Megaduodenum : an unusual presentation of amyloidosis ?

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Abstract

Amyloidosis, a potentially fatal disease, is characterized by an abnormal deposition of autologous proteins. Heart, liver, kidneys, lung, thyroid, skin and the gastrointestinal tract can be involved ; in this last case mucosal alterations or disturbances of the motility leading to pseudo-obstruction, bleeding, diarrhea and malabsorption can be present. However, the data concerning the possible gastrointestinal presentations of amyloidosis are scanty and heterogeneous.

We report the case of a patient presenting severe gastrointestinal symptoms caused by a megaduodenum. The patient was thoroughly investigated and lesions appeared limited to the upper gastrointestinal tract in the absence of a systemic disorder. However, at follow up the patient developed cardiac dilatation and bioptic samples revealed the presence of amyloidosis. (Acta gastroenterol. belg., **2010**, 73, **287-291**).

Key words : amyloidosis, endoscopy, megaduodenum, neuroendocrine cells.

Introduction

Amyloidosis is a potentially fatal disease characterized by extracellular deposits of abnormal proteins. These proteins are heterogeneous (monoclonal immunoglobulin light chains, β2-microglobulin, apolipoproteins), but the final structure and morphology of the deposits are similar, characterized by a core of antiparallel β strands lying perpendicular to the long axis of the fibrils. They are similarly identified through a polarized light microscope, after staining with Congo red on the basis of an apple-green birefringence. Systemic amyloidosis can be classified as primary or idiopathic light-chain amyloidosis (AL), which is the most common form in Western countries with an incidence of 5-12 per million per year, and secondary or reactive form (AA) (1-3).

Clinical presentation can be highly variable according to the different organs and sites involved by the protein deposition and the prognosis is poor (3). Also gastrointestinal tract can be involved with motility disorders of different degrees of severity, sometimes leading to pseudo-obstruction, and/or organic macroscopic lesions (4), as macroglossia, gastric ulcer, polyps, perforation, ulcerative colitis-like lesions (5-17).

Here, we report a case of a patient affected by primary amyloidosis and an unusual clinical onset which led to diagnostic problems.

Case report

In 2005, a 55-year-old man was hospitalized at the Department of Gastroenterology for a 7-month history of vomit, abdominal distension, epigastric discomfort and a 3 kg weight loss. Family and past history of the patient was not contributory, except an alcohol intake of 10 g per day. Physical examination evidenced only severe abdominal meteorism, the body mass index was normal. Laboratory tests revealed an alkaline phosphatase of 157 U/L (normal range 35-112 U/L), while the other routine tests, including complete blood count, complete metabolic profile, urinalysis, and urine and sera protein electrophoresis were unremarkable. Due to the severe intestinal meteorism an abdominal ultrasonography (US) was impracticable ; a radiography after a standard barium meal showed a distended stomach and duodenal bulb, and a stenosis of the small bowel was suspected (Fig. 1A). At esophagogastroduodenoscopy (EGDS) grade C esophagitis (Los Angeles classification) was present together with hiatal hernia, distension of the stomach and a "sigmoid" megaduodenum containing food residues (Fig. 1B, C and D). Multiple biopsies with standard forceps were taken from esophagus, stomach and duodenum : esophageal biopsies, taken with the support of a methylene-blue dye (Fig. 1C), showed a specialized intestinal metaplasia with a low-grade dysplasia (Barrett's esophagus, Fig. 2A), whereas gastric and duodenal biopsies, stained with standard hematoxylin-eosin, were normal. X-rays of the thorax, electrocardiogram and echocardiography were normal. An abdominal computed tomography with intravenous contrast suggested a distal ileum wall thickening and no evidence of abdominal masses or lesions causing an intestinal compression or stenosis. The consequent ileocolonoscopy resulted normal as well as the histological findings of the ileal, colonic and rectal biopsies (hematoxylin-eosin staining). Ulterior research for the presence in serum of autoantibodies, β2-microglobulin and of Bence-Jones protein

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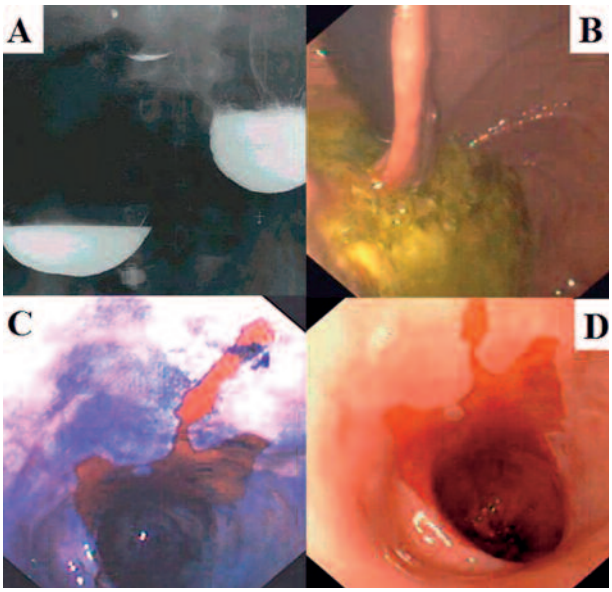

