Fabry Disease Simulating Crohn's Ileitis

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Abstract. *Fabry disease is an inherited (X-linked) lysosomal storage disorder caused by deficiency of α-galactosidase A, leading to accumulation of globotriaosylceramide in various tissues. A 57-year-old male with a family history and laboratory findings of Fabry disease, was consulted for severe abdominal pain, undulating pyrexia, weight loss and diarrhea. The tentative clinical diagnosis of Crohn's ileitis was supported at computed tomographic examination, at laparotomy and at inspection of the resected ileal segment. Histology revealed chronic and acute inflammation, thick-walled occluded vessels, fibrosis and characteristic bi-refringent lamellar deposits of globotriaosylceramide and calcifications. Multi-nucleated giant cells contained phagocytized bi-refringent material. Transmission electron microscopy showed cells with irregular cytoplasmic bodies displaying distinctive zebra-like lamellar structures. It is submitted that the gastrointestinal phenotype of Fabry disease may concur with symptoms resembling abdominal Crohn's disease.*

In 1898, Johannes Fabry, and William Anderson independently described a skin disease characterized by maculopapular lesions (1). Fabry called the disease *purpura haemorrhagica nodularis* and Anderson angiokeratoma. A third case was reported 14 years later by Frank Madden (1). In 1915, Johannes Fabry re-baptized the condition as angiokeratoma *corporis naeviforme* (1).

Anderson–Fabry or Fabry–Anderson disease, often referred to simply as Fabry disease (FD) (2, 3), is an inherited (X-linked) lysosomal storage disorder (LSD) caused by deficiency of α-galactosidase A, with the accumulation of globotriaosylceramide (GL-3) in the microvasculature, leading to endothelial injury throughout the body.

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FD probably starts in foetal life, affecting kidneys, heart, pancreas, lung and bowel. Untreated patients die of renal, cerebrovascular and cardiac complications (4).

Incidence estimations in the general population range from 1:40 000 to 1:60 000 males. A review of 18 screening studies in 21,256 patients on renal replacement therapy revealed a combined prevalence of FD of 0.1%. In individual studies, the incidence of FD disease among male patients ranged from 0 to 1.6% (4).

In a more recent comprehensive European survey of 342 patients with FD having gastrointestinal manifestations, the most common symptoms were nausea, vomiting, abdominal distension, episodic diarrhoea, constipation or recurrent attacks of abdominal pain; these symptoms are often associated with irritable bowel syndrome (5).

Only four previous reported cases of FD had severe abdominal symptoms requiring for surgical intervention (6-9). We report on a patient with known FD consulting for abdominal symptoms that raised the clinical suspicion of Crohn's ileitis. This preliminary diagnosis was supported at DT examination, at laparotomy and at inspection of the resected specimen.

Case Report

The patient is a 57-year-old male with a long history of scattered skin lesions, angiopathy, neuropathy and restrictive cardiomyopathy. He has six siblings; two brothers diagnosed with FD are being treated with enzyme substitution. One of his mother's cousins died at a young age from myocardial infarction and another, also young, from stroke. A blood test at age 46 confirmed the diagnosis of FD. Since then, the patient has been treated with enzyme substitution (Agalsidase Beta) (10, 11). Because of weight loss, abdominal pain, undulating pyrexia, diarrhea and blood in the stools, the patient was referred to the Department of Gastroenterology. Following intravenous contrast, an abdominal Computed Tomography showed in the distal ileum, a 20-cm long segment having thick walls with a central stricture (Figure 1). In addition, an inflammatory mass was seen in the juxtaposed mesentery. A retrograde ileoscopy revealed mucosal

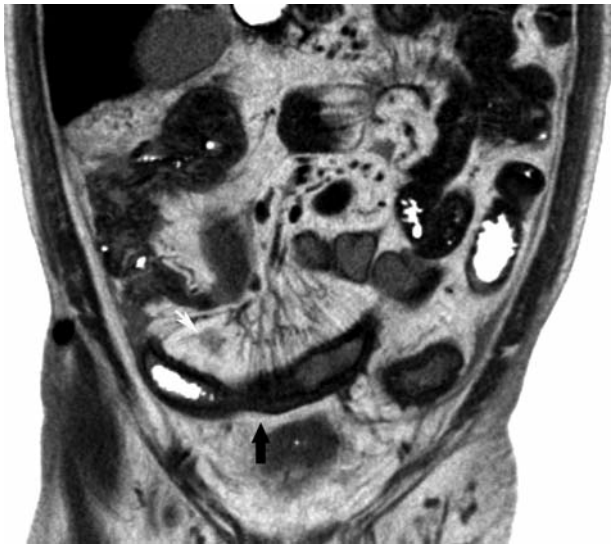

Figure 1. *Abdominal computed tomographic scan showing a 20-cm long segment in the distal ileum, having thick walls with a central stricture (black arrow). An inflammatory mass can be seen in the mesentery (white arrow).*

