a primary appendiceal NET. Subsequent pathologic examination of the appendix revealed no significant abnormality. The postoperative course was uneventful and the patient was discharged home 1 week after surgery in good condition. Histopathologic
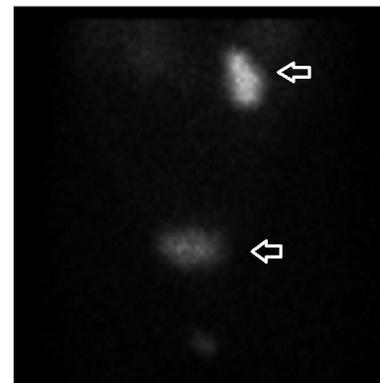

Figure 4. Octereotide scan showing somatostatin-avid tumor in the left abdomen (upper arrow) and normal uptake in the urinary bladder (lower arrow).

Figure 5. Resected specimen.

and immunohistochemical examination of the resected mass was consistent with the initial biopsy. The patient was seen in the clinic 2 weeks after the surgery and was doing well.

DISCUSSION

The retroperitoneum is a large area extending from the thoracic to the pelvic diaphragm between the iliac crests and the tips of the twelfth ribs laterally. There is a great variety of tissues in the retroperitoneum, including mesothelial, connective, and nervous tissues that are potential sites for tumor formation.[4] We describe a case of epithelial NET that was found incidentally during exploratory laparotomy for small-bowel obstruction. Retroperitoneal tumors with neuroendocrine features most commonly represent metastatic tumors with either a known or unknown primary. The primary tumors are usually neural NETs, such as paraganglioma, heterotropic pancreas, or adrenal tissues. In this case, the tumor was completely isolated from alimentary organs, including the pancreas and gut. On histologic examination, the tumor showed no evidence of lymph node, paraganglia, pancreatic, or adrenal tissues. Moreover, extensive evaluation failed to reveal any evidence of primary tumor elsewhere in the body. Finally, the anatomic location, the macroscopic and microscopic histologic examination, as well as the immunohistochemical analysis of the tumor were similar to the three other reported cases in the literature. It is therefore thought likely that this epithelial NET was a primary lesion originating in the retroperitoneal cavity.

The possibility that the tumor in this case is a metastatic disease of a missed small primary tumor somewhere else is a possibility. Neither the biochemical nor the radiologic investigations that are used in the evaluation of metastatic NETs is reliable in ruling out such possibility. The sensitivity of the 24-hour urinary 5-hydroxyindoleacetic acid testing has been reported to be as low as 35% and the specificity approximately 88%.[5] Chromogranin A, however, has a very high sensitivity though it still has poor specificity.[6] Overall sensitivity of the octreotide scan is reported to be as high as 90%; however, false negatives (ie, failed detection) may result from various technical issues including small tumor size,

or from inadequate expression of somatostatin receptors.[7] CT and magnetic resonance imaging (MRI) are important modalities used in the localization of carcinoid primaries and/or metastases. The median detection rate and sensitivity of CT and/or MRI have been estimated at 80%; detection rates by CT alone vary from 76% to 100%, whereas MRI detection rates vary from 67% to 100%.[7] CT and MRI are better for initial localization of the tumor than for metastatic disease because both imaging techniques may miss tiny lesions. One study has shown that metastatic lesions in 50% of patients were missed, especially in lymph nodes and extrahepatic locations.[8]

No well-established staging system exists for NETs. Despite the inability to establish a single system of nomenclature, grading, and staging for NETs of all sites, there are common features to form the basis of most systems. Those features include size, mitotic count, vascular and perineural invasion, nuclear polymorphisms, and Ki-67 labeling index.[9] The most recent World Health Organization classification divides NETs into well-differentiated endocrine tumors (benign or low-grade malignancy), well-differentiated endocrine carcinomas, poorly differentiated endocrine carcinomas, and tumor-like lesions. This differentiation is based on the tumor's histology, tumor size, morphology, and presence or absence of local invasion or metastasis.[10] This case was diagnosed by this classification as a low-grade, well-differentiated NET.

We conducted a literature review of all published cases of primary retroperitoneal NETs in the English language. To date, there have been only 4 reported cases. The first case was a 37-year-old woman who presented with an incidentally found retroperitoneal mass compressing the right colon.[11] At surgery, the mass was located in the retroperitoneum lateral to the right kidney without connection to the colon, kidney, or adrenal gland. The mass had a thick fibrotic capsule and was filled with hemorrhagic fluid. Histologic examination revealed a uniform population of round to oval cells arranged in sheets and nests. Mitotic figures were

Table 1. Reported series of primary retroperitoneal cancers			
Author, year	Number of patients	Benign tumors, no. (%)	Malignant tumors, no. (%)
Donnelly,[15] 1946	95	13 (13.7)	82 (86.3)
Newman and Pinck,[16] 1950	33	5 (15.2)	28 (84.8)
Melicow,[17] 1953	156	32 (20.5)	124 (79.5)
Pack and Tabah,[18] 1954	120	17 (14.2)	103 (85.8)
Tidrick and Goldstein,[19] 1955	32	2 (6.2)	30 (93.8)
North,[20] 1960	17	5 (29.4)	12 (70.6)
Braasch and Mon,[4] 1967	101	13 (12.9)	88 (87.1)
Mehta et al,[21] 1981	42	7 (16.7)	35 (83.3)
Singh et al,[22] 1984	5	1 (2.0)	4 (80.0)
Alvani et al,[23] 1993	6	0 (0.0)	6 (100.0)
Pal et al,[24] 2005	42	14 (33.3)	28 (66.7)
Kaliszewski et al,[25] 2010	7	6 (85.7)	1 (14.3)
Virseda Rodriguez et al,[26] 2010	37	6 (16.2)	31 (83.8)

observed. On immunohistochemistry, the tumor cells were positive for cytokeratin, BerHP4, CD56, synaptophysin, and chromogranin, but negative for CD99, D2-40, and S-100, consistent with a diagnosis of NET. No other hypermetabolic lesions were detected on imaging and a diagnosis of primary retroperitoneal NET with an epithelial origin was given.[11]

The second case was reported in a 71-year-old woman who presented with left abdominal pain and a mass.[12] Imaging demonstrated the mass to be in the superolateral left retroperitoneum, displacing the left kidney medially. Further imaging showed no other masses. At surgery, the mass was noted to be adhered to the aortoiliac perivascular tissues. Macroscopically, the tumor appeared to be a large cyst with a thin fibrous capsule and filled with hemorrhagic fluid. Microscopically, the tumor was composed of a uniform population of round neoplastic cells arranged in trabeculae and nests. Nuclear polymorphism was mild and mitotic figures were absent. Tumor cells were immunoreactive to cytokeratin, epithelial membrane antigen, neuron-specific enolase, chromogranin A, pancreatic polypeptide, and gastrin. Tumor cells were also weakly positive for Grimelius stain and negative for Masson-Fontana stain. Ultrastructural observation of neurosecretory granules confirmed the neuroendocrine nature of the tumor and the diagnosis of primary epithelial retroperitoneal NET was rendered. However, in light of the anatomic location of the tumor, which was tightly adherent to the perivascular at the same site where the organ of Zuckerkandl is normally located, and the presence of scattered S-100 positive cells, the possibility of a paraganglionic origin was considered.[12]

The third reported case was that of a 41-year-old woman who had left flank pain and was found to have a left abdominal mass on physical examination.[13] Imaging revealed a mass in the left retroperitoneum. At surgery, the mass was noted to be located in the retroperitoneal cavity isolated from other organs. The mass was solid and once again had a thick fibrous capsule. Further imaging revealed no other lesions and urine 5-hydroxyindoleacetic acid was within normal limits. Histologically, the tumor showed a trabecular pattern with a positive reaction for Grimelius stain, but negative reaction for Masson-Fontana stain. Tumor cells were negative for argentaffin and positive for argyrophil reactions. Immunohistochemically, vasoactive intestinal polypeptide, human chorionic gonadotropin-alpha, and somatostatin were identified. Electron microscopy revealed numerous neurosecretory granules in the tumor cells. No signs of lymph nodes, osseous or cartilaginous tissues, paraganglia, or pancreatic tissues were found on histopathologic examination. These findings, therefore, led the authors to conclude that the tumor was likely a primary NET of epithelial origin originating from the retroperitoneum.[13]

The 4th case was reported in a 14-year-old boy who presented with 3 months of vomiting.[14] Imaging showed a 4-cm × 3-cm-sized solid homogeneous mass located in front of the pancreas and dissociated from pancreatic and liver tissue. The mass was removed surgically. Surgical exploration of the mass showed no evidence of hepatic, pancreatic, or other metastatic disease or pathologic lymph node. Gross examination of the tumor showed a sharply demarcated solid grayish-tan colored lesion that was 3.5 cm × 3.5 cm in size, with punctuate foci of hemorrhage. Microscopically, the tumor was composed of nests and trabecular growth pattern. Immunohistochemically, tumor cells showed reactivity for pankeratin, neuron-specific enolase, synaptophysin, S-100, and CD 56. The rate of Ki-67 ranged from 2% to 5%. Histopathologic examination and immunohistochemical findings of the specimen were consistent with NET. Further evaluation was negative and the diagnosis of primary retroperitoneal NET was rendered.[14]

Since Morgagni first described retroperitoneal tumors in 1761, a large series of primary retroperitoneal tumors have been reported (Table 1). Thirteen series have reported a total of 699 cases of primary retroperitoneal tumors from 1946 to 2010.[15-26] The majority of these tumors originated from mesothelial and connective tissues of the retroperitoneal space. Approximately 82% of these tumors were malignant. The most common malignant tumors in this group were sarcomas and lymphomas. The most common age group affected was between the 4th and 7th decades of life; male to female distribution was equal. Interestingly, NETs were not reported in any of these series.

CONCLUSION

We present a case of a retroperitoneal NET that was discovered incidentally during exploratory laparotomy for small-bowel obstruction. The tumor was completely isolated from other retroperitoneal organs, and operative exploration did not reveal any other foci of carcinomatosis, metastases, or other primary lesions. Extensive biochemical and radiologic evaluation did not reveal any other primary or metastatic disease. Pathologically, there was no evidence of lymph node, paraganglia, pancreatic, or adrenal tissues present in the specimen. Finally, the gross description of capsule and hemorrhagic components as well as the histobiochemistry corroborate the findings of the other four case reports, with some very minor deviation of detail. Thus, we believe that this may be only the fifth reported case of primary epithelial NET arising within the retroperitoneum to date. Although exceedingly rare, the possibility of such a diagnosis should be considered in the differential diagnosis of a retroperitoneal tumor with similar clinical, anatomical, and pathologic features. However, in the absence of a biochemical test or an imaging tool with 100% sensitivity in detecting very small tumors, the possibility that this tumor might be a metastatic disease cannot be completely excluded and should be considered as well. ❖

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Scientific Solution

To conserve health and to cure disease: Medicine is still pursuing a scientific solution of this problem, which has confronted it from the first.

— Claude Bernard, 1813-1878, French physiologist, one of the first to suggest the use of blind experiments to ensure the objectivity of scientific observations