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LETTERS TO THE EDITOR

Resectability of Pancreatic Cancer and Diabetes

TO THE EDITOR: With great interest, we read the article by Pelaez-Luna *et al.* (1) entitled "Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: A retrospective review of CT scans and fasting glucose values prior to diagnosis," which has been published in a recent issue of the *Journal*. The authors concluded that, "Pancreatic cancer is frequently undetectable or resectable on CT scans done ≥6 months prior to clinical diagnosis. At onset of diabetes, pancreatic cancers are generally resectable." This important study is the best piece of evidence that suggests that the development of a sensitive and specific serologic marker for pancreatic cancer-associated diabetes could lead to the diagnosis of resectable pancreatic cancer. However, several issues regarding such a statement need further clarification.

First, the authors failed to provide information about body mass index (BMI), the inclusion of which would have been a major progress in our understanding of the relationship among them. Contrary to the above-mentioned study, another recent study done by Souza *et al.* (2) showed that neither BMI on admission nor the presence of diabetes or diabetes duration influenced tumor staging or resection in pancreatic cancer patients. It is presumable that most of the diabetics in the authors' study have type 2 diabetes (non-insulin-dependent diabetes) because this disease constitutes 80–90% of cases, and is typically found in older individuals (3). Furthermore, there is a strong connection between obesity and diabetes. Eighty-eight to ninety-seven percent of type 2 diabetes diagnosed in overweight people is a direct result of obesity.

Second, the authors provided no information about insulin levels. Thus, the study did not address the question of which type of diabetes might be associated with pancreatic cancer: type 1 diabetes (insulin-dependent diabetes), type 2 diabetes, or both. Many studies have demonstrated that diabetes in pancreatic cancer patients is characterized by peripheral insulin resistance (4). In patients with type 2 diabetes, the pancreas is generally exposed to substantial hyperinsulinemia for years (5), suggesting that insulin may be involved in the association between long-duration diabetes and pancreatic cancer.

Third, Pelaez-Luna *et al.* found that pancreatic cancer rapidly became unresectable once it was visible on computerized tomography (CT); however, they did not compare diabetics with nondiabetics in detail to determine whether the timeline of progression of pancreatic cancer from resectable to unresectable disease is shorter in diabetics. This is important because a number of studies have demonstrated that, in addition to hyperinsulinemia, the increased blood glucose and free fatty acids in diabetes may also promote the growth of pancreatic cancer (4).

Last, but not least, before conclusions could be drawn, long-term prospective studies are needed in large cohorts including a sufficient number of patients with diabetes.

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Response to Yang *et al.*

TO THE EDITOR: We thank Dr. Yang *et al*. for their comments on our study, "Resectability of pre-symptomatic pancreatic cancer and its relationship to onset of diabetes: A retrospective review of CT scans and fasting glucose values" (1).

1. The purpose of the study was to assess resectability of pancreatic cancer at the onset of diabetes. The question of premorbid body mass index (BMI) and its association with diabetes mellitus (DM) and pancreatic cancer is being addressed in a larger study by our group. We believe that the small number of patients and lack of noncancer controls would make it difficult to understand the link among diabetes, obesity, and pancreatic cancer in the current study.
2. This was a retrospective study; hence, no insulin levels were available. In those cases with long-standing diabetes, long-standing insulin resistance and hyperinsulinemia may play a role in cancer pathogenesis. However,

the majority of diabetes in pancreatic cancer is of recent onset, and is likely cancer-induced and not primary type 2 diabetes. Diabetes associated with pancreatic cancer is likely due to a combination of marked decline in beta-cell function and increased insulin resistance, the mechanism of which is yet to be determined (2).

3. We did not find any significant difference in the median time to progression between pancreatic cancer patients with and without DM (median 5 months *vs* 6 months, respectively); however, the number of patients in each group is too small to render solid data and draw conclusions; thus, we decided not to report it. We agree that long-term and larger cohorts are needed.

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The Timing of Colonoscopy Preparation Makes All the Difference in the Final Outcome

TO THE EDITOR: The recent study by Johanson *et al*. in this *Journal* demonstrates a marked preparation superiority in patients receiving sodium phosphate compared with polyethylene glycol (PEG) solution prior to colonoscopy procedures (1). As my practice involves the care of a large elderly population, I believe two important issues in this paper relevant to its conclusion should be addressed.

1. The timing of the dulcolax and PEG lavage administration was substantially different than that of the sodium phosphate tablets, and may well account for the preparation quality variations. The bisacodyl tablets were administered at 12 noon on the day prior to the colonoscopy, with the PEG lavage given 6 h after the bisacodyl, irrespective of the time of the colonoscopy. Subsequently, greater than 12–18 h may have elapsed prior to the colonoscopy examination, thereby allowing for significant chyme contamination of the colon precolonoscopy. The sodium phosphate dosing, on the other hand, occurred in a more logical fashion, with the first dose of Fleets given the night before the procedure and the second dose 3–5 h before the colonoscopy. In our practice, we routinely administer 2 L of PEG 5 h prior to the colonoscopy with bisacodyl given 5 h before the PEG. We find poor right colonic preparations to be uncommon with this protocol, and I submit to you that timing of the colonoscopic preparations played a major role in the preparation differences in this study.
2. Although no patients with "comorbid and cardiovascular or renal insufficiency" were included in this study, elderly patients not uncommonly manifest with silent renal and cardiac dysfunction. The development of irreversible renal dysfunction with sodium phosphate remains a concern for physicians in private clinical practice, and has occurred in our community. A normal creatinine level in an elderly slender women may be associated with significant renal disease. Sodium phosphate preparations may not be the best option for these individuals, particularly in the era of screening examinations, self-referral patterns, and sometimes less than thorough preprocedure evaluations.

