**Case Report:**

**Familial Visceral Myopathy with Carcinoma of Unknown Primary**

Farbod Darvishian and Kevin Basham
Department of Pathology, North Shore University Hospital, Manhasset, New York

**Abstract.** We report an autopsy case of a 35-yr-old man with familial visceral myopathy, a cause of primary intestinal pseudo-obstruction. The patient died from complications of familial visceral myopathy, sepsis, and generalized signet-ring cell carcinoma. The patient had massive distension of the large and small intestines, a dilated thickened esophagus, and fibroneoplastic adhesions between intra-abdominal and thoracic structures. This case provides an observation, not previously described in cases of familial visceral myopathy, which is fibrosis and atrophy of the outer longitudinal smooth muscle of the small bowel, alternating to involve only the inner smooth muscle layer of the large bowel. This case shows how a malignant neoplasm can compound the pathology of familial visceral myopathy. *(received 16 July 2001, accepted 13 October 2001)*

**Keywords:** familial visceral myopathy, signet ring cell carcinoma, neoplasia

**Introduction**

Familial visceral myopathy (FVM) is a rare group of inherited disorders transmitted by autosomal dominant, or recessive modes [1-4]. A mitochondrial mode of inheritance has also been suggested [5]. Other terms that refer to FVM include hereditary megaduodenum, megacystis, hereditary idiopathic intestinal pseudo-obstruction, and hereditary hollow visceral myopathy. The chief pathological finding in FVM is myopathic degeneration involving any or all portions of the gastrointestinal tract, and urinary bladder [3,6]. In the intestine, FVM has a predilection for involvement of the outer longitudinal smooth muscle [2,4,7,8].

We report an autopsy case of FVM that showed involvement of the outer longitudinal smooth muscle in the small intestine, alternating to involve the inner circular muscle in the large intestine. The disease course was complicated by a signet-ring cell adenocarcinoma of undetermined origin with disseminated carcinomatosis.

**Case Report**

A 35-yr-old man was admitted to our hospital in November 1999, presenting with manifestations of urinary tract infection, including fever, chills, rigor, and dysuria. He also reported increasing abdominal pain and weight loss for the 7 mo prior to admission. On examination, he appeared febrile and cachectic. The abdomen was distended and tender. The patient had a chronic indwelling Foley catheter for urine, a gastrostomy tube for feeding, and jejunostomy and ileostomy tubes to relieve intestinal obstruction. He had received total parenteral nutrition prior to admission.

The patient’s past medical/surgical history was remarkable for familial visceral myopathy diagnosed when he was 19-yr-old, hypertension, chronic renal insufficiency, and an exploratory laparotomy following colovesical fistula formation. He was married with no children. His family history was significant for the death of a brother at age 19 yr from the complications of FVM. One sister was
also afflicted by FVM. His father had recently died (cause unknown); his mother is alive and suffers from “gastrointestinal problems”.

Computerized tomography (CT) scan of the abdomen showed bilateral hydronephrosis and pericholecystic fluid accumulation. Abdominal sonography revealed a gallbladder that contained sludge with a thickened wall.

The patient’s hospital course was complicated by upper GI bleeding, multiple sites of infection, septicemia, and worsening renal insufficiency. The sputum and blood culture grew methicillin-resistant *Staphylococcus aureus*. The patient received broad-spectrum antibiotics including vancomycin, but he developed pseudomonas pyelonephritis. His renal function worsened, leading to anasarca. His blood urea nitrogen and creatinine concentrations reached 176 mg/dl and 4.8 mg/dl, respectively. Due to urosepsis and bilateral hydronephrosis, he underwent bilateral nephrostomy.

The patient was febrile throughout his hospital course. His condition continued to deteriorate with eventual seizures and respiratory failure. He became hypotensive and unresponsive and he died on the 20th day of hospitalization.

