Intractable Diarrhea Due to Secondary Gastrointestinal Amyloidosis in a Patient with History of Leprosy

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ABSTRACT

Amyloidosis is not a single disease but a term for diseases that share a common feature: the extracellular deposition of pathologic insoluble fibrillar proteins in organs and tissues. 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.

A 30 years-old male, complained of diarrhea since 4 months prior to admission. The colonoscopy examination revealed pancolitis, ileitis, and the result from histopathological examination showed chronic destructive ileocolitis with 40-70% amyloidosis of mucosa.

The abdominal ultrasonography showed chronic cholecystitis, multiple cholelithiasis and minimally ascites. The esophagogastroduodenoscopy revealed candida esophagitis, erosive pangastritis grade V, pyloring gapping, erosive duodenitis, bile reflux gastritis and esophagitis, and the result from histopathological examination showed amyloidosis on gastric mucosa.The immunofixation electrophoresis was negative for monoclonal light chains, and the serum protein electrophoresis showed normal pattern. Enteral and parenteral nutritional therapy were given. Secondary infection was treated by antibiotics. Complication and organ failure occured lately. This chalenging case demonstrated complicated management of gastrointestinal amyloidosis

Keywords: *gastrointestinal amyloidosis, intractable diarrhea, leprosy*

INTRODUCTION

Amyloidosis is not a single disease but a term for diseases that share a common feature: the extra cellular deposition of pathologic insoluble fibrillar proteins in organs and tissues.[1,2,3,4] In the mid-19th century, Virchow adopted the botanical term "amyloid," meaning starch or cellulose, to describe abnormal extra cellular material seen in the liver at autopsy.[1,2,3]

The amyloidosis are classified according to the identity of the fibril-forming protein. Systemic amyloidoses are neoplastic, inflammatory, genetic, or iatrogenic in origin, while localized amyloidosis or organ-limited amyloidoses are associated with aging and diabetes and occur in isolated organs without evidence of systemic involvement.[2]

The two major types of systemic amyloidosis are AL (primary amyloidosis or myeloma-associated amyloidosis) and AA (secondary or reactive amyloid). The former is due to deposition of N-terminus fragments of immunoglobulin kappa or lambda light chains, and the latter is associated with the acute phase reactant Serum Amyloid A (SAA) as the precursor of the amyloidogenic protein.[3]

Systemic amyloidosis is generally progressive and fatal, however the natural history remains poorly understood, partly due to the lack of clinical recognition until the process is advanced. Amyloidosis is not restricted to any age or gender group. Clinical presentation depends on the distribution and the amount of amyloid deposited, but symptoms may be protean

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and generally nonspecific. Well-known signs and symptoms of systemic involvement include macroglossia, nephrotic syndrome, renal failure, carpal tunnel syndrome, sensory motor or autonomic neuropathy, cardiac failure or arrhythmia, hepato-splenomegaly, diarrhea, malabsorption, ulcerations, lymphadenopathy, clotting factor deficiencies, capillary fragility, and abnormalities of platelet aggregation.[3]

The reported incidence of systemic AL amyloidosis is one case/100,000 person years in Western countries. Renal dialysis-related amyloid and amyloid in brain tissue, which is related to the 12 million patients with Alzheimer's disease, are worldwide. On the contrary, AA amyloidosis, related to familial Mediterranean fever, is associated with certain ethnic groups: Sephardic Jews (37%) and Armenians living in Armenia (24%), and less frequently in Ashkenazi Jews, Turks, and Arabs (8% to 12%). AA amyloidosis reportedly affects 17% of patients suffering from tuberculosis and leprosy and 0.5% to 13% of patients with ankylosing spondylitis, rheumatoid arthritis, and Crohn's disease.[3]

CASE ILLUSTRATION

A 30-years-old male, with diarrhea since 4 months ago, was admitted to Cipto Mangunkusumo hospital at November 2nd 2006. The patient had chronic watery, non-bloody diarrhea about 5-6 times a day, the frequency increased when he got more meals. He had periumbilical cramps, nausea and vomiting, but no fever. The patient had also anorexia, malaise, weight loss of 20 kg in 4 months He had no palpitation. The patient had leprosy at six years ago, was admitted to Sitanala hospital and had been treated. He got remission nine months ago. Since last year, he got tumor in his neck, painless, and there was no dysphagia. He smoked sometimes. There was no history of free sex or drug abuse (IVDU). He had no history of jaundice.

