

## Primary amyloidosis presenting as small bowel encapsulation

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Amyloidosis is a pathological process which encompasses a spectrum of diseases that result from extracellular deposition of pathological fibrillar proteins. Clinical presentations vary depending on the organs involved. There is no documented case of amyloidosis presenting as small bowel encapsulation.

A previously healthy 62-year-old man developed a small bowel obstruction in 1997. At surgery, a peculiar membrane encasing his entire small bowel was discovered. This appeared to have no vascularity and was removed without difficulty, exposing a grossly normal bowel.

Histopathology revealed thick bands of collagen overlying the peritoneal surface, which was congo red positive and showed apple green birefringence. The findings were consistent with encapsulating peritonitis due to amyloidosis. There was no history or symptoms of any chronic inflammatory condition and he became symptom-free postoperatively. An abdominal fat pad biopsy failed to demonstrate amyloidosis. Endoscopic duodenal biopsies revealed classical primary amyloidosis. Quantitative immunoglobulins, lactate dehydrogenase, C3, C4 and beta-2 microglobulin were normal. Protein electrophoresis identified monoclonal paraprotein, immunoglobulin G lambda 3.7 g/L. Bone marrow biopsy and aspirate revealed only a mild plasmacytosis (5% to 10%). Echocardiogram and skeletal survey were normal. He had mild proteinuria. Complete blood count, C-reactive protein, calcium, albumin and total protein were normal. No specific therapy was instituted.

In January of 1998 the patient remained asymptomatic with no gastrointestinal, cardiovascular or constitutional symptoms. He had developed nephrotic range proteinuria (3.95 g/24 h), microalbuminuria, hypoalbuminemia and a renal biopsy consistent with renal amyloidosis. In 1999 there was an increase in the monoclonal paraprotein (6.2 g/L). The remaining investigations were normal except for an echocardiogram which showed left ventricular hypertrophy but a normal ejection fraction and no diastolic dysfunction. He went on to have high-dose chemotherapy and an autologous stem cell transplant in September, 2000. He has subsequently developed renal insufficiency. To our knowledge this is the first reported case of primary amyloidosis presenting as small bowel obstruction from encapsulating peritonitis.

**Key Words:** Amyloidosis; Encapsulating peritonitis; Primary amyloidosis; Small bowel encapsulation

## Amyloïdose primaire se présentant sous forme d'encapsulation du grêle

L'amyloïdose est un processus pathologique qui englobe diverses maladies et résulte de la formation de dépôts extracellulaires anormaux de protéines fibrillaires. Le tableau clinique varie selon les organes touchés. On n'avait encore jamais signalé d'amyloïdose se présentant sous la forme d'encapsulation du grêle.

Un homme de 62 ans, auparavant en bonne santé, a développé une obstruction du grêle en 1997. La chirurgie a mis au jour une membrane anormale enveloppant tout le grêle. La membrane ne semblait pas vascularisée et a été retirée sans difficulté, exposant un intestin à première vue normal.

L'analyse histopathologique a révélé la présence d'épaisses bandes de collagène tapissant la surface péritonéale; ces bandes se sont révélées positives à l'épreuve au rouge congo, avec biréfringence vert pomme. Ces résultats concordaient avec une péritonite encapsulante secondaire à une amyloïdose. Le patient ne présentait aucun antécédent ou symptôme de maladie inflammatoire chronique et la situation s'est corrigée après la chirurgie. La biopsie d'un prélèvement pratiqué sur le coussinet adipeux abdominal n'a pas permis de confirmer la présence d'amyloïdose. Des biopsies duodénales endoscopiques ont révélé une amyloïdose primaire classique. Les dosages d'immunoglobulines, de lactico-déshydrogénase, des microglobulines C3, C4 et bêta-2 se sont révélés normaux. L'électrophorèse des protéines a révélé la présence de l'immunoglobuline G lambda (3,7 g/L), une paraprotéine monoclonale. La biopsie et la ponction de moelle osseuse n'ont révélé qu'une légère plasmocytose (5 à 10 %). L'échocardiographie et l'examen du squelette étaient normaux. Le patient présentait une légère protéinurie. La formule sanguine complète, le dosage de la protéine C réactive, du calcium, de l'albumine et des protéines totales étaient normaux. Aucun traitement spécifique n'a été instauré.