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Response to Dr. Kartsonis

TO THE EDITOR: Dr. Kartsonis' point regarding the timing of dosing in our study comparing the safety and efficacy of sodium phosphate (NaP) tablets and 2L polyethylene glycol (PEG) solution plus bisacodyl tablets accounting for preparation quality variations may be correct; however, this study was not designed to favor one product over another. The dosing used in our study was based on the dosing instructions approved by the Food and Drug Administration (FDA) for each product. When this study was conducted, the U.S. prescribing information for 2L PEG plus bisacodyl recommended taking four bisacodyl tablets at 12 noon followed by 2L PEG solution approximately 6 h later, all the day prior to colonoscopy. At the same time, the U.S. prescribing information for OsmoPrep tablets recommended taking 20 tablets the evening before the colonoscopy and 12 tablets in the morning of the colonoscopy.

Patients with comorbid conditions and cardiovascular or renal insufficiency were not included in our study, but elderly patients with a creatinine up to 2.0 mg/dL were included in this study and other studies with NaP tablets without incident (1, 2). NaP tablets have been shown to be safe and, when compared to bowel preparations containing PEG solution,

they are more efficacious and better tolerated in many patients (3); however, NaP tablets may not be an appropriate choice for every patient. It is important for clinicians to choose the safest, most efficacious, and well-tolerated bowel preparation available based on a patient's medical condition and history in order to avoid missing pathological lesions, canceling a procedure, or requiring a repeat examination.

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An Interleukin-6 (IL-6) Receptor Polymorphism Affecting Serum Levels of IL-6 Does Not Increase the Risk of Cholangiocarcinoma in Primary Sclerosing Cholangitis

TO THE EDITOR: We read with great interest the article by Cheon *et al*. (1) on the diagnostic utility of serum interleukin-6 (IL-6) levels in primary bile duct cancer. In patients with primary sclerosing cholangitis (PSC), cholangiocarcinoma (CCA) is a common and severe complication (2). Genetic polymorphisms may serve as markers of a greater CCA risk (3) and could, in the future, aid in the identification of patients in need of frequent surveillance for CCA development.

Recently, a nonsynonymous single nucleotide polymorphism (SNP) in the IL-6 receptor gene (rs8192284) was found to affect the circulating levels of IL-6 in large panels of healthy European Americans as well as African Americans, using so-called admixture mapping (4). In the context of the findings of Cheon *et al*. and the observation that IL-6 enhances the growth of malignant cholangiocytes in experimental models (5), we investigated the possibility that PSC patients with CCA may possess a genetic background associated with high IL-6 serum levels. The rs8192284 SNP was genotyped in 365 PSC patients, out of which 49 had developed CCA. Genotyping was performed with TaqMan Assay-on-Demand C__16170664_10 (Applied Biosystems, Foster City, CA) and the χ^2 test was used for association analyses.

No significant differences in genotype frequencies (AA: CCA 43.8% *vs* no-CCA 37.9%, AC: CCA 37.5% *vs* no-CCA 47.5%, and CC: CCA 18.8% *vs* no-CCA 14.6%), $P_{\text{genotype}} = 0.42$, or allele frequency (C-allele: CCA 37.5% *vs* no-CCA 38.4%), $P_{\text{allelic}} = 0.87$, were observed when comparing PSC patients with and without CCA.

These findings add to the observations of Cheon *et al*. in several aspects. First, although IL-6 most likely engages in the pathogenesis of CCA, genetic factors influencing IL-6 levels do not serve to exaggerate this process. Importantly, the study of Cheon *et al*. did not include PSC patients, and it cannot be ruled out that IL-6 is more important in CCA patients without PSC and that other mechanisms override the effect of rs8192284 in the setting of chronic inflammation. There is also the possibility that the IL-6 levels increase secondary to the development of clinically detectable CCA and that primary cancer-promoting effects of greater IL-6 levels conferred by rs8192284 on preclinical CCA are small or absent.

In sum, our findings suggest that variation in the rs8192284 SNP in the IL-6 receptor gene does not increase the risk of CCA in PSC. Further studies on both genetic polymorphisms and serum markers seem warranted to dissect the molecular pathogenesis of CCA.

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Response to Dr. Melum *et al*.

TO THE EDITOR: We thank Dr. Melum *et al*. for their interest in our study. IL-6 is produced during the inflammatory reaction and in immune-mediated processes. Bile duct

cancer (BDC) arises from bile duct inflammation. Therefore, it is very important to define the relationship between IL-6 levels and BDC, and the IL-6 levels should be assayed under conditions of minimal active inflammation.

In the study by Dr. Melum *et al*. (1), there were no significant differences in genotype or allele frequencies between primary sclerosing cholangitis (PSC) patients with and without BDC. However, PSC is a chronic cholestatic liver disease characterized by inflammation, sclerosis, and obliteration of the biliary tree. The effect of IL-6 may be masked in the chronic inflammatory setting of PSC, regardless of whether it is associated with BDC. Our study (2) examined BDC patients without PSC, and assayed the IL-6 level after the cholestatic condition had improved following biliary drainage and antibiotics. We tried to eliminate factors responsible for the increased level of IL-6 that are not related to BDC. The observed decrease in the IL-6 level associated with the decrease in tumor volume after photodynamic therapy also supports the autocrine effect of IL-6 in BDC (3, 4) indirectly. An additional study comparing BDC with and without PSC should be conducted to confirm the role of IL-6 in BDC.