On physical examination, he looked moderately ill, compos mentis, blood pressure 100/70 mmHg, pulse rate 88 times/minute, respiratory rate 24 times/minute, body temperature 36.5˚C, nutritional status: worse, conjunctivas were pale and scleras were not icteric, there were no oral thrush, thyroid gland palpable, diffuse, painless, heart and lung were normal, the abdomen was flat, supel, tenderness on abdomen, the liver and spleen were not palpable. There were no extremities oedema.

Laboratory examination showed Hb 7.5 g/dL, white blood cells count 5,600/µL, platelet count 217,000/µL, ureum 38 mg/dL, creatinine 1.1 mg/dL, AST 12 µ/L, ALT 16 µ/L, sodium 136 meq/L, potassium 1.8 meq/L, chloride 106 meq/L. Blood gas examination revealed pH 7.36, pCO_2 20.40 mmHg, pO_2 127.90 mmHg, HCO_3 11.60 mmol/L, O_2 saturation 98.50%, and the electrolytes after correction with KCl 50 meq in NaCl 500 ml/12 hours were sodium 133 meq/L, potassium 3.03 meq/L, chloride 102 meq/L, blood chemistry cholinesterase 1,402 U/L, total protein 4.1 g/dL, albumin level 2 g/dL, globulin level 2.10 g/dL, Fe (SI) 4 µg/dL, TIBC 115 µg/dL, transferrin saturation 12.17%, ferritin 512.4 ng/ml, TSHs 14.5 ì IU/mL, free T4 0.530 ng/dL. From the stool examination showed greenish, watery stool, there were no blood, many white blood cells, red blood cells 5-6, yeast cell positive. Electrocardiogram showed sinus rhytm, QRS rate 100 times/minute, normoaxis, no ST changes, T inverted in lead II, III, aVF, and poor R in lead V3-V4. The chest X-ray showed no infiltrate and normal figure.

From the preliminary data, the problem were chronic diarrhea with low food intake, anemia microcytic hypocrome, electrolyte imbalance, history of leprosy, diffuse thyroid enlargement, and inferior coronary arterial disease.

The initial treatments for this pasient were rehydration with parenteral fluid normal saline infusion 500 ml/6 hours, high calory and high protein diet of 1,700 kkal, ranitidin 1 ampule twice daily, intravenous ceftriaxone 1 g twice daily, New Diatab 2 tablets three times daily, packed red cells transfusion untill the haemoglobine level reach 10 g/dL, corrected the potassium level with potassium chloride 50 mEq in normal saline of 500 ml/12 hours, and gave potassium suplementation tablet KSR twice daily. The patient was also given the tablet Ascardia 80 mg once daily and oxygen therapy 3 liter/minute with nasal canule.

After a couple of days, the evaluation from this patient's electrocardiogram showed sinus rhytm, QRS rate 80 times/minute, normoaxis, there were no ST and T changes, no LVH and RVH. It showed normal pattern in his electrocardiogram. The pattern of inferior coronary arterial disease on the first electrocardiogram might be due to hypoxemia in this patient.

The colonoscopy examination indicated internal hemorrhoid grade II, pancolitis, ileitis, and the result from histopathological examination showed chronic destructive ileocolitis with 40-70% amyloidosis of mucosa. The screening for HIV was examined and the result showed non reactive. The CD 4 count was 749 (44%).

The abdominal ultrasonography showed chronic cholecystitis, multiple cholelithiasis and minimally ascites. The esophagogastroduodenoscopy indicated candida esophagitis, erosive pangastritis grade V, pyloring gapping, erosive duodenitis, bile reflux

gastritis and esophagitis, and the result from histopathological examination showed amyloidosis on gastric mucosa. The immunofixation electrophoresis was negative for monoclonal light chains, and the serum protein electrophoresis showed normal pattern.

During hospitalization, the patient's condition was not stable. He was treated every day with partial parenteral nutrition and all antidiarrheal drugs, but it was not successful to terminate diarrhea. The patient had severe protein losing enteropathy and sustained watery diarrhea. The patient had been monitored for the possible infectious complications to the intractable diarrhea. Some examinations of his stool showed microsporidia and also yeast cells.

Then, the problems in this patient were gastrointestinal amyloidosis with intractable diarrhea, malnutrition with hypoalbuminemia and electrolyte imbalance, hypothyroidism with diffuse thyroid enlargement as the clinical appearance, and also pancytopenia during hospitalization.

It had been evaluated that high calory and high protein nutrition was not suitable for this patient because gastrointestinal amyloidosis gave symptoms such as malabsorption, chronic dismotility and protein-losing enteropathy. It had been tried to give simple formation of nutrition for this patient and also parenteral nutrition such as Triofusin 500, KaEN 3B, amino acid infusion, and multivitamin. The supportive therapies were also given to this patient such as antidiarrheal drugs attapulgite (New Diatab®), loperamide hydrochloride (Imodium®), metoclopropamide injection, pancreatin 50 mg, papain 10 mg, ox bile 50 mg, curcuma rhizoma 35 mg and liver extract 50 mg with vitamin and minerals in one tablet (Vitazym®), Smecta® 1 sachet three times daily, lactobacillus (Lacbon®), Oralyte® sachets, mesalazine (Salofalk®) 500 mg, sucralfate C1 three times daily, L-thyroxine Na (Thyrax®) 1/2 tablet twice daily, potassium suplementation KSR 1 tablet twice daily, codein 20 mg three times daily, albendazole 400 mg twice daily to treat the secondary infection.

This patient had been consulted to the consultant of gastroenterology division for the further treatment. Finally, the prognose of this patient was not good, and the aim of the treatment was just palliative treatment because there were still limited researches about the treatment of amyloidosis. It had been considered to give steroid to this patient, but the patient had been complicated by secondary fungal infections to his gastrointestinal tract.

It had been planned to give intravenous metilprednisolone 62.5 mg twice daily to this patient but it was considered to treat fungal infection first as the secondary infection before giving the steroid.

The evaluation for chronic infection had been established. C-reactive protein was examined and it showed high value on the first laboratory result, it was 30.4 mg/L. This value increased higher on the next evaluation, it was 161.3 mg/L. This patient had been consulted to dermatology department to asses the possibility of active chronic leprosy infection. The assesment from his clinical appearance showed n fiinactive infection and it was concluded that this patient had recovered from leprosy. Skin biopsy had also been planned in this patient to ensure whether the infection had been inactive. But unfortunately, it had been cancelled due to his severe condition.

During the hospitalization, this patient got hypotension, his body weight lost about 1-2 kg every week though his calories had been added through enteral and parenteral nutrition. We had also tried to correct hypoalbuminemia, electrolite imbalance, and anemia. We had frequently given serum albumin infusion, potassium chloride infusion, and packed red cellstransfusion.

The last laboratorium test indicated pancytopenia and also bilirubin level increased in this patient. At the end of hospitalization, it became more difficult to treat the problem of weight loss and electrolyte imbalance. It had been considered to use central venous access as parenteral nutritional access in this patient, but it had been cancelled due to the problem trombocytopenia.

The fungal infection in this patient became a systemic infection due to immunocompromized condition. We had tried to give antifungal medication fluconazole 50 mg twice daily and antibiotic ceftriaxone 2 g once daily for non specific bacterial infection. But these medications could not be optimized because of financial problem.

Finally, we had difficulties to handle the systemic infection problem in this patient. Beside, the general condition of this patient became worse. The antibiotics and also antifungal could not work optimally because of malnutrition and hypoalbuminemia. This patient finally died due to septicemia.

DISCUSSION

This case is a rare demonstration case of amyloidosis with problem in management. This patient manifested severe diarrhea unresponsive to conventional treatment, hypoproteinemia, and protein leakage. In this patient, biopsied tissues from the upper and lower gastrointestinal tract showed extensive deposition of amyloid. Amyloidosis is a unique metabolic storage disease that results from deposition of insoluble fibrillar proteins or aberrantly folded and assembled protein fragments in a variety of tissues. Classifications have grown from the simple notion of

primary and secondary amyloidosis, based on the broad concepts of association with myeloma (primary) or chronic illnesses (secondary), or concepts of "systemic" or "localized" to current designations that reflect the precursor protein. Treatment considerations and prognosis depend on such identification.[3]

The presence of disease in more than one organ system should increase the index of suspicion of a systemic amyloidosis as the unifying diagnosis. The pathological diagnosis of amyloidosis is established by the identification of fibrillar tissue deposits. We suspected this patient had a systemic amyloidosis though only gastrointestinal tract had been biopsied to establish the diagnosis amyloidosis. We suspected other organs also clinically affected such as thyroid gland, adrenal gland because there were some clinical symptoms such as hypothyroidism, hypotension (the blood pressure of this patient always around 80/50 mmHg), hyponatremia, hypokalemia, weakness, anorexia, nausea, and vomiting. However, these organs had not been biopsied due to some considerations such as social condition and comfort for the patient.

Systemic amyloidosis is generally progressive and fatal; however, the natural history remains poorly understood, partly due to the lack of clinical recognition until the process is advanced. Amyloidosis is not restricted to any age or gender group. Clinical presentation depends on the distribution and the amount of amyloid deposited, but symptoms may be protean and generally, nonspecific. Well-known signs and symptoms of systemic involvement include macroglossia, nephrotic syndrome, renal failure, carpal tunnel syndrome, sensory motor or autonomic neuropathy, cardiac failure or arrhythmia, hepato-splenomegaly, diarrhea, malabsorption, ulcerations, lymphadenopathy, clotting factor deficiencies, capillary fragility, and abnormalities of platelet aggregation.[3]

AL amyloidosis should be ruled in or out promptly because it is the most common type of systemic amyloidosis, can progress rapidly, and has a poor prognosis if untreated.[5] Since AL amyloidosis is the most common type, a search for clonal plasma-cell dyscrasia is the first step. Most commonly, AL (primary) amyloidosis occurs in the setting of plasma cell or B cell dyscrasias or monoclonal gammopathies; amyloidosis may proceed clinically overt multiple myeloma. In up to 15% of cases, no apparent underlying cause is found. Involvement of the gastrointestinal tract in AL amyloidosis (7%) may cause life-threatening hemorrhage. The prognosis of AL amyloidosis is poor: 12 to 15 months or less if associated with multiple myeloma, liver involvement (9%) does not impact this low survival rate.[3]

The presence of a monoclonal serum protein alone is not diagnostic of amyloidosis; however, when it is present in a patient with biopsy-proven amyloidosis, the AL type should be suspected.[5] Monoclonal immunoglobulins or light chains are detected in 90% of patients with AL amyloidosis by means of immunofixation electrophoresis of serum or urine a more sensitive technique than simple protein electrophoresis.[3] The immunofixation electrophoresis in this patient was negative for monoclonal gammopathy. This evidence guided us to other types of amyloidosis beside AL.

If there is no evidence of a plasma-cell dyscrasia, consideration should be given to another form of amyloidosis. Although a family history of amyloidosis or unexplained progressive neuropathy strongly suggests familial ATTR amyloidosis, a variant transthyretin should be sought in all patients who do not have a plasma-cell dyscrasia. Transthyretin can be identified by isoelectric focusing of the serum, which will separate variant and wild type transthyretin. The finding of a variant transthyretin should prompt specific genetic testing to identify the site of the mutation. It is important to verify that the patient has a plasma-cell dyscrasia before aggressive treatment is undertaken. If none can be detected, however, AL amyloidosis may still be present and should be suspected if the patient has macroglossia with the involvement of other, typical organ systems and no variant transthyretin in the serum.[3,5,6] The pattern of serum electrophoresis in this patient was normal.

AA (secondary) amyloidosis was strongly suspected in this patient because he had the underlying infectious condition, leprosy. AA (secondary) amyloidosis occurs in the setting of chronic inflammatory or infectious conditions; the most common of the former are rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. Malaria, leprosy, and tuberculosis are chronic infections that may be associated with AA amyloidosis. AA amyloidosis may also occur in association with Hodgkin's disease, and gastrointestinal (GI) or genitourinary (GU) malignancies. The precursor proteins include liver-derived acute phase reactant serum amyloid A (SAA) lipoproteins. The prognosis of AA amyloidosis is reported as 50% 5-year survival and 25% 15-year survival; however, hepatic involvement in AA amyloidosis is a late manifestation and in contrast with AL amyloidosis is associated with a significantly reduced survival rate.[3,5] Unfortunately, the identification of an AA amyloid deposit by immunohistochemical staining with permanganate sensitivity had non been done yet.

The prevalence of clinically apparent gastro-intestinal involvement varies considerably, depending on the type of amyloidosis. Gastrointestinal disease was reported in up to 60% of patients with AA amyloidosis secondary to rheumatoid arthritis. By contrast,

gastrointestinal manifestations appear to be less common in patients with AL amyloidosis. In a large series of 769 patients with primary amyloidosis, only 8% had biopsy proven gastrointestinal involvement, leading to symptoms in only 8 patients. Among these symptoms, bleeding events were less prevalent compared with other symptoms, such as malabsorption, chronic dysmotility, or protein-losing enteropathy. However, cases of severe and sometimes lifethreatening bleeding events were reported not only in patients with AA amyloidosis, but also in those with AL amyloidosis, which may reflect unique patho-physiological mechanisms.[7]

Furthermore, some cases showed possible causes of induction of intractable diarrhea (operation, infection or extraarticular manifestation). SAA, which is the precursor of amyloid a protein, is known to be synthesized in the liver and the process is stimulated by macrophage derived cytokines such as interleukin 1, interleukin 6 or tumor necrosis factor, thus it rapidly increases in blood at the time of acute inflammation in parallel with acute phase proteins such as C reactive protein. It is considered that high activity of arthritis, infection; surgery and extraarticular manifestation of RA induce a rapid increase of SAA and promote the deposit of amyloid, which might contribute to the onset of intractable diarrhea. With regard to renal function, most patients had normal values of creatine. Even in one patient who had increased concentrations of creatinine at the time of the onset of intractable diarrhea, those values returned to normal after recovery from dehydration. It is generally assumed that intractable diarrhea tends to manifest earlier than renal dysfunction. In fact, in 15 cases (63%) the opportunity to diagnose amyloidosis was the onset of intractable diarrhea. Other opportunities to diagnose amyloidosis were at the time of the endoscopic upper gastrointestinal screening of amyloidosis and the onset of other digestive symptoms. There was no case of nephropathy such as renal failure or massive proteinuria before the onset of intractable diarrhea. With regard to clinical symptoms, abdominal pain, nausea and vomiting were seen in almost all cases. Abdominal distension with decreased bowel sounds on auscultation was recognised in about two thirds of the cases, which suggested the impaired peristalsis resulted from amyloid deposit, a characteristic finding of gastrointestinal amyloidosis. During the course of diarrhea, all cases showed severe hypoproteinaemia and hypoalbuminaemia. These results suggested malabsorption or protein loss. Moreover, highly increased values of C reactive protein during the clinical course were pathognomonic of intractable diarrhea. The increased value of C reactive protein is assumed to be caused by severe intestinal inflammation. In addition, we speculate that ischemia of the intestinal mucosa and gastrointestinal infection is the causes of intestinal inflammation. With regard to infection, no causative bacteria such as *Shigella*, *Salmonella*, *Vibrio* or enteropathogenic *Escherichia coli* were detected in faces culture. Thus, it cannot be denied that change or increase of some kind of intestinal bacterial flora or viral infection may have triggered the gastrointestinal inflammation. From these clinical symptoms and abnormal laboratory data, the impaired motility and inflammation of the intestine are assumed to be important pathogenic factors of intractable diarrhea. It is probable that amyloid infiltration of the intestinal smooth muscle or gastrointestinal neuropathy with amyloid involvement of the autonomic nerves caused impaired motility of the intestines.[8,9]