**Autopsy Findings**

Autopsy showed that the entire abdominal gastrointestinal tract was matted together into a mass that was firmly adherent to the abdominal wall and to the intra-abdominal organs (Fig. 1). The esophagus was thickened and dilated to 6 cm in circumference. The small intestine and colon were both markedly thickened and dilated, containing ~3 L of black, foul-smelling fluid. The urinary bladder showed a diffusely thickened wall, which was adherent to the rectum. Gross examination of the upper urinary tract confirmed the presence of bilateral hydronephrosis and hydroureters.

Microscopic examination revealed two basic pathological processes. The first process encompassed the pathologic changes of familial visceral myopathy, affecting the small and large intestine and urinary bladder. The second process, unexpectedly, was the finding of a signet-ring cell adenocarcinoma of undetermined origin with disseminated carcinomatosis, which led to fibroneoplastic interloop adhesions and microscopic metastases throughout multiple organs.

Histologic examination of the small intestine showed marked atrophy, fragmentation, and muscle fiber dropout, with vacuolar degeneration and occasional eosinophilic debris in the outer longitudinal layer of the muscularis propria. Masson’s trichrome stain showed diffuse replacement of the outer muscle layer by dense collagen fibers. The inner circular muscle layer and muscularis mucosa were intact (Fig. 2). The myenteric plexus appeared normal. There were no inflammatory infiltrates in the histologic sections. Sections of small intestine showed infiltration of the submucosa, muscularis propria, and serosa by a poorly differentiated adenocarcinoma with signet-ring cell features.

Myopathic alterations of the colon were identical to those of the small intestine, but contrary to the latter, the inner circular smooth muscle layer was affected; the outer longitudinal layer of the colonic muscularis propria and the muscularis mucosa showed no appreciable pathologic changes.
The adenocarcinoma was also seen to infiltrate the submucosa, muscularis propria, and serosal layers of the colon. The urinary bladder revealed the myopathic changes (ie, hypertrophic muscularis propria alternating with atrophy, fragmentation, vacuolization, and fibrosis). The carcinoma infiltrated the urinary bladder transmurally with numerous foci of intravascular permeation. The carcinoma was noted to encircle the ureteral orifices, leading to stricture of the ureterovesical junction.

The adenocarcinoma was identified in multiple organs, including skin, heart, bone marrow, lymph nodes, pleura, adrenal gland, psoas muscle, gallbladder, as well as the entire GI tract from the esophagus to the rectum. The urinary bladder and gallbladder were the only two organs that showed transmural infiltration by the carcinoma. The neoplastic cells exhibited pleomorphism and signet-ring cell morphology (Fig. 3).

Immunohistochemically, the neoplastic cells showed positive reactivity with antibodies to cytokeratin 7 (Ventana), cytokeratin 20 (Ventana, Tucson, AZ), and carcinoembryonic antigen (CEA) (Ventana), but failed to show reactivity for antibody to thyroid transcription factor-1 (TTF-1) (Zymed, San Francisco, CA). These findings point to a neoplasm originating in the upper GI (eg, stomach, gallbladder, pancreas) or urinary bladder.

**Discussion**

FVM is a cause of primary intestinal pseudo-obstruction [1,9]. In 1938, Weiss described 6 members of a German family who suffered from megaduodenum and megacolon. For the first time, his observation pointed to an inherited subset of intestinal pseudo-obstruction [10]. FVM, although clinically well described, remained unexplained at the microscopic level for about 40 yr after it was first reported. The early reports failed to show the pathologic changes of FVM [11,12].

In 1977, Schuffler and Pope [1] demonstrated the pathologic changes of intestinal smooth muscle in a 15-yr-old girl with inherited idiopathic intestinal pseudo-obstruction. Since several hollow viscera were involved, they coined the term “hereditary hollow visceral myopathy” for this subset of familial primary intestinal pseudo-obstruction [1].