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Abnormal Pap Smears in Women With Crohn's Disease: Is There a Role for Defensin Deficiency?

TO THE EDITOR: Current management guidelines for inflammatory bowel disease (IBD) patients do not recommend considering more frequent screening for cervical cancer with Pap smears. However, in a report from Kane *et al*., that is to be published soon in an upcoming issue of the *American Journal of Gastroenterology*, a strong argument for reconsidering this recommendation is given (1). In that study, women with IBD were reported to have both more frequent and more severe abnormal Pap smears when compared with healthy controls (1), data that confirmed the results from other groups (2). Moreover, the authors pointed out the role of immunosuppressant drug exposure as a worsening factor for these abnormalities (1). Although case-control studies have well-known weaknesses that are difficult to avoid, these observations are of major importance. The clinical impact of these findings is large, especially in the context of both the widespread diffusion and early use of immunosuppressants in IBD patients and the recent availability of the quadrivalent human papillomavirus (HPV) vaccine (3). Although prospective evaluations of this issue are needed, it nevertheless seems reasonable to closely screen women with IBD for cervical cancer, especially if they have received immunosuppressant drugs, similar to those women who are treated with immunosuppressive therapy for transplantation or autoimmune diseases, and to consider vaccination for young girls with IBD prior to the initiation of sexual activity.

With this very relevant clinical implication, the data presented by Kane *et al*. (1) also suggest a possible role for a direct susceptibility to sexually transmitted HPV in IBD patients, mainly Crohn's disease patients, because 32 of the 40 patients studied were Crohn's disease patients. In regard to this point, a recent discovery concerning the properties of alpha-defensin 1–3 and 5 against nonenveloped viruses, such as HPV, seems, in our view, to be of major interest (4). Evidence for considering human defensins (HD) as potent antagonists of infection by both the cutaneous and mucosal papillomavirus types is now available, and microscopic studies of papillomavirus inhibition by alpha-defensins revealed that they block virion escape from endocytic vesicles (4). Moreover, HD-5 has been reported to be present in the female genital tract at levels in the range of those that inhibit HPV *in vitro*, suggesting that they could present a natural barrier to the sexual transmission of HPV (4, 5).

Defensins are also a major component of the innate immunity of the gut, where they are produced by Paneth's cells. It has recently been demonstrated that the expression level of defensins is decreased in Crohn's disease patients independently of the local level of inflammation in the ileum (6). *In vitro*, this decreased expression of defensins was associated with a decrease in the antibacterial activity of the ileal biopsies, as compared with normal healthy subjects (6). Moreover, a mutation in nucleotide-binding oligomerization domain 2 (NOD2), the muramyl dipeptide recognition receptor, is found in some Crohn's disease patients that leads to an even more pronounced alpha-defensin decrease.

In our opinion, it seems worthwhile to consider these facts together, and to investigate the possibility of a common

decrease in both genital and intestinal defensins as part of the same disease, and not to consider the susceptibility of women with IBD to HPV infection as only a consequence of immunosuppressant drug exposure.

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In Response to Drs. Savoye and Lerebours

TO THE EDITOR: I appreciate the letter from Drs. Savoye and Lerebours and their insight as to an alternative explanation for our clinical findings. A primary or secondary deficiency in defensins is an attractive biologic mechanism for the increased incidence of abnormal cervical cytology. Further research into this hypothesis is warranted.

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Hyperinsulinemic Hypoglycemia After Bariatric Surgery

TO THE EDITOR: We read with interest the excellent review by Decker *et al*. (1) discussing associated gastrointestinal and nutritional complications of bariatric surgery recently published in the *Journal*. In the review, the authors performed thorough research, and considered all levels of evidence with more emphasis on larger randomized trials. They state that, "the risk of dumping syndrome by the procedure of laparoscopic adjustable gastric banding (LAGB) and Roux-en-Y gastric bypass (RYGB) is rare and occasional, respectively." in table 1 of the article. However, they left out the complication of hyperinsulinemic hypoglycemia, which may lead to a potentially life-threatening deficiency of glucose in the central nervous system (*i.e*., neuroglycopenia), and should not be mistaken for those of the so-called "dumping syndrome"—flushing, dizziness, palpitations, diaphoresis, hypotension, and weakness—that are commonly seen in gastric bypass patients. We would add hyperinsulinemic hypoglycemia to the list of complications presented in table 1 of the review. Symptomatic hyperinsulinemic hypoglycemia with nesidioblastosis has been described in a small series of patients with severe, medically complicated obesity after gastric bypass surgery (2–4). Although the causal links between gastric bypass surgery and pancreatic nesidioblastosis have not been established, the few reported cases indicate that nesidioblastosis is more frequent among patients who have had gastric bypass than in the general population. Possible explanations include the growth of beta cells and islets caused by glucagon-like peptide 1 (GLP-1) or another intestinal hormone, and reduction in insulin resistance produced by weight loss in the setting of beta-cell hypertrophy and hyperfunction commonly found in obesity. To ameliorate the problem of nesidioblastosis in the postgastric bypass patient, partial removal of the pancreas is warranted. However, the most appropriate surgical management is undefined. Recurrence of hyperinsulinism may occur in some patients, possibly because not enough of the pancreas was removed. Limited pancreatic resection guided by calcium angiography can provide long-term glucose control in most patients with adult nesidioblastosis. Nevertheless, subtotal or total pancreatectomy may be required for definitive management of refractory hyperinsulinism and symptomatic hypoglycemia.

