Gastrointestinal amyloidosis: a case of chronic diarrhoea


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Abstract. – Amyloidosis is a rare disease caused by extracellular deposits of insoluble fibrillar proteins in various organs and tissues. There are different forms of amyloidosis distinguished by the type of protein fibrils, by the sites of deposition and by associated conditions. Gastrointestinal involvement is common both in primary and secondary amyloidosis, while isolated gastrointestinal amyloidosis is rare.

We describe a case of AL amyloidosis with a gastrointestinal involvement and restrictive cardiomyopathy.

A 64 year old woman came to our attention with a history of chronic diarrhoea and weight loss, associated with dysphagia, dry mouth, xerophthalmia, chronic gastritis and depression. Clinical diagnosis has been difficult because of aspecificity of symptoms that mimed other more common diseases, like gastro-paresis, epigastric discomfort, gastric or duodenal ulcers, perforation, malabsorption, intestinal pseudo-obstruction.

There is an important risk of misunderstanding and diagnostic delay. Indeed in this patient a diagnosis of irritable colon syndrome was erroneously established two years before admission in our hospital. Therefore gastrointestinal amyloidosis should be considered among differential diagnoses of chronic diarrhoea and weight loss when other more common diseases have been excluded.

Key Words:
Amyloidosis, Chronic diarrhoea, Malabsorption.

Introduction

The amyloidoses are a group of rare diseases that have in common the extracellular deposition of pathologic, insoluble fibrils in various tissues and organs. The fibrils have a characteristic configuration that produces apple-green birefringence under polarized light when stained with Congo red dye 1. Different proteins can form amyloid fibrils, and the types of amyloidosis are classified on the basis of the amyloidogenic protein and of the distribution of amyloid deposits. There are six types of amyloidoses: primary (light chain (L)-associated AL amyloidosis), secondary (AA), hemodialysis-related (Amyloid β2-microglobulin amyloidosis), hereditary (transthyretin amyloidosis), senile, and localized. In systemic amyloidoses the amyloidogenic proteins are produced at a site distant from the site of amyloid deposition, while in localized disease the place of proteins’ production and deposition is the same. The nomenclature uses 2 letters, being A the first letter, (for amyloid), followed by another one which describes of the precursor protein 2.

Gastrointestinal involvement is common both in primary and secondary amyloidosis (respectively in 70% and 55% of cases), while localized gastrointestinal amyloidosis is rare 1.

The non-specific and vague nature of symptoms associated with different forms of amyloidosis frequently leads to delay in diagnosis, when organ dysfunction is already advanced.

Chronic diarrhoea is defined as a condition lasting more than four weeks 3, while acute and subacute diarrhoea last for less than two weeks and for two-four weeks respectively. Several conditions could determine chronic diarrhoea: bowel resection, drugs (laxatives in particular), infections, endocrinopathies, glucose mal-absorption, chronic mesenteric ischemia, lymphatic obstruction, celiac disease, pancreatic failure, wall alterations (amyloidosis, Whipple disease, microscopic colitis or collagenous colitis). Chronic diarrhoea is quite a frequent situation in clinical practice and requires a thorough analysis.
Case Report

We describe the case of a patient with a history of chronic diarrhoea and weight loss.

A 64 years old woman was admitted to our hospital on November 2007 with chronic diarrhoea, weight loss (about 12 kg in the last year), dysphagia, dry mouth, xerophtalmia, chronic gastritis and depression. Diarrhoea started about 2 year before and was characterised by 10 emissions/day of liquid yellow stool without abdominal pain and fever. She suffered from recurrent tracheitis and pharyngitis since childhood, with a worsening in the last 2 years. She lamented cough after deglutition, too.

*Helicobacter pylori* was found twice in 1996 and 2000; antibiotic therapy was performed with benefit. In 2006 oesophago-gastro-duodenoscopy documented chronic gastritis with intestinal metaplasia and rare erosions in antral and pyloric stomach. The patient referred that colonoscopy was negative. In the same year she complained of tachycardia and heartburn: they were explained as somatic conversion in an anxious-depressive syndrome. Nevertheless ansiolitic-antidepressant therapy was not been effective. To study dry mouth and xerophtalmia a Schirmer test was negative, as SSA and SSB autoantibody too. In the same period a weight loss started, although she did not reduced feeding. In 2007 stool exams (parasites and common microbes research, blood) and screening for celiac disease resulted all negative. She started a therapy with pancreatic enzymes and rifaximine a month before admission to our hospital, with benefit in terms of reduction of stool emissions (from 10 to 4/day).