En janvier 1998, le patient était toujours asymptomatique, indemne de tout problème gastro-intestinal, cardiovasculaire ou constitutionnel. Il avait développé une protéinurie néphrotique (3,95 g/24 heures), de la microalbuminurie, de l'hypoalbuminurie et sa biopsie rénale concordait avec une amyloïdose rénale. En 1999, on a noté une augmentation de la paraprotéine monoclonale (6,2 g/L). Les autres analyses étaient normales, sauf l'échocardiogramme qui montrait une hypertrophie ventriculaire gauche, mais une fraction d'éjection normale en l'absence de dysfonction diastolique. Le patient a subi une chimiothérapie à fortes doses et une transplantation de cellules souches autologues en septembre 2000. Il a par la suite développé une insuffisance rénale. À notre connaissance, il s'agit du premier cas signalé d'amyloïdose primaire se présentant sous la forme d'une obstruction du grêle dû à une péritonite encapsulante.

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Sclerosing encapsulating peritonitis (SEP) is a rare condition in which the bowel and mesentery become encapsulated within a fibrous cocoon-like sac. The sac is covered by a layer of attenuated mesothelium that is separated easily from the underlying bowel (1). This may lead to intestinal obstruction, intestinal necrosis and enterocutaneous fistulas (2). SEP is synonymous in the literature with peritonitis chronica fibrosa incapsulata, peritonitis fibroplastica incapsulata, chronic encapsulating peritonitis, sclerosing peritonitis, fibrous peritonitis and abdominal cocoon (1-4). The etiology of SEP can be idiopathic or secondary to the use of beta-blockers, LeVeen shunt, chronic ambulatory peritoneal dialysis and surgery (3). Cases of idiopathic encapsulating peritonitis have previously been described in young girls (4).

Patients frequently present with symptoms of acute or subacute small bowel obstruction (4). A preoperative diagnosis may be suggested by a number of imaging modalities including barium meal, ultrasonography and abdominal computed tomography (CT). Characteristic imaging features of SEP have been discussed in a number of papers (2,5-9). Management has included surgical decortication and long term hyperalimentation depending on the symptom severity. Spontaneous resolution of symptoms with conservative therapy has also been reported (10).

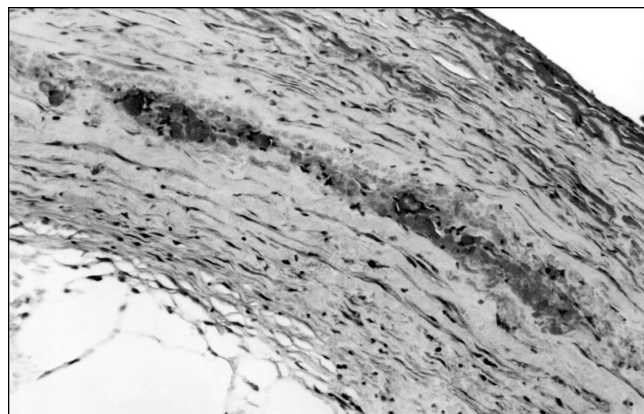
We describe a 62-year-old man with small bowel encapsulation as a first presentation of amyloidosis. To our knowledge, this is the first reported case of small bowel encapsulation as a result of primary amyloidosis.

### CASE PRESENTATION

A previously healthy, 62-year-old man presented in July, 1997 with a three day history of nausea, bilious vomiting, mild abdominal distention and constipation. He lost 5.45 kg within the last two months. This man had no history of gastrointestinal pathology or abdominal surgery.