Hyperinsulinemic hypoglycemia has also been reported after LAGB (5), the most common bariatric procedure performed in Europe. The mechanism of transient asymptomatic hyperinsulinemic hypoglycemia, which occurs in 3–4% of patients after LAGB, is uncertain. Therefore, further elucidation of the pathogenesis of transient hyperinsulinemic hypoglycemia after LAGB will require longitudinal studies of insulin function in patients undergoing LAGB.

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Response to Yang *et al.*

TO THE EDITOR: We thank Dr. Yang and colleagues for their interest in our article. We are aware of hyperinsulinemic hypoglycemia and nesidioblastosis after bariatric surgery. We agree that it should have been listed as a potential complication, and we thank them for pointing out this deficiency.

The mechanism proposed for this condition after Roux-en-Y gastric bypass is that nutrients are rapidly presented to the distal ileum, where glucagon-like peptide 1 (GLP-1) is secreted by stimulated L cells (1). The GLP-1 in turn stimulates the pancreatic islet cells, which can become hyperplastic, leading to hyperinsulinemic hypoglycemia. If a patient continues to develop hypoglycemic episodes in spite of dietary counseling, the diagnosis of nesidioblastosis should be considered. It is important that patients considered for partial pancreatectomy be evaluated thoroughly by an endocrinologist as there are other mechanisms that might explain the patient's hypoglycemia, such as reduced insulin resistance in the setting of rapid weight loss. Fasting insulin and C-peptide levels, computed tomography or magnetic resonance imaging, and a selective arterial calcium stimulation test are required before surgery is recommended (2).

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Cannabinoid Hyperemesis

A 46-yr-old man was admitted for epigastric pain, nausea, and vomiting for a 3-wk duration. The patient was seen in the emergency room several times prior to admission for IV hydration and antiemetics. He described a 20-lb weight loss associated with the symptoms, and he had been unable to work. The patient did not admit to exacerbating factors, but did note that taking prolonged (3–5 h) hot baths and showers prevented his nausea from progressing to emesis. The patient had previously been diagnosed with cyclic vomiting syndrome for recurrent symptoms of nausea and vomiting every few weeks to months. The pattern had persisted for 3 yr. He had a full workup that included: esophagogastroduodenoscopy, capsule endoscopy, and colonoscopy. During his workup, he was noted to have a transient computer tomography (CT) finding of intussusception that resulted in exploratory laparoscopy, jejunotomy, and exploratory enteroscopy that were unrevealing. In addition to antiemetics, he was treated with topiramate that had minimal effects on his symptoms. The patient admitted to chronic daily cannabis use since childhood, rare alcohol use, and no tobacco use. He described his use as "4 hits off a bong" daily, but noted that this did not relieve his nausea. We learned of a case series from Australia, which noted 19 patients with chronic daily cannabis use and similar symptoms of nausea, vomiting, and compulsive bathing in hot water (1). We asked the patient to refrain from further cannabis use. At outpatient follow-up at 6, 10, and 18 weeks after stopping cannabis use, the patient had complete resolution of symptoms. Urine drug screens at both visits were negative for tetrahydrocannabinol. Cannabinoid hyperemesis is characterized by a history of several years of cannabis abuse preceding the onset of clinical symptoms, cyclic vomiting every few weeks to months. Cessation of cannabis use abates symptoms and reinitiating use heralds a return of nausea and vomiting. The compulsion to bath for hours in hot water is also characteristic during the symptomatic cycles. Of particular interest is that many patients increase or continue the use of cannabis because of the known beneficial effects on nausea. An Australian study of 19 patients with chronic cannabis use and a cyclic vomiting syndrome showed that cessation of cannabis abuse led to cessation of symptoms. Three patients were rechallenged with cannabis and had recurrence of symptoms. Nine of the 10 patients showed the compulsive hot water bathing behavior during the active phase of their illness (1). A follow-up letter to the editor described a strikingly similar case of a 21-yr-old man in the United Kingdom (2). Other cases in The Netherlands and in Britain have been reported since the case series by Allen *et al.* was published (3, 4). To our knowledge, this is the first case of cannabinoid hyperemesis being described in the literature in the United States. With the prevalence of cannabis users in the United States estimated at 4% (5), we suggest considering this in the differentiation of patients with cyclic vomiting syndromes.

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Dosage and Drug Interactions of Domperidone

TO THE EDITOR: I would like to clarify recommendations about dosage and drug interactions of domperidone made by Reddymasu *et al*. in the review article "Domperidone: Review of Pharmacology and Clinical Applications in Gastroenterology" (1).

In accordance with the product labeling, the maximum approved oral daily dose of domperidone is 20 mg given four times per day. This may be given as a tablet or oral suspension. Suppository forms of domperidone are available, and the maximum approved dose is one 60-mg suppository two times per day. These doses have been shown to be effective and well tolerated for the labeled indications of dyspepsia, nausea, and vomiting.

Current drug labeling also informs the physician about interactions with other drugs. The main metabolic pathway of domperidone is through CYP3A4. *In vitro* and human data show that concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Examples of CYP3A4 inhibitors include: azole anifungals such as fluconazole, itraconazole, ketoconazole, and voriconazole; macrolide antibiotics, such as clarithromycin and erythromycin; HIV protease inhibitors, such as amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, and saquinavir; calcium antagonists, such as diltiazem and verapamil; amiodarone; aprepitant; nefazodone; and telithromycin.