At the hospital physical examination did not found any abnormality of heart and lungs. Abdomen was not aching itself or after deep palpation; gut resulted stretched in left iliac part. Subcutaneous hypotrophy secondary to weight loss was evident.

Lab tests (white cells count, iron, B vitamins, inflammation parameters, Ig levels, protein electrophoresis, coagulation) were all normal, except for a mild normochromic normocytic anaemia (Hb 11.7 g/dl), a reduction of total protein and p-cholinesterases (6.2 g/dl and 4651 UI/l respectively). Lactulose breath-test was positive for ileal contamination and we started rifaximine without symptom’s resolution. Stool research of *Salmonella* species, *Campylobacter jejuni* and *Escherichia coli* was negative, while *Blastocystis hominis* were present. A treatment by metronidazole was not useful. Urine exam showed leucocytes and ossalates but no germs.

Electrocardiography showed electric voltage reduction in all derivations and alterations compatible with a past inferior myocardial infarction (Figure 1).

Thoracic radiography evidenced left ventricle’s enlargement as for pressure overload. Patient did not suffer from hypertension.

Upper gastrointestinal endoscopy showed atrophy of gastric glands, gastritis and chronic duodenitis; *Helicobacter pylori* was not found. Histological examination of biopsy specimen showed intestinal metaplasia in stomach and deposition of eosinophilic material in duodenogastric mucosa, submucosa and blood vessel walls. A sample of the deposit had an apple-green birefringence by Congo red stain under polarizing light.

These results suggested the diagnosis of amyloidosis. When we repeated history the patient confirmed mild myalgias, and paresthesias of tongue and big toes. Echocardiography showed reduced dimension and normal wall thickness of left ventricle (Figure 2), hyperechogenicity of anterior papillary muscle (Figure 3) and Doppler signal of initial restriction. This description was compatible with an initial form of amyloidotic cardiomyopathy.

Physical examination and familial history provided no evidence of hereditary, inflammatory, neoplastic disease and chronic respiratory infections. Serum amyloid A (SAA) and Ig, levels were normal. Laryngoscopy did not evidence vocal muscles’ alterations. A bone marrow fine-needle aspiration was performed: it excluded multiple myeloma because plasmacellular clone was less than 5% of total cells. Bence Jones protein (λ chains) was present in urine.

We concluded for a AL amyloidosis with gastrointestinal involvement and an initial form of amyloidotic restrictive cardiomyopathy.

![Figure 1](image-url)
Patient was treated with chemotherapy to reduce production of insoluble proteins.

We concluded that patient suffered from a secondary AL amyloidosis, with gastrointestinal and cardiology involvement.

Discussion

In this patient, clinical diagnosis has been difficult because symptoms were aspecific and mimed other more common diseases like Irritable Bowel Syndrome (IBS), gastropareisis, peptic ulcer, malabsorption.

Before oesophago-gastro-duodenoscopy, we had founded two conditions: ileal contamination and gut infestation by Blastocystis hominis. Our question was: are these able to explain chronic diarrhoea and weight loss? What about other symptoms and signs (such as dysphagia, dry mouth, xerophthalmia, chronic gastritis, cough after deglutition and upper airways recurrent infections; electrocardiographical alteration without hypertension)?

In differential diagnosis we considered Sjögren syndrome, psychosomatic condition or infiltrative systemic disease.

Dysphagia, dry mouth, xerophthalmia, upper airways recurrent infections, heartburn were compatible with Sjögren syndrome, but Shirmer test, SSA and SSB were founded negative twice and there was not superficial corneal disease. Two of European-American clinical criteria were satisfied, but Shirmer test was negative and autoantibody SSA SSB were not found. A xerophthalmia after 60 years old could be caused from ageing rather than Sjögren syndrome.

A psychosomatic condition could explain almost all symptoms (chronic diarrhoea, weight loss, dysgeusia, dysphagia, heartburn, palpitations, dyspepsia, anxious depressive state) and was supported by normality of inflammation parameters. Nevertheless there were three elements against this explanation: nightly diarrhoea occurred when patient stayed in hospital (in IBS the diarrhoea is only during the day); secondly, there were electrocardiographical abnormalities without evident explanation; thirdly, psychiatrist excluded this hypotesis.

The last possibility was an infiltrative disease. It can cause all symptoms (except for anxious depressive syndrome) and was supported by contemporory involvement of different organs and electrocardiographical abnormalities. We did not found a chronic inflammatory disease, evident myeloproliferative disorders or familial history of systemic syndrome, but histological examination of gastric biopsy was diriment.

