CLINICAL VIGNETTE

Gastrointestinal Neuroendocrine Tumors: Increasing Incidence Requires Increasing Awareness

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Cases

A 54- year old African American male presented for a screening colonoscopy. His past medical history includes prior CVA on clopidogrel and pre-diabetes. There was no family history of gastrointestinal cancers. At colonoscopy, four polyps were removed. The pathology was: one benign 8mm neuroendocrine tumor of the rectum, two 2-4mm tubular adenomas and one 5mm hyperplastic polyp. The margins of the neuroendocrine tumor were negative. Surveillance flexible sigmoidoscopy 6 months later showed no evidence of recurrent disease. However, polypectomy scar was still present and biopsied, which did not show any histological evidence of recurrent disease. Surveillance colonoscopy in 5 years was recommended.

A 39-year-old male presented for a screening colonoscopy due to family history of early colon cancer in his father. His father was diagnosed with adenocarcinoma of the colon at age 49. The patient was asymptomatic, without rectal bleeding, changes in bowel habits, unintentional weight loss. At colonoscopy two polyps were removed. Pathology showed 5mm well differentiated neuroendocrine tumor from the rectum and a benign 3mm tubular adenoma of the transverse colon. The neuroendocrine tumor exhibited low grade dysplasia (G1) without lymphovascular invasion. Surveillance flexible sigmoidoscopy was advised 6 months after his colonoscopy but was not completed.

Discussion

Gastrointestinal neuroendocrine tumors (GI NET) also known as "carcinoids" are increasingly common since 2000.[1] These two cases were found within 2 days of each other in a community GI practice. The incidence of GI NETs has increased x8 fold in the past 20 years, with approximately 8,000 cases/year in the United States. GI NETs are more common in African Americans and females.[2] Women are affected 2.5 times more than males, although rectal NETs are more common in men.[3] GI NETs are the second most common GI tumor after colorectal cancer. GI NETs are found most commonly in the small intestine (45%), followed by the rectum (20%), appendix (16%), colon (11%) and stomach (7%).[4] The vast majority of GI NETs are benign, and GI NETs represent only 2% of all malignant gastrointestinal cancers. Patients with genetic risk factors such as MEN type 1 and Neurofibromatosis type 1 have greater likelihood of developing these tumors and account for 20% of cases.[4] More recently a mutation in IPMK gene has been associated with causing the condition "familial small intestinal neuroendocrine tumor."

Endoscopically rectal NETs are smooth, sessile lesions located within 10-15cm from the anal verge in 80-90% of cases. GI NETs are characterized histologically by containing: chromogranin A (CgA), synaptophysin and neuron specific enolase. GI NETs are subdivided into 3 grades based on Ki-67 index and mitotic index: 1 (low), 2 (intermediate) and 3 (high). Grades 1 & 2 are frequently referred to as "carcinoids", while type 3 is referred to as "GI NET carcinoma". Endoscopic ultrasound (EUS) plays an important role in determining depth of invasion in rectal NETs and whether or not mucosal resection will be adequate or if surgical intervention will be required. Although metastases are rare, the liver, bones and lungs are the predominate sites for GI NETs.

GI NETs can secrete hormones, typically serotonin, with about 40% actively secrete hormones.[4] High serotonin levels can result in "carcinoid syndrome", characterized by diarrhea, flushing and wheezing. Typically, carcinoid syndrome occurs in patients that have metastatic disease to the liver because the liver can no longer metabolize the extra serotonin. For those select NETs of the pancreas, the main hormone secreted is gastrin, followed by insulin, glucagon and somatostatin.[4] The predominate symptoms of actively secreting pancreatic NETs include: diarrhea, steatorrhea and multiple peptic ulcers. Tracking GI NETs response to therapy includes monitoring: urine 5-hydroxyindoleactic acid (5-HIAA), serum CgA and serum gastric levels. It is important for clinicians to understand that certain foods and medications can affect the levels of these monitoring tests. Bananas, kiwis, plantains, avocados, tomatoes, eggplant, turkey, and chicken are all rich in tryptophan. Nearly 70% of tryptophan is metabolized by GI NETs into serotonin, in comparison to the typical 1% by normal GI tract cells. As a result, these foods can falsely raise urine 5-HIAA levels.[4] Certain medications such as: acetaminophen, nicotine, caffeine, guaifenesin, phenobarbital and methamphetamines can also raise urine 5-HIAA levels. In comparison, medications including: alcohol, aspirin, levodopa, isoniazid and monoamine oxidase inhibitors can lower urine 5-HIAA levels.[4] Proton pump inhibitors can raise both CgA and gastrin levels.

Thus, patients should avoid these foods and medications when having these tests drawn to improve accuracy.

GI NETs are notorious for not being responsive to chemotherapeutic agents and thus endoscopic and or surgical intervention remain the preferred treatment. Standard polypectomy for rectal NETs were found to provide curative resection in only 30.9% of cases.[5] Thus the preferred method for removing rectal NETs is endoscopic mucosal resection (EMR) during EUS those lesions that are <2cm in diameter. Piecemeal resection is discouraged as this distorts the lateral and deep margins. Low anterior resection is the preferred management for lesions >2cm in diameter. Chemotherapeutic agents include: capecitabine, 5-fluorouracil, doxorubicin, etoposide, dacarbazine, streptozocin, temozolomide, oxaliplatin. Chemotherapy cycles include 3-4 weeks of treatment for a total of 4-6 cycles. Patients with carcinoid syndrome from metastatic disease with somatostatin analogues such as long-acting octreotide 20-30mg intramuscularly every 4 weeks.[6] Telotristat erthyl 250mg three times daily can be used in conjunction with octreotide for those patients with refractory carcinoid syndrome.[7] Radiation therapy can be useful for patients with metastatic disease to the liver.

Rectal NETs <1cm with grade 1 or 2 histology do not require surveillance. If the rectal NET is <1cm but grade 3, annual colonoscopies for 5 years are recommended. For rectal NET 1-2cm regardless of histological grade should undergo: colonoscopy, EUS and MRI at 12 months; followed by colonoscopy every 5 years. If the rectal NET is > 2cm and histological grade 1 or 2, the patient should have annual colonoscopy, EUS and MRI for 5 years after diagnosis. Finally, for rectal NET >2cm with histological grade 3, following LAR, the patient should undergo colonoscopy + EUS + MRI every 4-6 months the first year after diagnosis, followed by annually for the next 5 years.[8]

Conclusion

These two cases demonstrate some of the classic features of rectal NETs. Gastroenterologists (GIs) need to be familiar with the various histological stages of these tumors in order to correctly manage these tumors. A teaching point from the literature review suggests the first patient was subjected to an unnecessary flexible sigmoidoscopy given the size and histological state of the tumor. It also important for clinicians to be aware of that diet and medications can impact the surveillance markers for advanced disease and counsel patients appropriately for accurate testing.

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