Product labeling also states that "Electrophysiological *in vitro* and *in vivo* studies have shown that domperidone, at high concentrations, may prolong the QT interval." This effect on QT interval is summarized in the review article, but the importance of avoiding drug interactions and of adhering to recommended doses to avoid increasing domperidone plasma concentrations needs to be strongly emphasized.

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Diagnosis of Cystic Lymphangioma of the Pancreas with Endoscopic Ultrasound-Guided Fine Needle Aspiration

TO THE EDITOR: A 57-yr-old woman presented for consultation with a 3-month history of epigastric abdominal pain, nausea, and weight loss. A magnetic resonance imaging (MRI) of the abdomen was performed that revealed multiple small, retroperitoneal cystic areas just inferior to the uncinate process and proximal body of the pancreas. The conglomerate area measured approximately 2.5 × 5.5 cm in size. The pancreatic parenchyma appeared normal. The patient denied any personal or family history of pancreatitis or pancreatic disease. She did not endorse steatorrhea and was not diabetic. Rather than proceeding directly to surgical resection of this

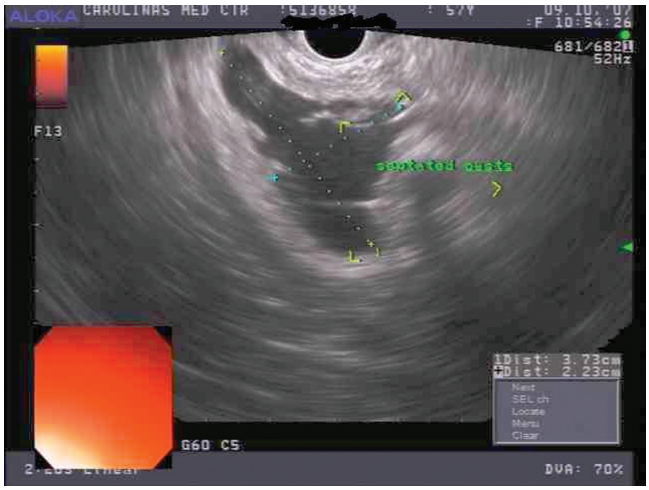

Figure 1. Linear echoendosonography image revealing a 3.7 × 2.2 cm thinly septated cystic lesion within the retroperitoneum adjacent to the uncinate process of the pancreas.

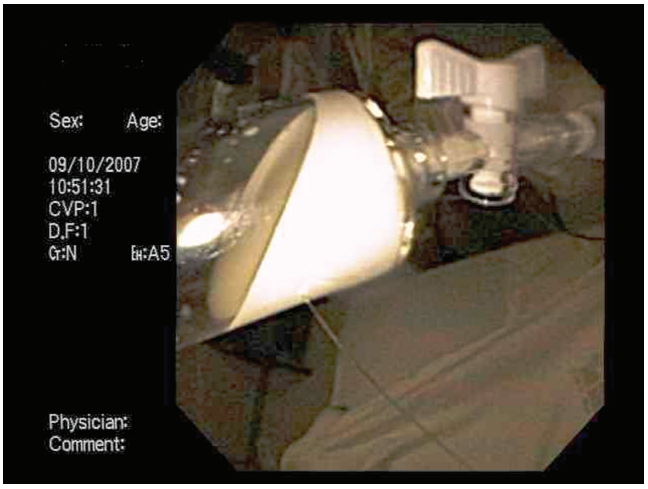

Figure 2. Fluid aspirated from the cyst; note the milky, opaque appearance consistent with chyle.

lesion, radial and linear endoscopic ultrasound (EUS) was performed that revealed a retroperitoneal cystic lesion adjacent to the uncinate process and third portion of the duodenum. It measured 3.7 × 2.2 cm in size and contained several thinly septated anechoic chambers without internal debris (Fig. 1). The remainder of the pancreas appeared endosonographically normal. Two passes were made with a 22-gauge ultrasound aspiration needle using a transduodenal approach. Eight milliliters of opaque, white, viscous fluid was aspirated that had a milky appearance (Fig. 2). Carcinoembryonic antigen (CEA) and amylase levels in the fluid were 0.3 ng/mL and 81 U/L, respectively. The triglyceride level was 6,069 mg/dL, and cytology revealed numerous lymphocytes and macrophages. The MRI and EUS findings, along with appearance and cytological/chemical analysis of aspirated fluid, were diagnostic for a cystic lymphangioma of the pancreas.

Lymphangiomas are benign endothelium-lined cystic tumors that are the result of blockage of the lymphatic system, leading to lymphangectasia. Most often a result of congenital abnormalities of the lymphatic drainage system, cystic lymphangiomas are usually rare, benign lesions in children (90% diagnosed by the age of 2), and most often occur in the neck or axillary region (1). Only 5% of lymphangiomas are present in the abdomen and of these, only 5% are present in the retroperitoneum or adjacent to the pancreas. There have been less than 20 cases reported in the literature (2). Traditionally, they have been diagnosed at surgery performed on a patient with a retroperitoneal cyst of unclear etiology (3). In a large review of pancreatic lesions, pancreatic cystic lymphangioma accounted for only 0.2% of all lesions encountered (3).

Conventional radiology (computerized tomography [CT] and MRI) has generally been inadequate for the evaluation of pancreatic cystic lesions of the pancreas. EUS with fine-needle aspiration (FNA) is a safe and accurate method for diagnosis, evaluation, and treatment of such lesions (4). The most frequently encountered lesions are pseudocysts (~90%) and cystic neoplasms (~10%).

This patient represents only the second case in the literature where a pancreatic cystic lymphangioma has been diagnosed by EUS with FNA (2). Given the likely benign nature of this lesion, she will be monitored with close follow-up and imaging studies.