Amyloidosis is not a single disease but includes different conditions. Every type of amyloidosis is characterised by an abnormal folding of a protein that is normally soluble. In all types of amyloidosis, proteoglycans and serum amyloid P protein interact with the amyloid fibrils or deposits and promote fibril formation and stability. Organ dysfunction results not only from disruption of tissue architecture by amyloid deposits but also from a direct cytotoxic effect given by amyloidogenic precursors or precursor aggregates.

The most common type of systemic amyloidosis is light-chain (AL) amyloidosis, having and incidence similar to that of chronic myelogenous leukemia and Hodgkin's lymphoma. The amyloidogenic protein in AL amyloidosis is an Ig light chain or a fragment of a light chain produced by a
clonal population of plasma cells in the bone marrow. About 10-15% of patients affected by AL amyloidosis have multiple myeloma. The kidneys and the heart are the organs most commonly affected in AL amyloidosis, although any tissue other than the brain could be involved. Kidney involvement usually presents as nephrotic syndrome with progressive worsening of renal function. About 10% of patients present amyloid deposition in renal vasculature or tubulointerstitium and consequently have renal dysfunction without significant proteinuria. Fibrilar deposition in the heart causes a restrictive cardiomyopathy that presents with a progressive heart failure. Hepatomegaly is common and can occur as a result of either congestion from right heart failure or amyloid infiltration of the liver. Since infiltration occurs in the sinusoids, hepatic amyloidosis is characterised by a profound elevation of alkaline phosphatase with only mild elevation of transaminases. Autonomic nervous system involvement leads to orthostatic hypotension, early satiety, erectile dysfunction and intestinal motility issues. The usual manifestation of peripheral nervous system involvement is a painful, bilateral, symmetric, distal sensory neuropathy that progresses to motor neuropathy. A soft tissue involvement can be observed in form of macroglossia, carpal tunnel syndrome, skin nodules, submandibular gland enlargement, pectoral purpura, hoarseness of voice. Macroglossia is a hallmark feature of AL amyloidosis but it is present in a minority of patients.

The diagnosis of amyloidosis should be considered in patients with unexplained symptoms simultaneously or sequentially developed, like proteinuria, cardiomyopathy, neuropathy, or hepatomegaly. In all cases certain diagnosis requires demonstration of amyloid deposits in tissues, highlighted by apple-green birefringence when stained with Congo red and viewed under polarizing microscopy. Tissue's samples (such as abdominal fat, minor salivary glands, gums, gut, rectum, skin) are taken by fine-needle aspiration or biopsy or surgery, depending on the most involved organ. Nevertheless abdominal fat is the most used because it is positive for amyloid deposits in about 70% of patients with amyloidosis. In case of AL amyloidosis, confirmation of AL disease requires demonstration of a plasma cell dyscrasia by a bone marrow biopsy or by the presence of a monoclonal light chain in the serum or urine. Immunofixation electrophoresis should be performed on the serum and urine because in AL amyloidosis the concentration of the monoclonal light chain often is too low to be detected by simple protein electrophoresis (in contrast to multiple myeloma). Recently serum free-light-chain (FLC) assay has been introduced: it is a nephelometric and quantitative immunooassay with a greater sensitivity for circulating free light chains than immunofixation electrophoresis. The FLC assay is useful both in diagnosis and in following disease progression or response to treatment. In case of AL amyloidosis, confirmation of AL disease requires demonstration of a plasma cell dyscrasia by a bone marrow biopsy or by the presence of a monoclonal light chain in the serum or urine that can be associated with AL amyloidosis (Waldenström’s macroglobulinemia, monoclonal gammopathy of uncertain significance [MGUS]). Because of the high incidence of MGUS in elderly individuals, further testing should be done to exclude familial or senile forms of amyloidosis, such as immunohistochemistry, immunofluorescence or immunogold electron microscopy of amyloid deposits to identify the amyloidogenic protein, or genetic testing to rule out familial forms of amyloidosis.

In this patient we excluded a multiple myeloma thanks to a bone marrow fine-needle aspiration (plasmacellular clone was less than 5% of total cells). The presence of Bence Jones protein-λ chains in urine gave the confirmation of AL disease.

In a recent review an in-depth analysis of gastrointestinal amyloidosis has been performed. Gastrointestinal involvement is common both in primary and secondary amyloidosis, while localized gastrointestinal amyloidosis is rare. We will deal about bowel involvement and gastrointestinal amyloidosis in singular amyloidoses.