At present, the most effective approach to the treatment of the systemic amyloidoses involves shutting down or substantially reducing the synthesis of the amyloid precursor. In reactive amyloidosis (AA), control of the underlying inflammatory disorders can result in regression of the disease.[10]

Supportive treatment for all forms of amyloidosis is an important adjunct to major antiamyloidogenic treatment. It can enhance the effectiveness of major treatments and improve the quality of life for all patients. Autonomic neuropathy may be clinically manifested as severe orthostatic hypotension or gastrointestinal dysfunction. Metoclopropamide may be helpful to increase gastric motility. Intestinal motility dysfunction may cause constipation, diarrhea, or alternating symptoms of both. Diarrhea may respond to limiting fat in the diet ($\leq$ 40 g), medium-chain triglyceride oil supplements, medications to decrease bowel motility (loperamide), or to increase bowel contents psyllium hydrophilic muciloid. Some patients with gastrointestinal dysfunction may benefit from oral nutritional supplementation, but some may require parenteral nutritional support to avoid malnutrition.[5] We had tried to give optimal supportive treatment to this patient. We tried to give simple form of oral nutritional supplementation and partial parenteral nutrition. Finally, we considered giving total parenteral nutrition through central venous access, but unfortunately the condition of this patient became worse and it was impossible to do more invasive action.

At present, the major therapeutic strategy is treatment of the primary inflammatory disease in order to reduce the circulating levels of the amyloid precursor protein SAA. Intensive treatment that lowers SAA levels to less than 10 mg/L may halt disease progression and induce a slow progressive recovery of renal function. Accounts exist of the disappearance of the amyloid deposits associated

with tuberculosis or chronically infected burns with appropriate treatment of the infection. Similarly, case reports exist of the disappearance of amyloid deposition associated with chronic inflammatory bowel disease after resection of the affected section of bowel.[10]

The following are new approaches to the treatment of AA amyloidosis that are currently undergoing clinical trials:[11]

- A low–molecular-weight sulfonated molecule has been developed that interferes with fibril formation and deposition of amyloid by inhibiting interaction of SAA with glycosaminoglycans. In experimentally induced murine AA amyloidosis, this drug (NC-503) has been shown to reduce the amount of amyloid deposits.[12]
- Dimerization of human SAP molecules in vivo with a palindromic compound (CPHPC) triggers very rapid clearance of the complexed protein by the liver, depleting SAP from the circulation within a few hours of drug administration.
- Anti–IL-6R therapy appears promising for the treatment of AA amyloidosis.
- A case report exists of severe protein-losing enteropathy with intractable diarrhea due to systemic AA successfully treated with corticosteroids and octreotide.[13]
- A single patient with AA amyloidosis secondary to Hodgkin disease was administered 4'-iodo-4'deoxydoxorubicin as antitumor therapy, this patient has been reported to show a reduction in proteinuria and the liver amyloid burden on biopsy. The response was not complete and the resolution on liver biopsy may have been the result of sampling differentially infiltrated portions of tissue; nonetheless, the result is potentially exciting.
- A more experimentally and theoretically based approach uses the observation that anionic sulphonates interfere with the deposition of AA fibrils in a murine model of inflammatory amyloidosis. One of these compounds is in clinical trials, the results of which should be available over the next 2 years. Little or no toxicity was shown in the preclinical testing.

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