On examination the abdomen was slightly distended, bowel sounds were normal and the abdomen was soft with no tenderness or palpable mass. Abdominal x-rays revealed dilated loops of small bowel with air-fluid levels and a paucity of air in the rectum and right colon. He was admitted with a diagnosis of partial small bowel obstruction. Small bowel follow-through was normal and the patient was managed conservatively with symptom resolution over a one week period.

Eight weeks later the patient presented again with a three week history of epigastric abdominal discomfort, nausea and abdominal distension. Blood work showed a normocytic, normochromic anemia. The white blood cell count, vitamin B<sub>12</sub> and folate levels were normal. The platelet count was  $222 \times 10^9/L$ . An antinuclear antibody was negative. Quantitative immunoglobulins, lactate dehydrogenase, complement, C-reactive protein and beta-2 microglobulin were normal. A serum protein electrophoresis showed a monoclonal immunoglobulin (Ig) G, (3.7 g/L) with lambda light chain restriction. Urinalysis showed mild proteinuria. Urine protein electrophoresis showed a polyclonal and monoclonal IgG band, trace IgA, a kappa polyclonal band and a lambda monoclonal band. Vitamin D, calcium and prostate specific antigen were normal. Smooth muscle antibody was normal and albumin was 27 g/L. A CT scan of the abdomen and pelvis showed marked dilation of the proximal small bowel as well as a sharp change in caliber within the ileum in keeping with a chronic small bowel obstruction.



**Figure 1)** Amyloid deposits seen between the collagen fibers of the peritoneal lining and in the walls of the capillaries. Cresyl violet stain. Original magnification  $\times 200$ .

The patient underwent a laparotomy 18 days after admission. Intraoperatively the peritoneum was noted to be thickened and the small bowel was totally encased in an inflammatory 'peel'. The upper abdomen, liver, stomach and subdiaphragmatic areas were encased with some obliteration of the peritoneal cavity. The stomach and duodenum were grossly dilated. The encasing membrane was avascular and was easily removed from the small bowel. Once the membrane was removed, the small bowel was normal in appearance.

The histology of this membrane revealed bands of thickened collagen overlying the original peritoneal surface. A mild, nonspecific inflammatory, neutrophilic infiltrate was present. There were two distinct patterns of amyloid distribution, the first in the blood vessels and the second beneath a thickened peritoneal surface. This unusual pattern of deposition was present in the form of a thick band not associated with any recognizable anatomic structure. Also, the blood vessels in the proximity of this band contained amyloid suggesting that the patient had pre-existing systemic amyloidosis, developed chronic peritonitis and within chronically inflamed tissue had subsequent amyloid deposition. There was a layer of amorphous eosinophilic material lining the site of the original peritoneal surface, which stained congo red and demonstrated apple green birefringence. The amyloid also stained with cresyl violet (Figure 1). Immunohistochemical stains for kappa and lambda were negative within these amyloid deposits. Beta-2 microglobulin and beta amyloid stains were also negative. Potassium permanganate pretreatment eradicated the congo red positivity, suggesting that the amyloidosis was secondary in nature rather than primary. There was no evidence of malignancy or other systemic inflammatory disease.

Postoperatively, the patient's bowel habit normalized and his weight stabilized. Small bowel biopsies for amyloidosis showed extensive amyloid deposition in the distal duodenum. A bone marrow biopsy showed only a mild plasmacytosis (10%) via staining with antilambda antisera. An echocardiogram showed no changes consistent with amyloid infiltration or evidence of diastolic dysfunction. A skeletal survey was normal.

In January, 1998 the patient was seen in follow-up and was asymptomatic. The monoclonal protein measured 5.6 g/L.

In 1999, the presence of mild microscopic (2+) proteinuria was observed along with an increase in the monoclonal protein to 6.2 g/L. No urinary electrophoresis was done. Over the course of the next 12 months he developed nephrotic range proteinuria and a renal biopsy confirmed the presence of amyloidosis. A two-dimensional echocardiogram revealed left ventricular wall hypertrophy with normal left ventricular function and no evidence of diastolic dysfunction.