In small bowel, vasculature is usually involved, with a high risk of ischemia and infarction of gut in case of narrowness and occlusion of the vessels. Moreover fibrils settle between muscle fibers and causes atrophy. Until massive deposits of amyloid destroy all mucosal structures, mucosal architecture usually remains normal. Nerves could be damaged by direct pressure of fibrils in some hereditary amyloidoses, causing neuropathy. The following symptoms have been described in patients affected by small intestine amyloidosis: infarction, mesenteric ischemia, hemorrhage, steatorrhea, diarrhea, protein loss, obstruction, perforation, intussusception, pneumatosis intestinalis, constipation and pseudoobstruction.

Malabsorption has been described in 8.5% and 23% of patients with AL and AA amyloidosis, respectively. The main causes are dismotility from autonomic neuropathy or enteric nervous system, ischemia, bacterial overgrowth, muscle infiltration, pancreatic insufficiency.
Diarrhoea could be determined by different situations: (1) a rapid transit; (2) an autonomic dysfunction; (3) steatorrhea secondary to biliar acid malabsorption (a consequence of bacterial overgrowth or rapid transit); (4) exocrine pancreatic insufficiency (due to ischemia from amyloid deposition in the arteries and arterioles or to infiltration of acinar tissue by amyloid). Diarrhoea usually does not respond to conventional therapies, while somatostatin analogues or enterostomy have been efficacy in case studies. As evidenced in literature, in our patient diarrhoea did not respond to conventional therapies, so we started a therapy with somatostatin. Gastrointestinal amyloidosis should be considered in patients presenting with diarrhoea, anorexia, and weight loss.

When amyloid fibrils infiltrate colon, amyloidosis must be differentiated from inflammatory bowel disease, ischemic colitis, malignant diseases and collagenopathies. Macroscopic aspect varies from polypous lesions to nodules, ulcerations, petechial lesions. Patient could have motility disorders or develop complications, such as pseudo-obstruction, acute obstructive symptoms, rectal bleeding, superficial hemorrhage and colonic dilatation.

In case of dialysis-associated amyloidosis (β2-microglobulin), fibrils deposit preferentially in deep tissues: biopsies should be normal while bowel resection are diagnostic. β2-microglobulin, the light chain of the class I major histocompatibility antigen, is a circulating protein impermeable to dialysis membranes. Clinical manifestations do not usually become evident until after 5 years of hemodialysis or peritoneal dialysis. β2-M amyloidosis usually presents with musculoskeletal manifestations and less commonly with visceral symptoms, such as intestinal necrosis, malabsorption, chronic diarrhoea, abdominal pain, visceral perforation, pseudoobstruction, gastric and colonic dilatation.

In ATTR, amyloid is found in muscularis mucosa and damages nerves, with an minor extension than this observed in AL and AA amyloidosis. A rare form of hereditary non-neuropathic amyloidosis is due to abnormalities in lysozyme. Gastrointestinal symptoms and hepatic hemorrhage have been reported in two families affected by lysozyme amyloidosis.

Different manifestations of gastrointestinal involvement have been described in secondary amyloidosis. In Waldenström macroglobulinemia gastrointestinal complications are unusual but often treatable. Chronic diarrhoea, protein-losing enteropathy and recurrent venous thromboses have been reported in a patient suffering from Waldenstrom macroglobulinemia without amyloid fibrils in small bowel biopsy. In a patient with multiple myeloma and secondary amyloidosis, oesophageal involvement expressed itself with recurrent bleeding as hematemesis. Endoscopy showed nodular lesions and ulcers in gastric antrum. Histological analysis of lesions evidenced amyloidosis.

Senile amyloidosis mainly involves the heart, but is also seen throughout the GI tract, mainly in the large and small bowel.

Local amyloidosis has been found in esophagus, stomach, small bowel and colon.

**Conclusion**

There is an important risk of misunderstanding and of diagnostic delay. In our patient a diagnosis of IBS was erroneously established for two years before admission in the hospital. Even if the clinical symptoms were not obvious two years before, the hypothesis of gastrointestinal amyloidosis should be considered among the possible diagnoses in patients with chronic diarrhoea and weight loss when other more common diseases have been excluded. When diagnosis of amyloidosis is established, the second step, guided by clinical symptoms, is to identify the type of amyloidosis and to research other site of fibril deposition.

**References**