CLINICAL VIGNETTE

Goblet Cell Carcinoid of the Appendix in an Immunosuppressed Patient

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Introduction

Goblet cell carcinoid tumors of the appendix were first described in 1907.[1] They are a rare form of neuroendocrine malignancy arising from the goblet cells of the appendix.[2] Common clinical features often vary, ranging from an asymptomatic presentation to obstructive symptoms includes pain, nausea, and vomiting.[2] In the event of metastasis to the liver, goblet cell carcinoid can release serotonin and other vasoactive compounds into the systemic circulation, causing the carcinoid syndrome. This syndrome commonly consists of any combination of flushing, diarrhea, bronchospasm, and right heart failure.[2] The incidence of carcinoid tumors of the appendix is exceedingly rare, with a prevalence of 0.47% in a longitudinal study on roughly 1,500 appendectomy patients.[3] We describe a case of appendicitis secondary to goblet cell carcinoid in a 46-year-old female with history of multiple sclerosis treated with natalizumab.

Case Report

A 46-year-old female with history of multiple sclerosis presented with 6 days of right lower quadrant abdominal pain and emesis. She denied changes in bowel habits, fever, chills, anorexia, dysuria, diarrhea, chest pain, hematuria, hematochezia, and back pain. Past medical history was significant for multiple sclerosis (MS) with concomitant optic neuritis diagnosed fourteen years ago that was treated with monthly intravenous natalizumab infusions. Her MS had been previously stable but noted that her symptoms had worsened in the preceding 5 years, now requiring a mobility walker. Additionally, she reported a history of well managed depression on bupropion and citalopram. Medications on hospital admission included natalizumab, baclofen, bupropion, citalopram, modafinil, calcium carbonate, vitamin D, vitamin B complex, and alpha lipoic acid. She had no known drug allergies. She reported quitting smoking 11 years ago, did not use illicit drugs, and consumed roughly 0.5 ounces of alcohol per week. She had a family history of colon cancer in her maternal grandmother, and Alzheimer's in her paternal aunt. A review of systems was otherwise unremarkable.

On admission to the ED, her temperature was 98.9 F, blood pressure 136/81, heart rate 100, respiratory rate 16 and her oxygen saturation 99%. Physical exam was significant for abdominal tenderness at McBurney's point. Hypoactive bowel sounds were present throughout the abdomen. Laboratory studies were notable for an elevated white blood cell count of 12.65 with 62% neutrophils, hemoglobin of 12.4, and platelets of 322. INR was 1.0 and basic metabolic panel was within normal limits. Liver function tests were normal, Lipase was 10, albumin 4.1 and urinary analysis was unremarkable.

CT scan of the abdomen (Figure 1) demonstrated layering sludge in the gall bladder and a 5.5 x 3.8 centimeter heterogeneous inflammatory mass containing small locules of fluid in the right lower quadrant, adjacent to the cecal tip. This is representative of a phlegmon or early abscess indicative of ruptured appendicitis.

The patient was admitted to medicine service with general surgery consultation, and treated with bowel rest, IV fluids and IV piperacillin and tazobactam. Given a lack of peritoneal signs, the decision was made to defer surgery and continue conservative treatment. The patient improved over the next three days and was transitioned to oral metronidazole and ciprofloxacin. She was subsequently discharged with outpatient surgical follow-up in one month to determine the necessity of an appendectomy.

Upon one-month follow-up, a repeat abdominal CT found the mass shrank to a size of 2.3 x 1.5 centimeters in the region of the medial cecal base with a punctate focus of associated calcification that reflects a small appendicolith. She felt well at this time and decided to forgo an appendectomy. Two more months passed before the patient's right lower quadrant pain returned and she opted for surgery. Her laparoscopic procedure consisted of the lysis of adhesions, resection of the omentum, and ileocecectomy. Histopathological analysis determined the mass was a goblet cell carcinoid of the appendix, obstructing the appendiceal orifice and leading to appendicitis. Following the discovery of malignancy, she was scheduled for a right hemi-colectomy with ileo-transverse colostomy to screen for metastasis. Surgical histopathology following her second resection showed colonic and small bowel mucosa with no diagnostic histopathologic abnormality. Six lymph nodes from the resected portion of her bowel were also negative for malignancy. Postoperatively, the patient was managed with hydromorphone and prophylactic enoxaparin. Her recovery period was complicated by diarrhea secondary to C. Difficile colitis discovered on post operation day 3. Management with oral metronidazole was successful and she was discharged two days later.

Discussion

Goblet cell carcinoid of the appendix is a rare neoplasm associated with age, at an average presentation at 58.9 years, and schistosomiasis.[4,5] It is a secretory neuroendocrine tumor defined by its ability to cause the carcinoid syndrome secondary to releasing mass amounts of serotonin and other vasoactive compounds.[2] The carcinoid syndrome commonly presents with flushing and diarrhea. Long standing carcinoid syndrome may eventually present with wheezing, pellagra, and right heart failure.[2] In the case of enteric carcinoid tumors, serotonin enters the portal system and is degraded by the liver before it can reach the systemic circulation and cause the carcinoid syndrome.[2] For this reason, the carcinoid syndrome typically occurs with metastasis to the liver, allowing the malignancy to bypass the portal circulation.[2]

