Chronic Diarrhea Due to Intestinal Amyloidosis

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ABSTRACT

Amyloidosis is a rare disease, when diagnosed it's incurable and mostly affect over 40 years old male. Diagnostic is confirmed if histopathologic stained positive with Congo red and evidence of monoclonal protein. Survivals for untreated patients are 13 months in primary amyloidosis but if secondary to other chronic disease and systemic, survival could be 3-4 years. It can not be prevented but when affected, control of the underlying illness can prevent progression of amyloidosis.

We report a rare case of a 67 year old male, who came with chronic diarrhea. The stool analysis, there were no negative gram microorganisme found, only food maldigestion and fungus infection. Stool analyze from parasitology department were found microspore, but the stool culture were sterile. The patient underwent colonoscopy which revealed hyperemis mucosa in rectum, sigmoid, descending & transverse colon. From the biopsy was concluded intestinal amyloidosis. We treated the patient symptomatically and couldn't find the underlying inflammatory disease which causes the problem.

Keywords: *secondary amyloidosis, chronic diarrhea, malabsorption, colonoscopy, protein electrophoresis*

INTRODUCTION

Chronic diarrhea or signs of malabsorption are commonly encountered by general internists and gastroenterologists. A malabsorption syndrome may be associated with several diseases including infection and systemic diseases. Systemic amyloidosis, however, is often overlooked in the differential diagnosis of malabsorption.[1] Amyloidosis is a series of diseases in which there is extracellular deposition of a protein which folds into an insoluble â pleated sheet.[2-9] Primary amyloidosis is a monoclonal plasma cell disorder with an incidence of approximately 8 per million per year, its subtypes are classified according to the composition of the amyloid subunit protein.[1,3-5] This disease has a male preponderance of 60% to 65% and affects 99% patients older than 40 years of age.[3] Secondary systemic amyloidosis is a disorder in which insoluble protein fibers become deposited in tissues and organs impairing their function. It is found in association with chronic infection or chronic inflammatory disease.[4,5,6,7]

Fatigue and weight loss are the most common presenting symptoms. Light headedness due to autonomic neuropathy and or orthostatic hypotension is also common. Other symptoms like easy bruising, rapid onset of breathlessness, peripheral oedema, sensory change (including carpal tunnel syndrome) or postural hypotension should arouse suspicion of the disease.[2-5] Change in bowel habits like constipation, chronic diarrhea, steatorrhea, abdominal pain, distension, peritonitis, spontaneous gut perforation, anorexia even obstruction may occur in gastrointestinal amyloidosis. This could be due to direct mucosal infiltration, intestinal ischemia or from dysmotility caused by autonomic failure.[1-5]

From the physical examination there may be found purpura above the nipple line, webbing of neck, face and eyelids, macroglossia, submandibular lymphadenopathy, hepatomegaly, muscle atrophy, edema and signs of congestive heart failure if the heart is involved.[1-3]

Laboratory findings may reveal anemia, elevated sedimentation rate, proteinuria (could be in nephrotic range) with or without renal dysfunction, hypoalbuminemia, prolonged prothrombin time or other acquired coagulation abnormalities, pseudoinfartion on the electrocardiogram, restrictive hemodynamics on the echocardiogram. The most important measure to distinguish primary to secondary amyloidosis is protein electrophoresis with immunofixation which can be withdrawn from the serum or urine. Bone marrow aspiration and biopsy or fat aspiration could be performed if needed.[1-5] When negative, findings for underlying illness related to it should be investigated. Colonoscopy commonly reveals mucosal friability and erosions.[3,4,8] Hystologic evidence stained with Congo red (sensitivity of 90%) will demonstrate an apple-green birefringence under polarizing light.[1,3-9] This confirms the diagnosis but not the subtype.[2]

Prognosis depends on the specific type of amyloidosis and the organs involved.[2,3-5] The cause of death in most patients is cardiac and kidney related disease.[3,4] Hayman et al reported weight loss and low hemoglobin concentration as worse prognostic indicator on gastrointestinal amyloidosis.[1]

Management should remain supportive, diarrhea may be managed with agents as loperamide and ocreotide.[1,9] Treatment with alkylating agent-based chemotherapy, such as melphalan and prednisone may extend the median survival rate from 1 year to 90 months in primary amyloidosis.[2,3] But for secondary amyloidosis, aggressive control of the underlying cause can prevent progression of amyloidosis.[4,7,9]