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Spontaneous Regression of Hepatocellular Carcinoma

TO THE EDITOR: We report the case of spontaneous partial regression of a hepatocellular carcinoma, an extremely rare phenomenon for which we found only 62 other reported cases, and postulate the possible mechanism involved here.

A 76-yr-old man with a history of heavy alcohol intake presented with abnormal liver enzymes. Ultrasound scan of his liver revealed a mass in the right lobe. T1-weighted magnetic resonance imaging of liver, post-gadolinium contrast, showed a hyperenhancing lesion deforming the hepatic contour, consistent with a hepatocellular carcinoma, with two other lesions at the porta hepatis, in close association with the portal vein and the tip of the left lobe. Computer tomography (CT) scan showed a mass in segment 5, measuring 6 × 4.8 cm (Fig. 1). Biopsy confirmed a hepatocellular carcinoma in a cirrhotic liver. He stopped drinking alcohol, but was however lost to follow-up without any treatment. He re-presented

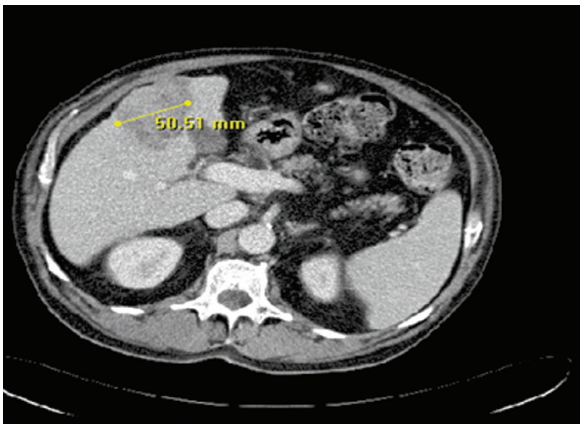

Figure 1. Axial scan in the portal venous phase demonstrating a large lesion in the right lobe, with a smaller lesion at the porta hepatis.

2 yr later with reduced mobility secondary to osteoarthritis, at which time his hepatocellular carcinoma was re-evaluated. CT scan (Fig. 2) revealed that the liver mass had decreased in size, with an interval change in maximum axial diameter from 6 cm to 3.3 cm in the 2-yr period, and that the two other lesions had disappeared. Development of splenomegaly and marked enlargement of the left lobe of the liver (*arrow*) was noted. The serum alpha-fetoprotein level also fell from 1,259 μg/L at original presentation to 10 μg/L.

Spontaneous regression of hepatocellular carcinoma is a very rare phenomenon, and suggested explanations include: hormonal influences, ischemia from rapid tumor growth, and immunological activation (1). Withdrawal of alcohol, as in our patient, has also been implicated (2). It is likely that in this case "autoembolization" occurred from a right portal vein tumor thrombus that was involving the porta hepatis, causing both initial atrophy of the right lobe and its hepatoma, with resulting compensatory left lobe hypertrophy and splenomegaly.

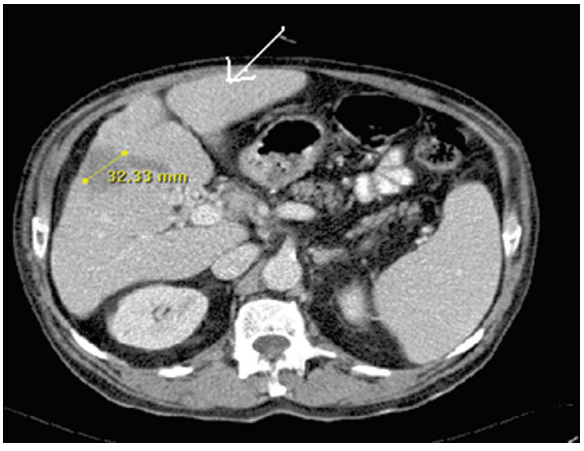

Figure 2. Axial scan at the same level, with a reduction in size of the single remaining tumor, hypertrophy of the left liver lobe (arrow), and splenomegaly.

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Ascaris lumbricoides and Iron Deficiency Anemia

TO THE EDITOR: We report herein a case of iron (Fe) deficiency anemia caused by *Ascaris lumbricoides* (*A. lumbricoides*) infestation diagnosed by means of double-balloon enteroscopy.

A 41-yr-old man was evaluated for a 6-month history of anemia (hemoglobin 10.2 g/dL [normal 13.5–16.0 g/dL], Fe profile compatible with Fe deficiency). Fecal occult blood test was positive. Stool specimen for parasites was negative, upper gastrointestinal endoscopy and colonoscopy with ileoscopy of the last 10 cm of the ileum were negative for bleeding, and the rest of the etiologies of Fe deficiency anemia were investigated and discarded. Double-balloon enteroscopy was performed, and we observed one large and mobile round worm in the proximal jejunum (Fig. 1). It was trapped with forceps and removed perorally. The round worm measured 17 cm in length (Fig. 2), and was determined to be *A. lumbricoides* by pathology.

Among the soil-transmitted helminth infections, *A. lumbricoides* has a particular worldwide importance. The estimated population infected by this pathogen is of 807–1,221 million people (1). Ingestion of fully developed eggs of *A. lumbricoides* is needed to become infected. *Ascaris* larvae penetrate the intestinal mucosa, enter the liver and the lungs, pass through the epiglottis, and re-enter the gastrointestinal tract to develop into egg-laying adult worms about 9–11 wk after egg ingestion. Important determinant factors for transmission and infestation are: climate (adequate moisture and warm temperature), poverty, and inadequate water supplies and sanitation.

The immune responses to soil-transmitted helminths include: production of cytokines, parasite-specific

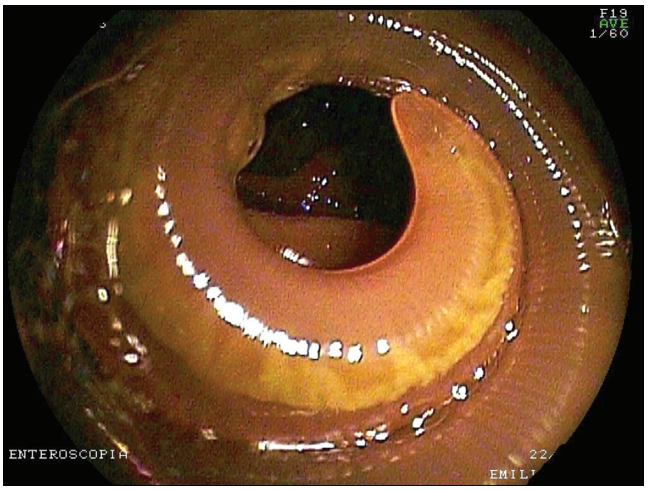

Figure 1. Double-balloon enteroscopic view of a large and mobile round worm in the proximal jejunum that was eventually trapped with forceps and removed perorally.

immunoglobulin and nonspecific immunoglobulin E, and expansion and mobilization of mast cells, eosinophils, and basophils. This response is known as the T-helper-2 (Th2) immune response (2). The clinical features during early larval migration include: wheezing, dyspnea, a non-productive cough, fever, and blood-tinged sputum produced by heavy infections, resulting in verminous pneumonia. The gastrointestinal parasitism can cause abdominal distention and pain, lactose intolerance, and malabsorption of vitamin A, which may result in growth failure in children (1). Adult worms can aggregate and cause partial obstruction, intussusception, volvulus, and complete obstruction, with consequent bowel infarction and intestinal perforation. Sometimes, a mass can be felt on the left lower quadrant. Worms can enter into the lumen of the appendix, leading to appendicitis. When the worm enters the duodenum and blocks the ampullary orifice of the common bile duct, it results in hepatobiliary and pancreatic ascariasis (3). Diagnosis is made by specific signs and symptoms and fecal examination for eggs. Ultrasonography and endoscopy are useful for diagnosis of ascariasis complications. The most common antihelmintic drugs are mebendazol and albendazol that bind to nematode β-tubulin and inhibit parasite microtubule polymerization, causing death of the adult worm.

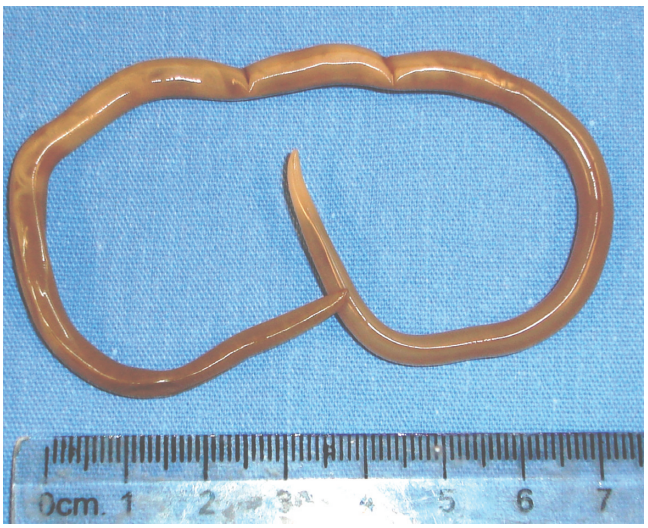

Figure 2. View of the round worm that measured 17 cm in length. It was determined to be *Ascaris lumbricoides* by pathology examination.

Fe deficiency anemia is more commonly caused by hookworm infection (*Ascaris duodenale* and *Necator americanus*) (4). In the case of our patient, a double-balloon enteroscopy was performed to evaluate a possible source of bleeding, not found by endoscopy and colonoscopy, on finding a round worm in the small intestine. After removal of the helminth, the patient was treated with albendazole for 1 day and this eventually resulted in resolution of anemia.

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Pancreatic Cancer Manifesting as Liver Metastases and Eosinophillic Leukemoid Reaction: A Case Report and Review of Literature

TO THE EDITOR: Pancreatic carcinoma is less commonly associated with paraneoplastic syndromes like Cushing's syndrome, dermatomyositis, panniculitis, arthritis, eosinophilia, and recurrent Trousseau's syndrome. Eosinophilic leukemoid reaction is rarely described with metastatic pancreatic cancer (1). We describe the second case in the English literature and overall in the published medical literature.

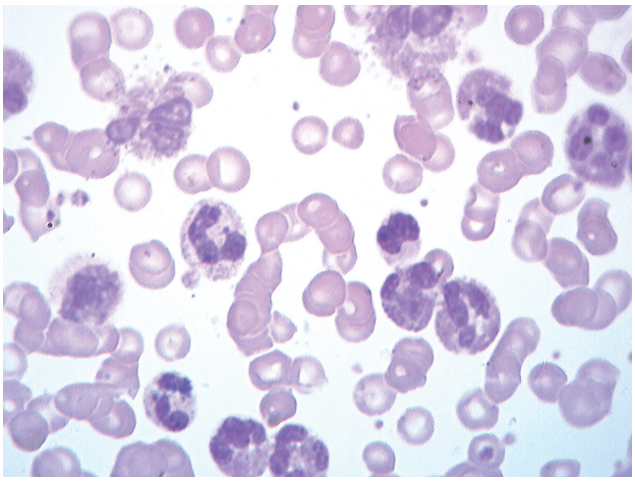

Figure 1. Peripheral blood film shows eosinophilia and some degranulation.

