

Paraneoplastic Auto-immune Hemolytic Anemia: An Unusual Sequela of Enteric Duplication Cyst

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Abstract. Enteric duplication (ED) cysts are rare congenital anomalies of the alimentary canal that present in childhood. Although benign in most case, ED cysts have the potential to cause complications including a rare association with secondary carcinomas. Autoimmune hemolytic anemia presenting as a paraneoplastic syndrome secondary to solid tumors is an unusual phenomenon. Here we report a patient case with ED cyst described in association with intestinal adenocarcinoma and warm-auto immune hemolytic anemia, with resolution of the hemolysis upon its surgical resection.

Gastrointestinal duplication cysts are rare congenital anomalies of the alimentary canal that present in childhood with an incidence of 2-3 cases per year. On rare occasions, duplication cyst can develop secondary carcinomas. Autoimmune hemolytic anemia (AIHA) presenting as a paraneoplastic phenomenon is an unusual consequence of a congenital cyst. Here we report a patient case with enteric duplication (ED) cyst described in association with secondary adenocarcinoma and warm-AIHA, with resolution of the hemolysis upon its surgical resection; an association to our knowledge never reported in literature with duplication cysts.

Case Report

A 59-year-old African-American male presented with abdominal pain, shortness of breath, dark urine, and fatigue of 1-month duration. He denied fever, chills, night sweats or weight loss. His medical history was significant for untreated

hepatitis C. Family history was notable for lung cancer in his father, but no history of autoimmune diseases. He was a lifelong tobacco smoker with no drug or alcohol abuse.

Physical examination revealed scleral icterus and a palpable spleen. Initial routine blood work showed profound anemia with a hemoglobin level of 6.8 g/dl (reference normal: 11.5-14.5 g/dl) with baseline being 13.5 g/dl about 5 months earlier. His white blood cell and platelet counts were normal. Further testing revealed, MCV of 112 fl (reference normal: 80-96 fl), reticulocyte count of 20.6% (reference normal: 0.8-2.5%), lactate dehydrogenase of 1423 IU/l (reference normal: 100-250 IU/l), indirect bilirubin of 10.1 mg/dl (reference normal: 0.2-0.7 mg/dl) and undetectable haptoglobin level. Direct Antiglobulin Test (DAT) was positive for immunoglobulin G and complement C3d, consistent with warm-AIHA. HIV and autoimmune panel tested negatively. A computed tomographic (CT) scan of the abdomen showed a spherical mass in the right abdomen measuring 6.6×6.6×8.3 cm abutting the inferior aspect of the duodenum (Figure 1). An endoscopic ultrasound revealing a well-circumscribed complex necrotic-appearing cyst 7×6 cm arising from the outer duodenal wall. The cytology with biopsy ruled out malignancy. The patient was started on prednisone for warm-AIHA. His hemoglobin improved with steroids, however, hemolysis flared on steroid weaning. The patient's active untreated hepatitis C with heavy viral load and chronic liver disease precluded treatment with rituximab or immuno-suppressants and splenectomy, respectively. In the interim, he was treated for hepatitis C with significant improvement of his viral load. He was followed-up for the duplication cyst with another CT scan, which showed stability of the lesion. The patient experienced flare up of episodes of anemia each time steroid was weaned. He was continued on low dose steroids for 18 months with a stable hemoglobin level. In the interim, the patient had worsening osteoporosis secondary to long-term steroid use.

At 2 years, he presented with complaints of recurrent abdominal pain and 15-pound (7 kg) weight loss. CT of the

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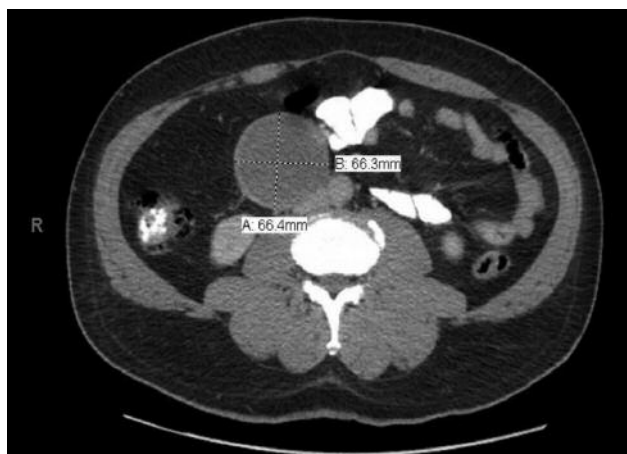


Figure 1. Cystic mass in the right abdomen measuring 6.6×6.6×8.3 cm abutting the inferior aspect of the duodenum.