Preoperative diagnosis of appendiceal goblet cell carcinoid is challenging due to its symptomatic similarities with acute appendicitis. Both present with right lower quadrant pain, diarrhea, nausea, loss of appetite, and vomiting.[3,5] In a patient suspicious for appendicitis with concomitant carcinoid syndrome, screening for goblet cell carcinoid of the appendix would be indicated.[2] A common screening method includes measuring 5-hydroxyindoleactic acid (5-HIAA) excretions in the urine over a 24-hour period. This test has a sensitivity of 90%, a specificity of 90%, and is the primary screening examination of choice.[6] 5-HIAA is a metabolite of serotonin, therefore an increase in the urine may suggest a carcinoid etiology.[7] The normal amount of 5-HIAA in the urine is 2-8 mg/day.[6] Those with enteric malabsorption syndromes present with an elevation at 30 mg/day and carcinoid itself usually presents from 90 – 2000 mg or greater a day.[6] It is recommended that patients avoid serotonin rich foods 24 hours before the test in order to avoid a false positive.[2]

Where blood or urine tests may fail, magnetic resonance imaging (MRI) and computed tomography (CT) may detect both the location and size of the tumor. Intravenous contrast can be used to confirm liver metastasis as metastatic carcinoid is often hypervascular.[7] A less common imaging modality, somatostatin-receptor scintigraphy (Octreoscan), works well in imaging carcinoid tissue because of the high amount of somatostatin receptors contained within them.[2] Octreoscan is doubly beneficial when screening for carcinoid as it can detect both primary malignancy and metastasis. However, it is not until the biopsy of the appendix is done can a true goblet cell carcinoid of the appendix can be confirmed.[2]

Treatment options for goblet cell carcinoid tumors discovered post appendectomy depend on the size of the neoplasm. Carcinoid tumors larger than two centimeters call for an additional right hemicolectomy while tumors less than one centimeter need no surgical follow-up post appendectomy. If there is suspicion of metastasis before or during the surgery, chemotherapy is recommended. There is current disagreement on the treatment of tumors between 1-2 centimeters. Some argue that in this case, a simple appendectomy would have been sufficient while others have recommended an addition of a right hemicolectomy, removing the draining lymph nodes of the appendix, and any residual disease on the meso-appendix.[2]

With regards to treating symptoms of the carcinoid syndrome, a subcutaneous injection of 150 micrograms of somatostatin three times daily was found to have a significant effect on the majority of carcinoid patients in a small study.[8] Diarrhea and flushing were promptly relieved in 88% of patients and urine 5-HIAA levels had decreased by 50% or more in 72% of patients, all of whom had had previously elevated levels present in their urine.[8] No toxicity was observed, therefore somatostatin injections were concluded to be an appropriate therapy for patients that do not respond to conservative measures.[8]

There are several recommendations on patient follow up post-surgical intervention depending on the size of the tumor and the period of time since the resection.[9] The North American Neuroendocrine Tumor Society recommends that patients with tumors less than one centimeters do not require routine surveillance tests.[9] Those with tumors between 1-2 centimeters with high grade histology or evidence of metastasis and tumors greater than 2 centimeters require follow up testing three to six months after surgery and subsequent screening 6 to 12 months for the next seven years.[9] Beyond a physical examination, it is recommended that follow up include screening for tumor markers, 5-HIAA and chromogranin, with additional computed tomography or magnetic resonance imaging compared between visits to screen for recurrence.[9]

This case presented an uncommon cause of appendicitis in a middle-aged female on chronic immunosuppression. While goblet cell carcinoid of the appendix is rare, it has a good prognosis with no lasting effects post appendectomy with hemicolectomy. Our patient was fortunate that she never developed the carcinoid syndrome and her malignancy was removed before metastasis could occur. Five years post-surgery, the patient has had no further signs of goblet cell carcinoid recurrence. It is important to keep in mind that appendicitis has a wide differential. If carcinoid symptoms are found in an appendicitis patient or an incidental appendiceal mass is found on imaging, testing 5-HIAA urine levels is a simple modality to assess for goblet cell carcinoid of the appendix. If caught early, surgical intervention is curative and can prevent metastatic disease.

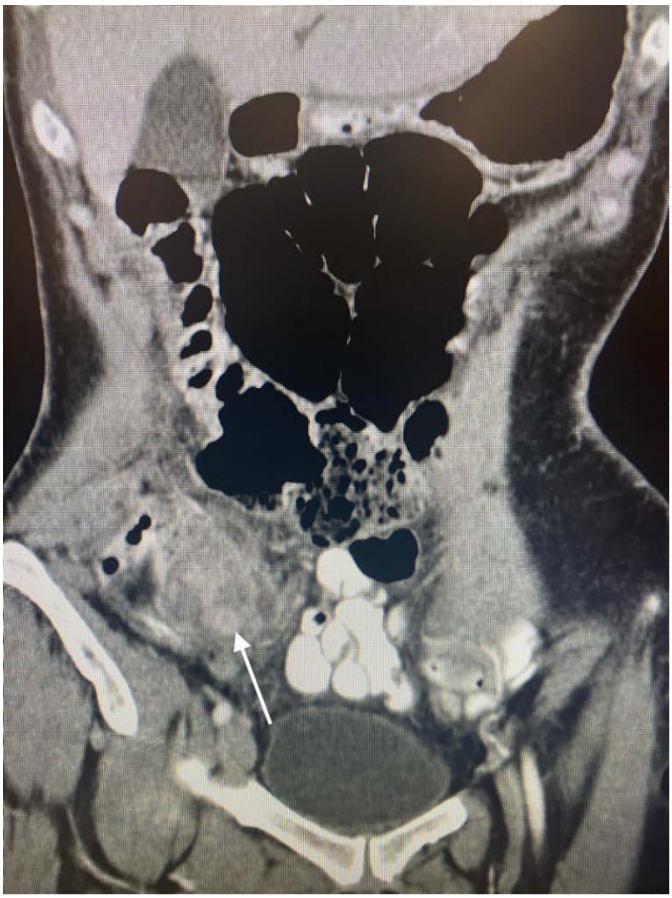

Figure 1

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