FVM is a rare inherited disorder. Autosomal recessive and autosomal dominant modes of inheritance have both been reported [1-4]. A mitochondrial mode of inheritance has also been proposed [5]. Affected individuals usually present with megaduodenum, megacystis and obstructive manifestations in the colon, including abdominal pain, nausea, vomiting, and abdominal distension [2,4,8]. The affected individuals usually become symptomatic after the first decade of life but...
childhood presentation has also been reported [4]. The differential diagnosis includes obstructive and pseudo-obstructive diseases of the gastrointestinal tract, such as congenital bands, scleroderma, amyloidosis, and Chagas’ disease, just to name a few. Judging from the family history, our patient appears to fall into the autosomal dominant subset of FVM. The exact mode of inheritance is not known, since neither parent was reported to have been diagnosed as having FVM, or been excluded from that diagnosis.

The primary pathologic findings in FVM include myopathic alterations of smooth muscle fibers, consisting of fragmentation, thinning, atrophy, and loss of myofibers, imparting a vacuolated appearance to the smooth muscle layer. As a byproduct of this degenerative process, dense eosinophilic bodies are readily identified in the histologic sections [7]. Finally, the dropped-out muscle layer is replaced by dense collagen fibers that accentuate the vacuolar appearance of the smooth muscle layer.

The distribution of the myopathic degeneration is variable. In some cases, the muscle fibers are reported to be focally involved, separated by normal-appearing intervening fibers [7]. In contrast, Jacobs et al [8] reported an autopsy case with involvement of the entire small intestine. However, there seems to be a predilection for the outer longitudinal layer of the muscularis propria to be affected by the myopathic process [2,4,7,8]. Although both inner and outer layers can be affected, the degeneration is more pronounced in the outer longitudinal layer [3,7]. Occasionally, the inner muscle layer undergoes compensatory hypertrophy, thereby preventing bowel distension [8]. The muscularis mucosa is invariably spared.

The intestinal manifestations in our case included massive dilatation of both small and large intestine in spite of multiple enterostomies. Microscopically, an interesting finding was the involvement of the outer longitudinal muscle in the small intestine, alternating to the inner circular muscle in the colon (Fig. 2). The lack of inflammatory reaction was noticeable in our material. Acute inflammation, represented by polymorphonuclear infiltration, has been cited in two reports; however, it was attributed to laparotomy as an acute phenomenon [2,6].

On microscopic examination, the urinary bladder revealed atrophy and degeneration of the muscle fibers alternating with hypertrophy. The latter, together with transmural infiltration of the wall by the adenocarcinoma, led to the stenosis of the bilateral ureteral orifices. As a result, bilateral hydronephrosis ensued and was complicated by pyelonephritis and deterioration of renal function. The unusual finding in our case was the association of FVM with malignancy in a 35-yr-old man. At autopsy, the bowel loops were matted together and adhered to the neighboring organs by a fibroproliferative process. Histologically, the neoplasm was a...
poorly differentiated adenocarcinoma with extensive signet-ring cell features (Fig. 3).

The carcinoma diffusely infiltrated the entire serosa and wall of the gastrointestinal tract, sparing the mucosa and submucosa. The desmoplastic reaction elicited by the diffuse neoplastic infiltration led to fibroneoplastic interloop adhesions. The autosomal dominant subset of FVM reportedly carries a fairly good prognosis, as long as appropriate operations are performed [5,9,12]. Nevertheless, in our patient, the disseminated neoplasm exacerbated the obstructive manifestations of the underlying FVM, leading to an early demise.

The origin of the adenocarcinoma in our case could not be determined with certainty. After a thorough examination at autopsy no gross primary lesion could be identified.

Microscopy of the stomach, esophagus, small and large bowel, gallbladder and urinary bladder revealed infiltrating adenocarcinoma; however the mucosal surfaces in these possible primary sites did not show an in-situ neoplastic process.

Histologically, after extensive study of multiple sections, the gallbladder and the urinary bladder were the only two organs that revealed transmural involvement by the carcinoma. The neoplastic cells, which showed prominent signet-ring cell features, reacted with cytokeratin 7, cytokeratin 20, and CEA, antibodies but not to the TTF-1 antibody. These findings point to a neoplasm originating in the gallbladder, stomach, or urinary bladder. However, the definite primary site remains elusive.

References: