A Gentleman with an Unusual Cause of Hypoalbuminemia

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Abstract: Protein-losing enteropathy (PLE) is a rare syndrome of gastrointestinal protein loss that may complicate a variety of diseases. The primary causes can be divided into erosive gastrointestinal disorders, nonerosive gastrointestinal disorders, and disorders involving increased central venous pressure or mesenteric lymphatic obstruction. Herein, we report on a 65-year-old man with PLE caused by invasive gastrointestinal stromal tumor (GIST). To our best knowledge, this is the first reported association between GIST and PLE. A brief review of the literature on the incidence, pathogenesis and management of GIST is also presented.

Keywords: Gastrointestinal stromal tumor, GIST, protein losing enteropathy, hypoalbuminemia, Tc-99m labeled human serum albumin scintigraphy

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Case Report

A 65-year-old man presented with three-month history of abdominal distension with associated bilateral ankle edema. The patient had past medical history of hypertension and benign prostatic hypertrophy well-controlled by medication. On physical examination, temperature was 37.1°C, blood pressure was 125/69 mmHg, the pulse 85 beats per minute, and oxygen saturation was 100% while he was breathing ambient air. Ascites was present in abdominal examination while the other parts of the body were unremarkable.

Laboratory data were: hemoglobin, 9.6 g/dL (normal 13.4–17.2); mean cell volume, 93.3 fl (normal, 83–98); white blood cell count, 13.4/mm³ (normal, 3.9–10.7); platelet count, 183/mm³ (normal, 152–358); sodium, 137 mmol/L (normal, 136–145), potassium, 3.8 mmol/L (normal, 3.5–5.1), urea, 3.6 mmol/L (normal, 3.5–8.1), creatinine, 63 umol/L (normal, 62–106), total bilirubin, 16 umol/L (normal, 5–20); alkaline phosphatase, 157 IU/L (normal, 46–127); alanine aminotransferase, 15 IU/L (normal, 10–57); albumin, 21 g/L (normal, 35–50); globulin, 24 g/L (no reference); Lactate dehydrogenase, 223 U/L (normal 213–395); spot urine total protein/creatinine ratio, 9 (normal, <23 mg/mmol Cr). Three serial fecal occult blood examinations were negative. The striking abnormality in the above preliminary laboratory data was severe hypoalbuminemia and the patient was suspected to have protein-losing enteropathy. The abdominal ultrasound revealed no obvious abnormality aside from ascites. The diagnostic paracentesis was performed; and the biochemical, cell count and microbiological result of the ascetic fluid were as follows: protein, 28 g/L; albumin 14 g/L; lactate dehydrogenase, 107 U/L; white blood cell 683/mm³; polymorphs, 615/mm³; lymphocytes, 68/mm³; Gram stain, negative and no bacterial growth; acid fast bacilli smear and culture were negative. Tc-99m labeled human serum albumin scintigraphy showed faint bowel radioactivity that was first noticeable in the right side of abdomen at five hours became highly intense in the ascending colon after 24 hours (Fig. 1). This was compatible with protein losing into ascending colon. Upper GI examination showed no abnormality down to second part of duodenum.

The patient experienced increasing abdominal pain; and the urgent contrast computed tomography (CT) of the abdomen was performed and revealed a large (11.4 × 7.2 × 8.1 cm) lobulated thick walled lesion filled with fluid and small amount of gas closely related to proximal jejunum and mesentery (Fig. 2). The provisional diagnosis was small bowel perforation due to tumor invasion with or without secondary bacterial peritonitis. The emergent exploratory laparotomy revealed that there was advanced retroperitoneal tumor of more than 10 cm in size just lateral to duodenojejunal junction invading the proximal jejunum, adjacent mesentery, and distal transverse colon superiorly and the pancreatic tail inferiorly. The tumor was resected en-bloc with the adjacent jejunum and a gastro-jejunostomy bypass was performed. The histology revealed the tumor consisted of packets of spindle cells invading the intestinal mucosa and the tumor cells had ovoid nuclei, prominent nucleoli and pink cytoplasm (Fig. 3A). The mitotic figures were up to 5 per 50 high power field (Fig. 3B). Tumor necrosis and hemorrhage were focally seen. Immunostain for c-kit was strongly positive (Fig. 3C). Thus the patient was diagnosed with gastrointestinal stromal tumor (GIST) with high risk of aggressive behavior at the proximal jejunum presented with protein-losing enteropathy.
enteropathy and complicated with bowel perforation and led to peritonitis.

**Discussion**

Protein-losing enteropathy (PLE) is characterized by a loss of serum protein into the gastrointestinal tract resulting in hypoproteinemia, which can be complicated by ankle edema, ascites, pleural and pericardial effusions, and malnutrition. The etiology can be divided into erosive gastrointestinal (GI) disorders, nonerosive GI disorders and disorders involving increased central venous pressure or mesenteric lymphatic obstruction. To our knowledge, it is the first reported association between PLE and GIST. The pathogenesis in this case might be due to the concurrent mucosal injury and lymphatic obstruction caused by the tumor invasion, resulting in increased mucosal permeability and direct leakage of protein-rich lymph respectively. Thus, it implies that PLE might be an indicator to predict the aggressive behavior of the tumor. The most commonly used and reliable method to determine enteric protein loss is to determine the clearance of α-1 antitrypsin (A1AT) clearance which requires both a blood sample and a 24-hr stool collection to determine plasma and stool A1AT level respectively. Recently, technetium-99m (99m Tc) labeled human albumin scintigraphy (HSA) has been shown
as a useful alternative means for diagnosis as well as in monitoring response to treatment. Although 99m Tc HSA has a high sensitivity in detecting the protein leak, it has two major pitfalls in that any gastrointestinal bleeding and in vivo breakdown of 99m Tc HSA yielding free pertechnetate may result in a false-positive accumulation of enteric 99m Tc HSA activity. In our case, the former was excluded by three serial negative fecal occult blood examinations and the latter by the absence of stomach or thyroid visualization.

GISTs are the most common mesenchymal tumors of the GI tract. They are believed to originate from the neoplastic transformation of the interstitial cells of Cajal, the interstitial pacemaker cells. They commonly have germline mutations in the kit or platelet-derived growth factor related alpha gene, resulting in a gain-of-function mutation and ligand-independent constitutive activation of the KIT receptor tyrosine kinase. Most affected have age of older than 50 years with no sex predilection. The most common sites involved are stomach (60%), jejunum and ileum (30%), duodenum (5%) and colorectum (<5%). The common presentations of GIST are GI bleeding, intestinal obstruction caused by the mass effect, and acute abdomen caused by tumor rupture. Like our patient, small intestinal GISTs have higher incidence of malignant potential as compared with gastric origin (40% vs. 20%). Metastases commonly develop in the abdominal cavity and liver; and can happen ten years after primary surgery necessitating long term clinical follow-up. Histologically, GIST appears as a friable, unencapsulated mass that arise in the muscularis propria of the GI tract and a spindle cell tumor with a fascicular pattern in hematoxylin and eosin stain. The most consistent histopathologic features used to predict aggressiveness are tumor size and mitotic index. High-risk tumors are defined as tumors greater than 5 cm with greater than 5 mitoses per 50HPF, like our patient. In general, complete excision is the main treatment. Patients whose tumors are unresectable or widely metastasized are treated with kit/PDGFR receptor inhibitors or downstream targets, such as protein kinase theta, may be warranted. Our patient was commenced with imatinib after the surgical resection of the tumor; and after two months of medication, the serum albumin level returned to level of 36 g/L. Clinically, the ankle edema and ascites were much improved.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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