In September, 2000 he underwent high-dose chemotherapy and an autologous stem cell transplant and made a good recovery. Six months post bone marrow transplant there remained a persistent monoclonal protein of 3.1 g/L along with nephrotic range proteinuria of 7 g in a 24 h period compared with a pre-transplant level of 3.95 g in 24 h. He had no gastrointestinal symptoms.

## DISCUSSION

Amyloidosis is a pathological process which encompasses a spectrum of diseases that result from extracellular deposition of pathologic fibrillar proteins (11-13). The three clinical forms of amyloidosis (primary [AL], familial and secondary) each differ in their pathogenesis (11). AL amyloidosis is associated with immunocyte dyscrasia and results from frequent amino acid substitutions in the light chain variable region leading to light chain destabilization and fibrillogenesis (14).

Clinical presentations vary depending on the organs involved. There are no documented cases of amyloidosis presenting as small bowel encapsulation. Mucosal, vessel wall and intramural involvement of the gastrointestinal (GI) tract are well recognized and may lead to intestinal ischemia, infarction, dysmotility and malabsorption (13). Symptoms of GI amyloid extend from the mouth to the anus and include macroglossia, diarrhea, constipation, fecal incontinence or rectal prolapse and dysphagia. Malabsorption occurs secondary to bacterial overgrowth, mucosal ischemia, pancreatic exocrine insufficiency or submucosal amyloid deposition. Dysmotility or antral amyloidoma may lead to gastric outlet obstruction. GI bleeding and intestinal infarction results from capillary and blood vessel involvement. Other GI manifestations include protein-losing enteropathy and hepatosplenomegaly (13).

The changes observed in our patient were those of chronic peritonitis with extensive peritoneal fibrosis and mild, non-specific inflammation. Of particular interest was the fact that

this patient had two distinct patterns of amyloid distribution. This is a curious phenomenon in a patient not previously known to have systemic amyloidosis.

This is an unusual pattern of amyloid distribution and amyloid deposition presenting in this manner has not been reported. The prognostic significance of this presentation is unclear. Traditionally, the clinical classification of patients into four groups: those with heart failure, nephrotic syndrome, peripheral neuropathy and other is useful for determining long term prognosis (15). Our patient has renal amyloidosis. Studies of patients undergoing dialysis have shown improvements in survival rates over the years, particularly in younger patients (15-20). Age greater than forty years is a factor in determining survival (21,22). Isoniemi et al (22) showed slightly better results in 1989 and attributed them to the use of cyclosporin. However, the mortality was still high.

The goals of amyloidosis therapy include supportive measures as well as targeting the underlying defect. Our patient most likely has the AL variant. Numerous studies have shown superior efficacy of a combination of oral melphalan and prednisone when compared with treatment using colchicine, prednisone and/or melphalan (23,24). Despite these results, response rates are still low, with a survival increase from a median of six months to 12 months in those receiving chemotherapy. Patients must survive long enough to receive several cycles of melphalan before survival benefit occurs (11). Treatment with high dose intravenous melphalan plus autologous blood stem cell support has resulted in complete remission of the plasma cell dyscrasia and substantial improvement in amyloid-related organ disease (11). More recently, van Gameren II et al (25) report a case series of 38 patients with AL amyloidosis treated with vincristine, doxorubicin and dexamethasone and high dose melphalan followed by autologous stem cell transplantation (ASCT). Six months after ASCT 78% of surviving patients showed a partial clonal response but none responded completely. Clinical condition improved in 67%. After a median follow-up of 25 months, 75% of the study group were alive (25). Subsequent experience with ASCT in patients with AL has shown success (26,27).

To date (November 2003), there has been no recurrence of gastrointestinal amyloidosis in our patient. However, he has developed end-stage renal insufficiency.

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