A 70-yr-old woman presented with complaints of pain in the right upper quadrant of the abdomen, anorexia for 1 month, weight loss of 10 kg, and breathlessness for 7 days. On examination, she had anemia, pedal edema, tachypnea, hemodynamic stability, and liver palpable 1 cm below the costal margin. Her laboratory investigations revealed a hemoglobin level of 10.2 g/dL, total leukocyte count of 99.01 thousand cells/mm^3, with a differential count of neutrophils 38%, eosinophils 56%, lymphocytes 2%, and monocytes 4%, without any band forms (Fig. 1), and an erythrocyte sedimentation rate (ESR) of 55 mm/first hour. Blood sugar, urea, creatinine, electrolytes, liver function tests, and amylase and lipase were within normal limits. Her serum total protein level was 6.4 g/dL with an albumin level of 3.0 g/dL. Her leukocyte alkaline phosphatase (LAP) score was elevated, ruling

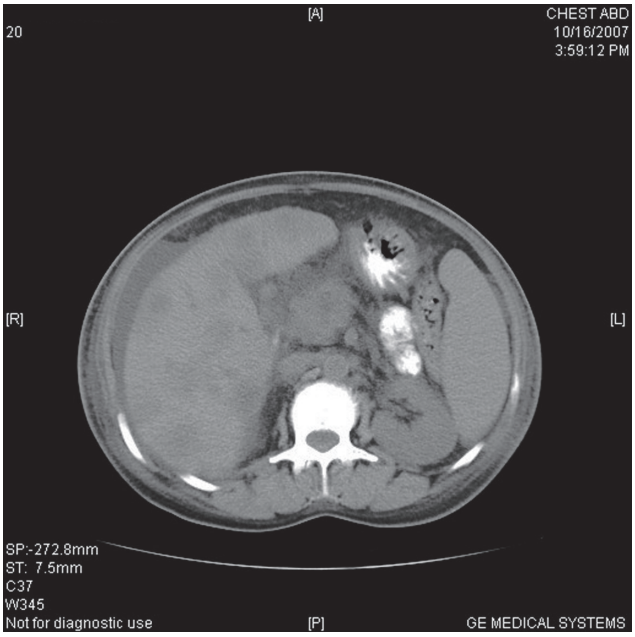

Figure 2. Contrast-enhanced computed tomography of abdomen shows hypodense lesion in liver, pancreatic mass, and ascites.

out chronic myeloid leukemia. Ultrasound of the abdomen showed hepatosplenomegaly with multiple hypoechoeic lesions in the liver and free fluid in the abdomen. Contrast-enhanced computed tomography of the chest and abdomen showed bilateral moderate pleural effusion, a mass in the head of the pancreas with a hypodense lesion in the liver and ascites (Fig. 2). An ultrasound-guided fine-needle aspiration from liver lesions was performed and that confirmed a metastatic adenocarcinoma of pancreatic origin.

Her blood cultures, urine cultures, and other workup of infective etiology were negative. Ascitic fluid and pleural fluid cytology were negative for malignant cells and eosinophils. Her interleukin-6 (IL-6) level was elevated at 30 pg/mL (normal 0–12 pg/mL) and carbohydrate antigen 19-9 level was elevated at $>$100 U/mL (normal 0–37 U/mL). She was managed with diuretics, a high-protein diet, pleural and ascitic fluid therapeutic paracentesis, oral levofloxacin, IV hydrocortisone, and nebulization. Her breathlessness improved over 7 days and she was discharged on oral steroids. She is planned for palliative chemotherapy with docetaxel and gemcitabine once her performance status improves.

Leukemoid reaction refers to a reactive leukocytosis with cell counts of $\geq$30,000–50,000/mm^3. The circulating neutrophils are usually mature and are not clonally derived, and the reaction is mainly described in association with lung, gastrointestinal, genitourinary, ovarian, and head and neck cancers (2). Leukemoid reactions in advanced malignancy are usually myelocytic, although eosinophilia may be seen (1). In this particular case, leukocytosis represented a true leukemoid reaction, as suggested by the elevated LAP score and no blast cells.

In about 50% of patients, the granulocytosis has an identifiable nonparaneoplastic etiology like infection, tumor necrosis, or glucocorticoid administration; none of these causes were identified in our patient.

The other mechanisms causing cancer-associated leukemoid reactions are due to proteins in urine and serum that stimulate the proliferation of bone marrow cells. There are various reports in literature of elevations in granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), or IL-6 in tumors of the nasopharynx, kidneys, and pancreas (3, 4). In this case, the IL-6 elevation may have had a significant role in inducing the leukemoid reaction (5). The tumor progression associated with an increase in inflammatory cytokines may have resulted in leukocytosis. Paraneoplastic granulocytosis resolves with treatment of the underlying cancer.

Eosinophilia is seen in patients with lymphoma, lung cancer, and cervical, gastrointestinal, renal, and breast cancer (2). Patients with markedly elevated eosinophil counts ($>$5,000/μL) can develop breathlessness and wheezing. All these finding were present in our case. Oral or inhaled steroids lead to symptomatic improvement.

In conclusion, our case is the second case of metastatic pancreatic cancer with eosinophilic leukemoid reaction with breathlessness responding to steroids.

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