LETTER

Small Intestine Bacterial Overgrowth: An Underdiagnosed Cause of Diarrhea in Patients with Pancreatic Cancer

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Dear Sir:

Pancreatic cancer is currently the fourth leading cause of cancer related death in the United States, with an overall survival rate at five years of diagnosis of less than 5%. It affects more men than women, with slight preponderance for African Americans and 77% of patients are diagnosed after the age of 60 years [1]. The majority of patients with advanced pancreatic cancer report a poor quality of life, with special compromise in the areas of emotional and social functioning, presumably due to anxiety and depression [2]. Among the physical symptoms reported to affect quality of life, fatigue and pain were ranked the highest. However, we are yet to understand how other less commonly recognized symptoms such as diarrhea and weight loss affect the functioning and comfort level of these patients. Small intestine bacterial overgrowth is a frequent, yet unrecognized, cause of diarrhea in patients with advanced pancreatic cancer.

We present a successful management of diarrhea associated with small intestine bacterial overgrowth in a patient with advanced pancreatic cancer in an effort to bring awareness among physicians taking care of this population of patients.

Case

In September 2008, a 62-year-old Caucasian male with a history of advanced pancreatic cancer arrived at the Yale Cancer Center with progression of disease on gemcitabine and erlotinib, seeking a second opinion. He was originally diagnosed in May of 2008, after three months of abdominal pain and vomiting. At presentation to our clinic, he reported a weight loss of

45 kg over a 9-month period. He also referred 4-6 loose watery stools daily that had been an ongoing problem for approximately 6 months. Diarrhea had been non-responsive to diphenoxylate/atropine and loperamide. These episodes typically occurred shortly after eating. At his initial visit, patient was given a prescription for pancreatic enzymes, along with instructions for use. Patient was seen again for treatment in October 2008. He reported continued episodes of diarrhea 4-6 times per day. Enzyme dose and frequency were reviewed and patient verified appropriate use and compliance. Oral intake was inquired and there were no identifiable contributors to the diarrhea. He again complained of gassiness, bloating and diarrhea after eating. Because of his poor baseline performance status (ECOG PS 2) no invasive diagnostic procedure was done and the patient refused to take a breath test. Instead, he was given norfloxacin 400 mg every 12 hours for 5 days and reported resolution of diarrhea at the 4th day, with one formed bowel movement daily. In addition, he had improvement in abdominal pain, gassiness and bloating. His weight also continued to improve. Due to his improved functional and gastrointestinal symptoms, the patient was treated with 5-fluorouracil and leucovorin successfully with subsequent decrease in CA 19-9 and stable disease on CT scan staging. No diarrhea more than grade 2 was seen during this chemotherapy regime.

Discussion

Diarrhea is a common problem experienced by patients with advanced pancreatic cancer. The etiology for this symptom is multifactorial including pancreatic insufficiency (most frequent), chemotherapy, cancer or its related surgical treatment and general medications such as stool softeners, opioids (leakage around an impaction) antibiotics, and Mg/K supplementation among others. If diarrhea continues despite having ruled out these entities, small intestine bacterial overgrowth should be considered as a cause, especially in those who have had a Whipple procedure or a bowel obstruction, although it can occur without structural abnormalities. In one series of 100 adult patients the

most frequent small intestine bacterial overgrowth related symptoms were diarrhea, weight loss, bloating, and excess flatulence [3, 4]. Malabsorption of fat, carbohydrate, protein, and micronutrients are usually present. The incidence of small intestine bacterial overgrowth specifically in patients with advanced pancreatic cancer is still unknown. Nonetheless in patients with cirrhosis the prevalence can be as high as 61% and in a small population of patients with chronic lymphocytic leukemia it was 50% of all cases [5, 6].

The "gold standard" for diagnosis is bacterial culture from small intestinal fluid although it is seldom performed due to difficulty to conduct it as an outpatient [7], patchy growth of bacteria, problems in culturing for anaerobes [8, 9], and contamination from oropharyngeal flora [10]. The ^{14}C-D-xylose, glucose H_2 and lactulose breath test can circumvent the invasiveness of cultures with sensitivities ranging from 60% to 68% and specificities from 44% to 85% [11, 12]. In patients with advanced pancreatic cancer however, even these simple tests can be misleading. Such patients usually have associated pancreatic insufficiency leading to carbohydrate malabsorption and hence a propensity towards a false positive result to the glucose based breath tests. The presence of a positive test, on the other hand, is no guarantee that the symptoms are entirely due to small intestine bacterial overgrowth given the multiple comorbidities, medications, and procedures these patients usually endure. For the most part, a single course of antibiotics as the initial approach seems reasonable and will serve in most cases to confirm the eradication of symptoms and therefore the presence of small intestine bacterial overgrowth as the major contributor to the diarrhea. In the presence of failure, further studies and therapeutic modalities could be applied until a diagnostic certainty is obtained.

The management of small intestine bacterial overgrowth can be divided into three major categories: maintaining an adequate nutrition and correct dietary deficiencies, controlling the intestinal flora to the point of no symptoms (antibiotics), and trying to reverse the underlying problem responsible for small intestine bacterial overgrowth. The antibiotic should be one directed at both aerobic and anaerobic flora ideally [13], but in most reports bacteria related to malabsorptive symptoms are usually restricted to the aerobic flora [14]. For patients with advanced pancreatic cancer we recommend a first line therapy consisting of a quinolone or rifaximin given their safety profile, efficacy and ease of administration [15, 16, 17]. In case of failure or intolerance multiple other choices have been well documented either alone or in combination [15, 16, 17, 18]. Nutritional status and correction of underlying cause should be conducted as in any other case of pancreatic cancer.

We report this case to remind specialists caring for advanced pancreatic cancer patients about the frequency and impact of small intestine bacterial overgrowth as a cause of one of the most troublesome

symptoms in this population of patients: diarrhea and weight loss. It is important to recognize that most treatment strategies in pancreatic cancer are aimed at improving quality of life, and certainly nutritional status is a key element not only as a marker of general health, but as a prognostic factor as well as an indicator of health reserve and ability of the patient to undergo more aggressive and potentially curative treatment.

Conflict of interest The authors have no potential conflicts of interest

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