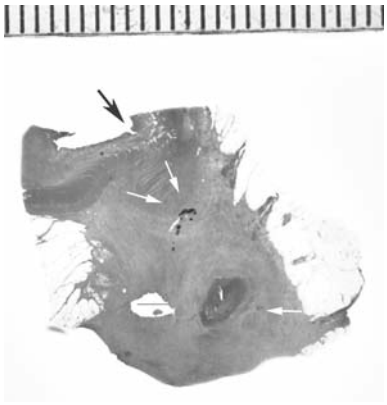

Figure 2. *Overview from a section from the resected ileum with mucosal ulceration (black arrow), transmural chronic inflammation with calcifications (double white arrows) and abscess (lower white arrow) (ileum; ×1).*

inflammation, circumferential ulcerations and stenosis 15 cm from the ileocaecal valve. Biopsies from that area showed chronic inflammation. Tissue culture of one of the biopsies was negative for tuberculosis. Medical treatment with antibiotics and high-dose corticosteroids were ineffective in controlling the symptoms and the patient's condition rapidly deteriorated. The plasma albumin level plummeted to 14 g/l. The inflammatory marker (CRP) was persistently elevated (50 mg/l). The patient developed *Escherichia coli* bacteraemia. A decision for surgical intervention was taken at a multidisciplinary conference.

At laparotomy, a 30-cm segment of the distal ileum showed transmural chronic inflammation. The intestine proximal to that lesion was moderately dilated. In the juxtaposed mesentery, an inflammatory mass with a central abscess adherent to the bladder and to the sigmoidal fat was found. The peritoneal cavity contained 200-300 cc ascites. A per-operative frozen section revealed chronic inflammation; no tumor was found. An *en bloc* resection of the inflamed distal ileum and the inflammatory mass adherent to the bladder was performed. At the time of resection, pus poured out from the inflammatory mass.

From the two remaining bowel ends, a temporary loop ileostomy was constructed. Based on gross inspection of the resected specimen, the preliminary surgical diagnosis was Crohn's ileitis.

Pathology. Gross examination: The resected specimen measured 30 cm in length. In the middle of the ileum, a stricture measuring 2 cm in length and a mesentery abscess measuring 3.5×2 cm were found. The intestinal mucosa exhibited multiple ulcerations. The intestinal wall was markedly thick and fibrotic. Based on gross inspection of the resected specimen, the pathologist on duty suspected Crohn's ileitis.

Histological examination: Haematoxylin and eosin (H&E)-stained sections from the resected ileum revealed mucosal ulceration, transmural chronic inflammation with microabscesses, calcifications and fibrosis (Figure 2). Thick-walled vessels with occluded lumen (Figure 3) and many multi-nucleated giant cells containing engulfed lamellar deposits were found. These lamellar deposits were bi-refringent under polarizing light (Figures 4 and 5). Other areas showed foci of pleomorphic calcifications amidst the chronic inflammation (Figure 6).

Neither epitheloid-cell granulomas nor amyloid deposits were present. Acid fast stain was negative.

Transmission electron microscopy: Ultra-structural examination showed cells with irregular intra-cytoplasmic bodies exhibiting lamellar, zebra-like structures (Figures 7 and 8). Calcifications were also found.

Follow-up. The patient quickly recovered during the immediate postoperative period. At day 8, however, the patient was re-operated because of wound dehiscence. The following second postoperative period was uneventful and he was discharged at day 12.

Six weeks after surgery, the patient was doing well and Plasmid 22037: pAlbumin and CRP had normalized. Five months after surgery, an ileoscopy of the afferent and efferent loops revealed normal mucosae. The patient is now scheduled for restoring surgical closure of the ileostomy.