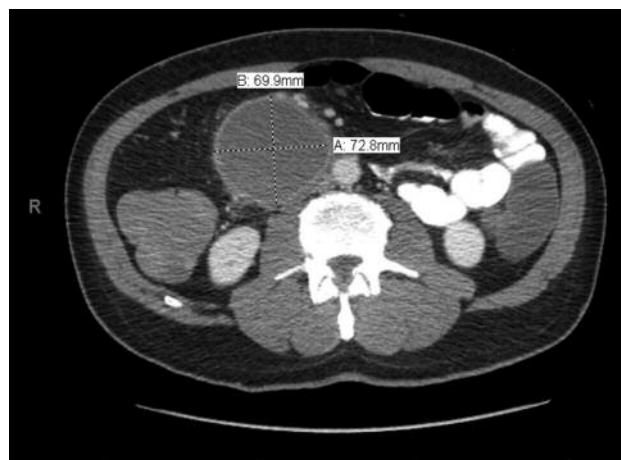


Figure 2. Complex right retroperitoneal mass measuring 7.2×6.9×8.4 cm, slightly increased in size from 6.6×6.6×8.3 cm 2 years earlier. New wall thickening with mild soft-tissue stranding in the adjacent fat was also apparent.

abdomen (Figure 2) showed an increase in size of the complex retroperitoneal mass, with wall thickening and soft-tissue stranding. The patient underwent upper endoscopy and biopsy, revealing intra-mucosal adenocarcinoma of the duodenum. He further underwent Whipple resection with final pathology showing stage IIA (pT3 N0 M0) duodenal adenocarcinoma with negative margins. The tumor involving the duodenum showed continuity with the underlying cyst (Figure 3). The cyst was predominantly necrotic, however, there was intact small bowel mucosal lining with smooth muscular layer consistent with ED cyst. The patient had a very complicated postoperative period resulting from intra-abdominal abscess requiring percutaneous drainage, steroid weaning and long-term antibiotics. At 2-month post-surgery, he had complete resolution of hemolytic anemia with negative DAT. Hemolytic anemia continues to be in remission at 1-year post surgery.

Discussion

ED cysts are rare congenital anomalies of the alimentary canal that usually present in childhood with an incidence of 2-3 cases per year. They occur on the mesenteric side of the associated alimentary canal with a common blood supply (1). Although they can occur anywhere along the digestive tract, the ileocecal region is the most commonly affected (2).

The location of ED cysts varies (ileum 30%, ileocecal valve 30%, duodenum 2-12%, jejunum 8%, colon 6-7% and rectum 5%) and the majority of cases become symptomatic during infancy (2, 3). Vomiting and distention are the most common presentation in infants, at times leading to complications such as volvulus and intussusception (3).

However in adults, symptoms associated with ED cysts are extremely variable and only a few cases have been reported in literature (4-6). The cysts are usually filled with clear fluid, but may also contain bile, pancreatic fluid and gall stones (6). The precise etiology of ED cysts remains elusive, with many proposed theories but none considered conclusive (7, 8).

ED cyst is defined by the three Rowling criteria: (i) the wall of the duplication is in continuity with one of the duplicated organ; (ii) the cyst is surrounded by a smooth muscular layer; and (iii) a layer of digestive mucosa is present, more often typical or heterotopic as gastric mucosa, colonic mucosa, bronchial or pancreatic structure (9). Duodenal duplication cyst consists of submucosa, *muscularis propria*, and a duodenal epithelial lining, with close attachment to the alimentary tract.

Our case presents two very rare associations of ED cysts: secondary malignancy and warm-AIHA. Carcinomas arising in duplication cysts are extremely rare complications and only few cases (<30 cases) have been reported in literature, including carcinoid tumors, squamous cell carcinomas and common adenocarcinomas (2, 10-37). Malignant transformation is more commonly reported in colonic and rectal duplication cyst. Only two cases other than ours were reported to originate from duodenal duplication cyst (31, 32). Due to early lymphatic spread with less chance of curative *en-bloc* resection, patients with these tumors are considered to have poor prognosis once malignant transformation occurs (2). Fortunately, our patient had no lymph node metastasis and has been doing well without adjuvant therapy for more than a year now.

