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CLINICAL VIGNETTE

A Presentation of Carcinoid Masked by Long Term Opioid Use: A Diagnostic Challenge in the Primary Care Setting

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A 48-year-old woman presented with a 3-year history of abdominal pain and intermittent flushing. Her abdominal pain was diffuse, cramping and associated with loud borborygmus. She denied nausea, diarrhea or constipation. She additionally described flushing episodes, lasting several minutes, which occurred most frequently during meals or periods of emotional duress. She sometimes experienced palpitations and feelings of panic. Her past medical history was notable for chronic lower back pain, which was treated with oxycodone as prescribed by her previous doctor. She also noted new onset diarrhea and recent worsening of abdominal pain after running out of oxycodone. On physical examination she appeared anxious, but otherwise well nourished. Her vital signs included a heart rate of 86, respiratory rate of 16, and blood pressure of 121/82. Her abdomen was diffusely tender, without localizing signs, guarding or rebound tenderness. The remainder of her physical examination was unremarkable. She declined laboratory testing, citing lack of medical insurance and requested refill of her pain medication. The patient was encouraged to return for further workup of her symptoms.

One month later, the patient returned with persistent palpitations and flushing. Her diarrhea and abdominal pain had improved after restarting oxycodone. She agreed to pay for limited studies. Electrocardiogram revealed sinus tachycardia. Laboratory tests including a complete blood count, basic metabolic panel, and thyrotropin stimulating hormone were all within normal limits.

Several months later, the patient presented to the clinic with increased palpitations and flushing, accompanied by worsening abdominal pain, recurrent diarrhea, and 5 pound weight loss. She was still taking oxycodone as prescribed. She had obtained health insurance coverage and additional testing included: 24-hour holter monitor which documented 5 episodes of sinus tachycardia with rates up to 120 beats per minute; elevated Chromogranin-A at 170 ng/ml (1.9-15 ng/ml), and elevated urinary 24-hour 5-Hydroxyindoleacetic acid (5-HIAA) of 53 mg/hr (2-6 mg/hr) with normal unfractionated urinary catecholamines. Computed tomography of the abdomen and pelvis revealed an 18 x 21 mm soft tissue mass within the small bowel mesentery with multiple liver masses. An octreotide scan identified disease within the liver and small bowel. Biopsy of the liver lesions confirmed a well differentiated neuroendocrine tumor, WHO Grade 2 (+Ki-67), solidifying a diagnosis of metastatic carcinoid tumor.

The patient was treated with lanreotide with subsequent improvement of her flushing, palpitations and diarrhea. She underwent exploratory laparotomy with partial small bowel resection, right and caudate lobectomy, appendectomy, cholecystectomy and microwave ablation of 7 liver lesions. Her postoperative course was complicated by persistent abdominal pain and depression. Opioids were aggressively titrated with little relief of her abdominal pain. Repeat abdominal imaging and endoscopy showed no recurrence of disease or evidence of bowel obstruction. Chromogranin-A levels decreased to 5 ng/ml. She was started on low dose nortriptyline 10mg daily 2-months postoperatively with some improvement in her abdominal pain and depressive symptoms.

Discussion

Carcinoid is a neuroendocrine tumor that is relatively uncommon with reported incident rates of 0.28 to 0.8 per 100,000 per year. According to the SEER data set, small bowel carcinoids are the most frequent occurring carcinoid tumors 1. Carcinoid syndrome, which includes the classic presentation of flushing, palpitations, diarrhea and bronchospasm, occurs with liver metastasis or with a high tumor burden, correlating with elevated circulating levels of serotonin, polypeptides, biogenic amines, and prostaglandins2. The diagnosis of carcinoid syndrome is based on assessment of clinical symptoms, elevated 5-HIAA and chromogranin-A levels, appropriate imaging studies, and biopsy confirmation.

This care illustrates several useful learning points for physicians encountering chronic abdominal pain in the primary care clinic setting. First, while rare, carcinoid tumor should be considered in the differential diagnosis for patients with chronic abdominal pain not otherwise explained. Small bowel carcinoid is difficult to recognize, as it may present with non-specific abdominal pain. Moertal, et al conducted a case series of 56 patients with carcinoid tumors at Mayo Clinic. He found the average duration of symptoms until diagnosis was 4 years, with a range of 2 weeks to 21 years1. Moertal also described episodic, colicky abdominal pain to be the most common presentation for small bowel carcinoids (10-55% of patients)[1]. Small bowel carcinoid should be suspected in individuals with persistent abdominal pain, diarrhea, flushing and unintentional weight loss. Bowel obstruction or gastrointestinal bleeding may be one of the first clinical signs of underlying small bowel carcinoid[2].