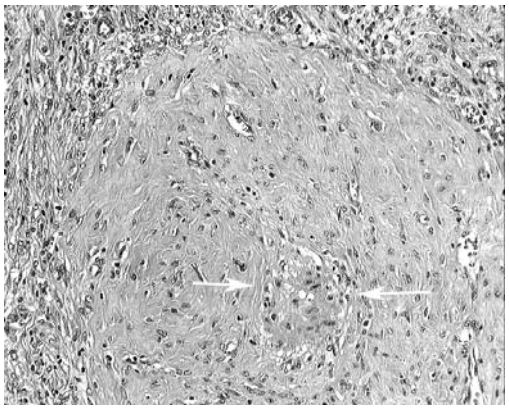

Figure 3. *Hypertrophic artery, with occluded lumen between arrows (×10).*

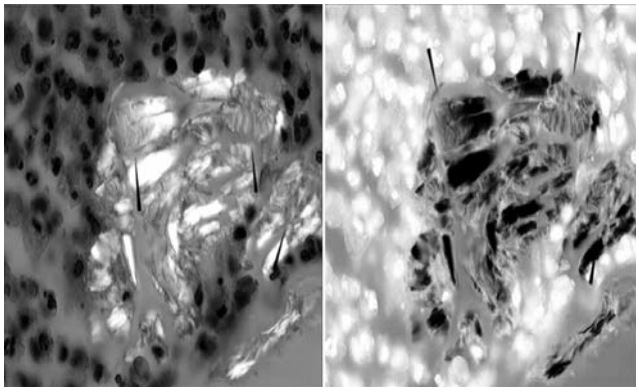

Figure 5. *Left panel: Cell with deposits of bi-refringent material. Note the lamellar structures at spears (polarizing light, Fabry disease, H&E, oil immersion, ×100). Right panel: Same picture using the INVERT function of a Photoshop program (Ps Adobe Photoshop CS3 extended), to enhance the lamellar structures, H&E, oil immersion, ×100).*

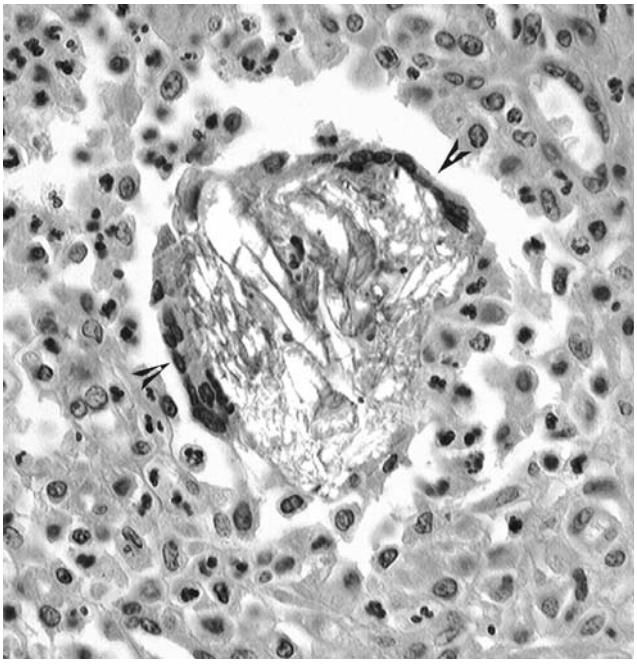

Figure 4. *Multi-nucleated giant cells at arrows with bi-refringent deposits of globotriaosylceramide (polarizing light, oil immersion; ×100).*

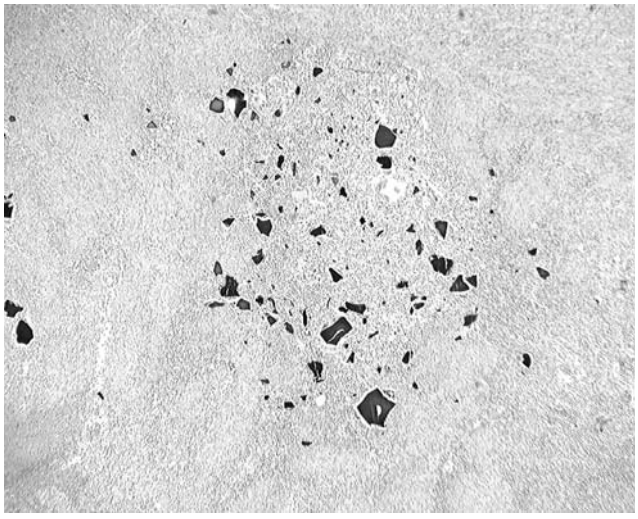

Figure 6. *Low-power view showing multiple calcifications in an area with chronic inflammation (ileum; ×4).*

Discussion

In the early 1960s, de Duve and colleagues discovered the lysosome, an ultra-structural cellular organelle responsible for the intracellular digestion and recycling of macromolecules (12). Subsequent studies lead to the discovery of LSDs often caused by the paucity of a particular lysosomal protein and rarely from non-lysosomal activities involved in lysosomal biogenesis or protein maturation (13).

