Multifocal appendiceal ganglioneuroma as the presenting symptom in a patient with PTEN hamartoma syndrome

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Ganglioneuroma is a benign, well differentiated neoplasm within the spectrum of neuroblastic tumors. These tumors arise from neural crest cells and are characterized by mature ganglion cells. The clinical presentation is varied and imaging is often useful in characterizing the neoplasm [1]. Here we describe a case of incidental multifocal ganglioneuroma discovered following laparoscopic appendectomy and the subsequent postoperative oncologic evaluation leading to the eventual diagnosis of PTEN hamartoma tumor syndrome (PHTS).

1. Case report

Patient is a 13-year old female with a history of sickle cell trait, asthma and Chiari malformation who presented with a 5 day history of abdominal pain. The pain was initially diffuse and then localized to the lower quadrants of the abdomen. The patient reported nausea, vomiting and constipation. On physical exam, the patient was non-tachycardic and afebrile. She had tenderness at McBurney’s point and a positive Roving’s sign. White blood cell count was elevated at 15.2 × 10^3/mL and anemia with a hemoglobin of 8.4 gm/dL. Abdominal ultrasound revealed a dilated, non-compressible appendix measuring 10 mm in diameter. The bowel wall appearance was normal.

She was taken to the operating room for laparoscopic appendectomy for presumed appendicitis. An inflamed appendix was visualized in the right lower quadrant (Fig. 1). The appendix was mobilized and divided using an endoGIA stapler. The meso-appendix was similarly divided and the specimen removed. She was discharged uneventfully on postoperative day one.

Final pathology revealed multifocal ganglioneuroma with microscopic nodular areas greater than 1.0 cm apart within the appendix. The largest lesion was located near the tip, polypoid in appearance, and measured 1.0 × 0.4 × 0.4 cm. The lesion was confined to the mucosa. Microscopic inspection displayed ganglion cells with surrounding spindle and inflammatory cells. There were no mitotic figures and the mucosal layer was intact (Fig. 2). Synaptophysin stains were positive in the ganglion and spindle cells. Due to the multifocal nature, further oncologic evaluation was recommended to rule out ganglioneuromatosis and other associated diseases.

On further history and exam, the patient was noted to have macrocephaly, upper lid lipoma, a large lipoma of the sternocleidomastoid, a breast nodule, and skin findings consistent with...
trichilemmomas. Her family history was significant for a variety of cancers including breast, uterine, and pancreatic, as well as possible thyroid issues. Thus the patient was referred for genetic testing and found to be heterozygous for a pathogenic variant in the PTEN gene, consistent with a diagnosis of PTEN hamartoma tumor syndrome. Due to the history of a Chiari malformation, a genome-wide microarray was also performed that showed no other clinically significant variants.

Further workup was initiated given the cancer predisposition syndrome. Urine catecholamines, serum metanephrines, and chromogranin A were within normal limits. Positron emission tomography (PET), metaiodobenzylguanidine scan (MIBG), and computed tomography of the neck, chest, abdomen and pelvis were performed. There was persistent expected inflammation in the postoperative region on PET scan, but this was not felt to represent residual ganglioneuroma, and MIBG and CT scans were negative. Thyroid ultrasound was normal. Urine catecholamines were done every 3 months for 1-year, followed by every 6 months for 2 year. Thyroid US and dermatology exams have been done yearly. Breast nodules are followed every 6 months with US. There has been no recurrence and no new symptoms corresponding to the patient’s PHTS, and the patient is now 18 months from surgical resection.

2. Discussion

Peripheral neuroblastic tumors arise from neural crest cells, the origin of the sympathetic nervous system. As they become increasingly well differentiated, neuroblasts develop into neurons with surrounding stromal component. Neuroblastoma and ganglioneuroblastoma are stroma poor in contrast to the stroma rich ganglioneuroma [2]. Ganglioneuromas may be isolated or occur in conjunction with neurofibromatosis type 1, Cowden syndrome or PTEN hamartoma tumor syndrome, and multiple endocrine neoplasia type 2B [3,4]. Those that arise spontaneously are typically located in the mediastinum, retroperitoneum, colon and mesentery [5].

Ganglioneuroma has a good prognosis compared to its counterparts. However, even with biopsy it can be difficult to characterize these neuroblastic tumors. Traditionally, the treatment recommendation for ganglioneuroma is surgical excision. A large French review suggested appendectomy alone was a sufficient intervention for incidentally identified ganglioneuroma within the appendix (rather than hemicolectomy) [6]. However two retrospective reviews have challenged the necessity of any operative intervention. In one series of 24 ganglioneuroma patients, four were left with residual disease but had no recurrence after an average of 84 months. There were also 6 patients with postoperative complications including bowel obstruction, urinary retention, scoliosis, and Horner’s syndrome [7]. A separate series of 24 ganglioneuroma patients found 30% had postoperative complications; again Horner’s and intestinal obstruction were included. There were more complications for thoracic versus abdominal resection. There was no evidence of tumor progression and no mortality at follow up, average 33.5 months [8]. If surgical excision of a suspected ganglioneuroma is pursued, consideration must be given to intraoperative catecholamine release as there can be tumoral hypersecretion. One recent case report highlighted unexpected hypertension during excision requiring intravenous stabilization. It is unclear who requires preoperative alpha blockade at this time and further studies are needed [9], however if patients have symptoms suggestive of tumoral hypersecretion (episodic headaches, hypertension, sweating, and tachycardia) then further workup is crucial prior to operative procedures.

PTEN hamartoma syndrome has variable manifestations arising from mutations in the PTEN gene, a tumor suppressor gene on chromosome 10. Patients typically have multiple hamartomas in more than one organ and an elevated malignancy risk [3]. In patients with incidentally diagnosed ganglioneuroma as part of the PTEN syndrome, colonoscopy should be performed as surveillance beginning at age 35 due to the increased risk for colorectal cancer [3]. Some authors propose additional surveillance of the thyroid, uterus and breast due to the association with these syndromes [10]. Because of our patient’s family history, she continues with yearly thyroid ultrasounds, and every 6 month breast ultrasounds.
3. Conclusion

Current recommendations for the treatment of appendiceal ganglioneuromas include surgical excision. However, consideration must be given for postoperative complications particularly in pediatric patients. PET scan may be useful to help assess the burden of disease peri-operatively. Thorough family history and clinical exam are imperative to ruling out cancer predisposition syndromes that may present with intestinal ganglioneuromas.

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Conflicts of interest

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References