Second, clinicians should carefully consider the risk of masking symptoms when treating chronic non-malignant pain with opioids. Chronic nonmalignant pain is defined as pain caused by injury or disease that persists longer than 3 to 6 months or longer than expected. Prevalence rates have been estimated to be from 5-50% in the primary care setting[3]. Olsen and colleagues have found that American primary care physicians prescribed opioids in 5% of all visits between 1992 and 2001[4]. While systematic reviews have found opioids to be effective in the treatment of chronic nonmalignant pain, side effects are common, including but not limited to addiction, overdose, opioid-induced hyperalgesia, immune dysfunction and endocrine dysregulation[5,6]. Kalso and colleagues found that 80% of patients experienced at least one adverse event with opioid use, and that 44% of 388 patients were still taking opioids 7-24 months after commencement[6].

Opioid withdrawal is precipitated by hyperactivity in the locus caeruleus, leading to increased norepinephrine release and characteristic symptoms of flushing, agitation, pupil constriction and diarrhea[5]. Carcinoid is similarly characterized by flushing, palpitations and diarrhea, but is caused by elevated circulating levels of serotonin and other biologic amines. In our patient, chronic opioid use delayed diagnosis by initially masking diarrhea. Once the patient had stopped oxycodone, her underlying carcinoid symptoms were elicited but confused for symptoms of opioid withdrawal. The persistence of palpitations and flushing despite successful pain management prompted a broader differential diagnostic consideration. Weight loss was an alarm sign that led to abdominal imaging and eventually led to the diagnosis of carcinoid. Had our patient not been treated with opioids for chronic non-malignant pain, her constellation of symptoms may have been recognized earlier as carcinoid syndrome.
Lastly, the patient's lack of health insurance coverage on presentation posed an additional challenge in establishing her diagnosis. The patient initially paid out-of-pocket for basic laboratory testing which proved costly. It was not until she had obtained full medical coverage, months after initial presentation, that appropriate and inclusive workup could be completed. Uninsured and underinsured patients are at risk for delay in diagnosis, and consequently, adverse healthcare outcomes. Martin and Ulrich recognized that US adolescents and young adults, individuals known to have the lowest rate of health insurance, diagnosed with cancer had lower survival rates than older or younger patients. Because of delay in diagnosis due to inadequate health insurance, they typically presented with a more advanced stage of disease[7]. In 2012, 15.4% of the US population, or 48 million Americans, were without health insurance. With the Affordable Care Act, the uninsured rate is expected to improve by roughly 60%[8]. Hopefully with rising rates of insured Americans, we will see increased utilization of primary care and better health outcomes due to timely diagnoses of serious medical illnesses.

REFERENCES

1. **Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH**. Life history of the carcinoid tumor of the small intestine. *Cancer*. 1961 Sep-Oct;14:901-12. PubMed PMID: 13771655.
2. **Modlin IM, Lye KD, Kidd M**. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003 Feb 15;97(4):934-59. PubMed PMID: 12569593.
3. **Apkarian AV, Baliki MN, Geha PY**. Towards a theory of chronic pain. *Prog Neurobiol*. 2009 Feb;87(2):81-97. doi: 10.1016/j.pneurobio.2008.09.018. Epub 2008 Oct 5. Review. PubMed PMID: 18952143; PubMed Central PMCID: PMC2650821.
4. **Olsen Y, Daumit GL, Ford DE**. Opioid prescriptions by U.S. primary care physicians from 1992 to 2001. *J Pain*. 2006 Apr;7(4):225-35. PubMed PMID:16618466.
5. **Ballantyne JC, Mao J**. Opioid therapy for chronic pain. *N Engl J Med*. 2003 Nov 13;349(20):1943-53. Review. PubMed PMID: 14614170.
6. **Kalso E, Edwards JE, Moore RA, McQuay HJ**. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004 Dec;112(3):372-80. Review. PubMed PMID: 15561393.
7. **Martin S, Ulrich C, Munsell M, Taylor S, Lange G, Bleyer A**. Delays in cancer diagnosis in underinsured young adults and older adolescents. *Oncologist*. 2007 Jul;12(7):816-24. PubMed PMID: 17673613.
8. United States Census Bureau 2012 report. 2013 Sept 17.

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