CASE REPORT

A 67 years old male, admitted to our hospital with complaint of diarrhea since 2 weeks before admission. He defecated 10 times a day, liquid stool, with yellowish color of stool, no blood, but sometimes contained mucus, his abdomen were bloated and cramped, too. He feltfeverish, and after self medication his diarrhea continued, aggravated with decrease of appetite, decreased body weight he felt so weak and the family took him to the hospital. The patient was a smoker for 37 years, but quit smoking since he knew he had coronary arterial disease. He had hypertension since 13 years ago, but after he was told he had coronary disease since 8 years ago, he controlled regularly to the cardiology outpatient department. Three years ago he had abdominal pain and dyspepsia and made him to undergo esofagogastroduodenoscopy and were told he had erosive gastritis, which changed his medication from aspilet to ascardia and had omeprazole added. About 2 years ago, he underwent coronary angio by pass graft (CABG). After his cardiac condition were improved, he got additional drug since then, simvastatin, which was stopped 1 month ago. He had history of stroke too, about 1 year ago. His physical examination on admission revealed no special remarks. He was fully alert, but had body mass index of 14,7 his blood pressure were 100/60 mmHg and other vital sign and physical examination were normal, included no webbed neck, macroglossia, lymphadenopathy, organomegaly nor purpura or other skin abnormalities.

The patients were given antidiarrheal agents, intravenous fluid besides enteral nutrition and non-specific antibiotic on admission. On the second day of admission he had melena, which stopped on the 8th day of hospitalization, but after that he still complaint of diarrhea. The patient underwent esofago gastroduodenoscopy and the result was grade C esophagitis, erosive pangastritis with atrophic gastropathy, which explained the cause of melena. The result of biopsy taken from esophagus was in concordance of Barrett's esophagus. He was given proton pump inhibitor and sucralfat, and we planned to evaluate this problem after 6 months of therapy. His ECG revealed poor R on V1-V3, inverted T on lead V4-V6, I, aVL. His Echocardiography revealed consentric left ventricular hypertrophy, with good systolic function, 61% ejection fraction and mild diastolic dysfunction.

From his stool analysis, there were no negative gram microorganism found, only food maldigestion and fungus infection. Stool analyze from parasitology department were found microspore, but the stool culture were sterile. Antifungal were given and antibiotics were stop. The patient underwent colonoscopy which revealed hyperemis mucosa in rectum, sigmoid, descending and transverse colon. With differential diagnosis of infective colitis, ulcerative colitis.

From the biopsy of the ileum, ascending colon and rectosigmoid were found the same microscopic abnormalities which concluded: intestinal amyloidosis. No signs of malignancy. Protein electrophoresis was taken after that and the results were normal.

DISCUSSION

This 67 years old male patient, came with chronic diarrhea, which according to the stool analysis was due to food maldigestion and opportunistic infection caused by fungi. Colonoscopy revealed infective colitis with differential diagnosis of ulcerative colitis, with hystologic result of amyloidosis. This can explain the chronic diarrhea due to malabsorption. Mechanism of malabsorption in patients with intestinal amyloidosis according to the literature, include autonomic neuropathy, myopathy and dysmotility that lead to

Figure 1. Histologic appearance showed chronic inflammation cells with amorf eosinophilic mass in lamina propria, with capillers circulating the eosinophillic mass (see arrow)

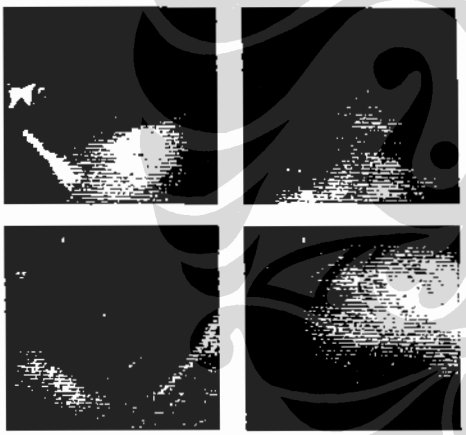

Figure 2. Colonoscopy showed hyperemis mucosa in rectum, sigmoid, descending and transverse colon

bacterial and or fungal overgrowth, vascular invasion, mucosal injury and ischemia.[9] Hayman et al stated that malabsorption occurs in less than 5% of patients with systemic amyloidosis with symptoms of diarrhea, steatorrhea, anorexia, dizziness, orthostatis, nausea or abdominal pain.[1]

The patient's age and sex were in accordance with primary amyloidosis, which is of male preponderance (60% to 65%) and affects 99% patients older than 40 years of age. The histologic result revealed amyloidosis, but the protein electrophoresis could not show any abnormal monoclonal immunoglobulin light chains, so amyloidosis in this patient is likely to be secondary cause and primary amyloidosis can be excluded. Besides, there were no symptoms and signs of above the nipple line purpura, webbed neck, macroglossia, submandibular lymphadenopathy, hepatomegaly, muscle atrophy nor edema. There were no signs of congestive heart failure, even the patient has coronary arterial disease and has history of coronary angio by pass graft. Anemia with hemoglobin of 10.2 g/dl and loss of body weight according to the literature are bad prognostic factor for gastrointestinal amyloidosis.[1]

Amyloidosis were based on histological result, not made with Congo Red stain, because there were no facility of polarization microscope with birefringence lens at that time which was needed to read the result and is the golden standard. Yet the histological pattern appeared no doubt of amyloidosis (see figure 1).

In both primary and secondary amyloidosis, the most commonly involved organ system is the gastrointestinal system, with the colon being the most frequently involved organ.[8] This suits the case, where the colonoscopy was found colitis. Other part of the gastrointestinal system which also can be affected is the esophagus, where the muscular and Auerbach plexus can be infiltrated with amyloid. The lower esophageal sphincter's tone will decrease, peristalsis impaired and cause gastroesophageal reflux.[1,8,10] This patient has abdominal pain and dyspepsia and underwent esofagogastroduodenoscopy with result of grade C esophagitis, erosive pangastritis with atrophic gastropathy. The histopathologic result showed Barrett's esophagus, which in this case were associated with chronic gastroesophageal reflux possibly due to involvement of amyloidosis in the esophagus, too. Other part of the gastrointestinal system such as gastric involvement usually manifest as gastric outlet obstruction, ulceration and bleeding with endoscopic abnormalities revealing loss of rugae or nodularity, which in this case only the bleeding happened and there were no nodularity or rugae loss so involvement of gastric amyloidosis is not proven.

Melena in this case was due to erosive pangastritis in associated with anatomic mucosal defects, due to prolonged use of NSAID and probably stressed ulcer, but still amyloidosis can aggravate this condition. Gastrointestinal bleeding related to amyloid is difficult to control, because of blood vessel fragility and mucosal stiffness, and if compounded by underlying coagulation abnormalities (such as thrombocytopenia, increased fibrinolytic activity, factor X deficiency, etc) it would be more massive.[10] In this case the platelet count was still normal, and the bleeding time, clotting time and prothrombine time were also normal and the bleeding were not massive but took six days before completely stopped.

Amyloidosis in this patient is supposed to be secondary, but until discharged from the hospital there

were no indication of inflammatory disease as primary cause. He has no multiple myeloma, rheumatoid arthritis, tuberculosis, systemic lupus erythomatosus, hairy cellleukemia, cystic fibrosis, ankylosing spondilitis, or other autoimmune or inflammatory disorder. Zhouli et al report one case with primary cause of hepatitis B, we couldn't check for serolomarker of hepatitis B in this case because of financial limitation.[12]

Secondary amyloidosis if happened can not be prevented and there is no specific treatment for the amyloid. The pathogenesis of amyloidosis is unknown and therefore no specific management is available at present. The treatment of amyloidosis aims at reducing the stimuli from chronic inflammation, inhibiting the production and deposition of amyloid protein and promoting the lysis of amyloid protein. Some chemotherapeutic drugs such as melphalan, prednisone and colchilcine are effective in primary amyloidosis. In secondary amyloidosis the treatment is towards management of underlying condition to prevent progression of amyloidosis. Aim of treatment is to control the underlying disease and the symptoms, which in this case is diarrhea and melena. We used antifungal (sporadic) as well as antibiotics (cefotaxime) to control the bacterial overgrowth and fungal infection We gave antidiarrheal agent (loperamide) and active charcoal with intravenous fluid to maintain balanced fluid. Although no randomized data are available, acid suppression therapy with proton pump inhibitors is reasonable, eventhough one series report that proton pump inhibitor does not prevent bleeding recurrence.[1,11] Sucralfate is to protect the gastric mucosa and domperidone is given due to dysmotility. Other supportive care was to give adequate nutrition and calories. Unfortunately the underlying disease in this case remains obscured.

CONCLUSION

The clinical manifestations of amyloidosis that caused by amyloid deposition could be various, which can make misleading diagnosis for many years after the onset of symptom. Primary or secondary amyloidosis should always be considered in malabsorptive chronic diarrhea, especially in over 40 years old male patients.

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