Hemolytic anemia is commonly associated with lymphoma and other lymphoproliferative neoplasms, drug use, connective tissue diseases, and infections but less commonly

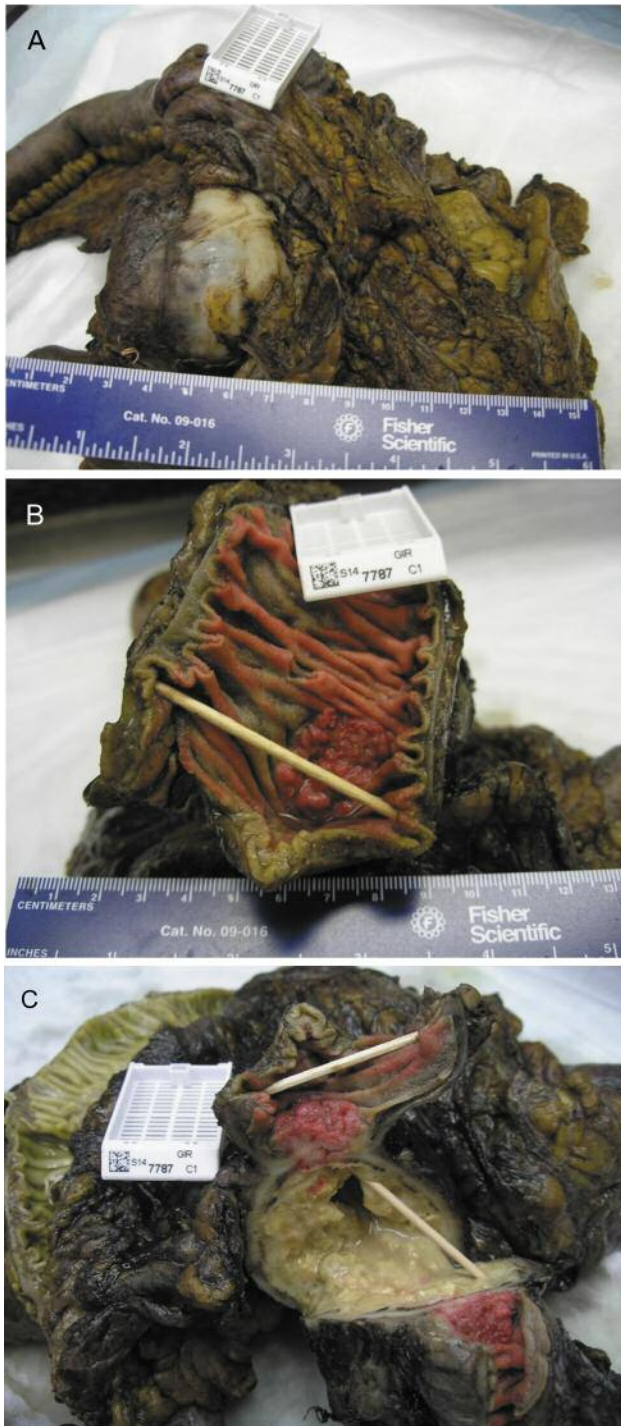


Figure 3. Gross views of the resected specimen showing the outer wall of the cyst (A), the tumor (B) and the duodenal carcinoma (C), which showed continuity with the underlying cyst.

associated with carcinoma (35). There are reports of the association of AIHA with renal cell carcinoma, ovarian carcinoma and hypernephroma, and very rare association with

ovarian dermoid cyst and mesenteric dermoid cysts (36-39). AIHA secondary to non-hematological malignancies has poor response to steroids with remission after removal of the tumor (39). In our patient, warm-AIHA was initially presumed to be hepatitis C-induced, however, the hemolysis failed to improve despite adequate control of the viral load. The temporal association of the resolution of hemolytic anemia with surgery favored a strong possibility of its association with malignancy. Although carcinomas are a known cause of secondary autoimmune hemolytic anemia, our patient presented with carcinoma-related symptoms only 2 years later. We hypothesize that the AIHA was a paraneoplastic phenomenon from an occult malignancy at the time of his initial presentation. Due to the rarity of ED cysts and non-specific presentation, early identification of malignant transformation might most often be missed and is often diagnosed at advanced tumor stages with nodal involvement of metastatic spread.

We present this report here as the case presented a diagnostic conundrum and treatment dilemma. The recognition of these associations can be invaluable for two main reasons. It presents an opportunity for definitive management of hemolytic anemia and spares the patient from unnecessary treatment. It would also offer a chance to potentially intervene, should there be an underlying occult malignancy.

Anecdotally, corticosteroids are less effective in secondary AIHA cases than idiopathic AIHA. Treatment of the primary disease results in remission of AIHA with DAT reverting to negative. Duplication cysts identified in the pediatric population are mostly benign; however, malignant transformation is mainly identified in the older population. Identification of duplication cyst in an older individual should lead to a thorough work-up and suspicion of potential malignant transformation.

Conflicts of Interest

There are no conflicts of interest or sources of funding declared for this report.

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