LSDs are a superfamily that encompasses at least 50 different genetic diseases (13). Some LSDs were empirically described many years before the discovery of lysosomes by de Duve and colleagues (12): Gaucher disease in 1882, and FD in 1898 (1).

We report here on a case of FD mimicking Crohn's ileitis. The diagnosis of FD was based on the family history and the laboratory findings. A preliminary clinical diagnosis of Crohn's ileitis was supported not only by computed tomography, but also at laparotomy and on inspection of the resected specimen.

In FD, accumulation of GL-3 in the microvasculature leads to endothelial injury and eventually to vessel occlusion,

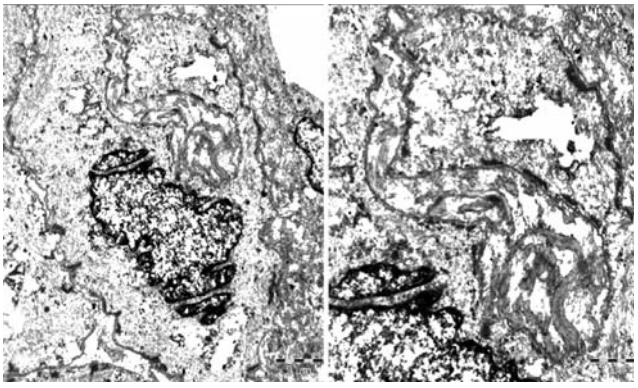

Figure 7. *Left panel: Transmission electron microscopy showing an endothelial cell with one large intra-cytoplasmatic inclusion exhibiting characteristic lamellar pattern (ileum; scale 2 μm). Right panel: A somewhat higher magnification highlighting the lamellar pattern (ileum; scale 1 μm).*

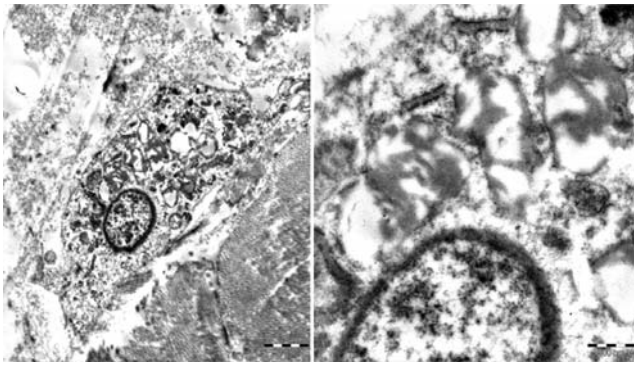

Figure 8. *Left panel: Transmission electron microscopy showing another cell with intra-cytoplasmatic inclusions exhibiting characteristic lamellar pattern. The inclusions occupy a great portion of the cytoplasm (ileum; scale 2 μm). Right panel: Higher magnification highlighting the zebra-like pattern (ileum; scale 500 nm).*

resulting in stroke, renal failure and vascular manifestations in many organs. In our case, thick-walled vessels with lumen occlusion caused ischemic changes, secondary chronic and acute transmural inflammation and abscesses. Multi-nucleated macrophages having characteristic lamellar structures with bi-refringent material, thick-walled occluded vessels and fibrosis were also seen. The obliteration of intestinal vessels is a significant finding in this case.

Calcifications in FD have been previously recorded, but only in the CNS (14). This appears to be the first case of FD with calcifications in the gastrointestinal tract (ileum).

In FD, bi-refringent lamellar structures have been reported in various organs (3, 15-18). We found bi-refringent lamellar deposits and calcifications in multinucleated macrophages, both in areas with chronic inflammation and in areas without inflammation in apparently uninvolved ileum. The latter setting suggests that GL-3 accumulation also takes place in apparently normal tissues, preceding thereby the appearance of severe vascular changes and chronic inflammation.

Transmission electron microscopy showed cells with osmiophilic irregular cytoplasmic bodies displaying lamellar, 'zebra-like' structures.

Today it is recognized that FD is not simply an ailment caused by pure storage dysregulation, but the result of perturbation of complex cell signalling mechanisms that in turn give rise to secondary structural and biochemical changes (19).

FD with early gastrointestinal manifestations seldom requires surgical intervention. The review of the literature showed that only four cases of FD with bowel complications requiring surgery are in record (6-9). Interestingly, Buda *et al.*'s patient was operated on for colonic pseudo-obstruction; the tentative preoperative diagnosis in that case was also Crohn's disease (6).

It is submitted that the gastrointestinal phenotype of Fabry disease may concur with symptoms resembling abdominal Crohn's disease.

Conflicts of Interest

None.

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