Fig. 1. — Imaging of the upper gastrointestinal tract by abdominal radiography with a standard barium meal showing a distension of the stomach and duodenal bulb (A) and EGDS showing : B) the duodenum in retrovision characterised by abnormal dimensions of the lumen (approximately from 10 to 12 cm of diameter) and presence of food residues ; C and D) an irregularity of the Z line with the suspicion of a Barrett's esophagus strengthened by the methylene blue staining.

in urine was negative. The probable dismotility of the upper gastrointestinal tract was further investigated and manometry of esophagus, gastric antrum and duodenum revealed an esophageal hypomotility characterized by reduced wave amplitude and low esophageal sphincter (LES) atony, and a severe hypomotility of antrum and duodenum. Severe acid reflux was observed at the 24-hours pH monitoring (35% time pH < 4).

As the presence of a motility disorder of the upper gastrointestinal tract was evidenced, visceral myopathy or ganglionopathy, systemic sclerosis sine scleroderma, hereditary megaduodenum or trypanosomiasis were evaluated and ruled out on clinical and serological grounds (18-24). Various reasons made these diagnoses improbable : his unremarkable family history, age, sex and the absence of travels in areas endemic for *Trypanosoma cruzi* ; the absence of ptosis or external ophthalmoplegia and urinary dysfunctions ; the limitation of the damage to the upper gastrointestinal tract ; the absence of pseudo-obstruction (the main symptom of visceral myopathy), and the absence of autoantibodies. Another hypothesis was an extremely unusual and atypical presentation of amyloidosis and so, despite the normal urinary and serological protein electrophoresis findings, all of the endoscopic bioptic specimens were re-examined using Congo red staining. These were negative for the presence of protein deposits in the blood vessels of the submucosa, which was carefully

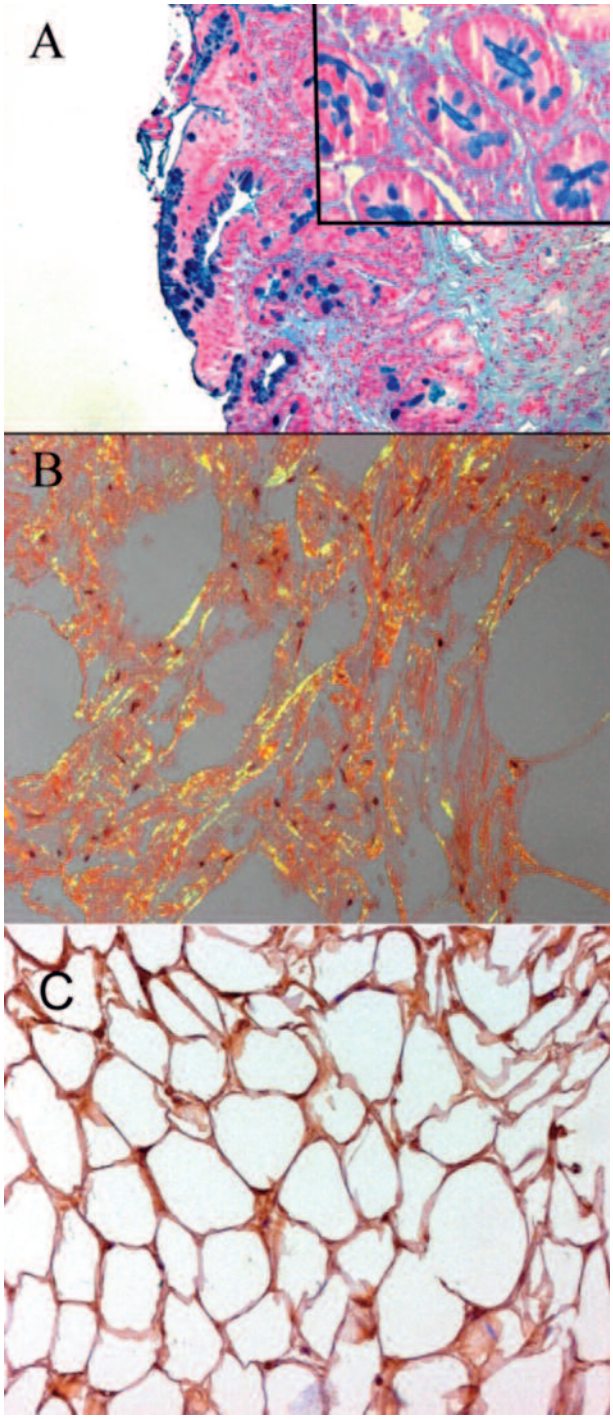

Fig. 2. — Histopathology of a specimen from esophageal biopsy showing specialized intestinal metaplasia (haematoxylin and eosin plus Alcian blue at a pH 2.5 staining) (A, 25× magnification and zoom 100× magnification). Periumbilical fat biopsy showing amyloid deposition (polarized light) (B, 100×) and protein A immunohistochemistry (C, 100×).

analyzed in all of the specimens, particularly the rectal biopsies. Full thickness biopsy of the duodenal wall was proposed, but the patient refused further investigations and, in the absence of a diagnosis, was discharged with acid suppressing therapy (high doses of proton pump

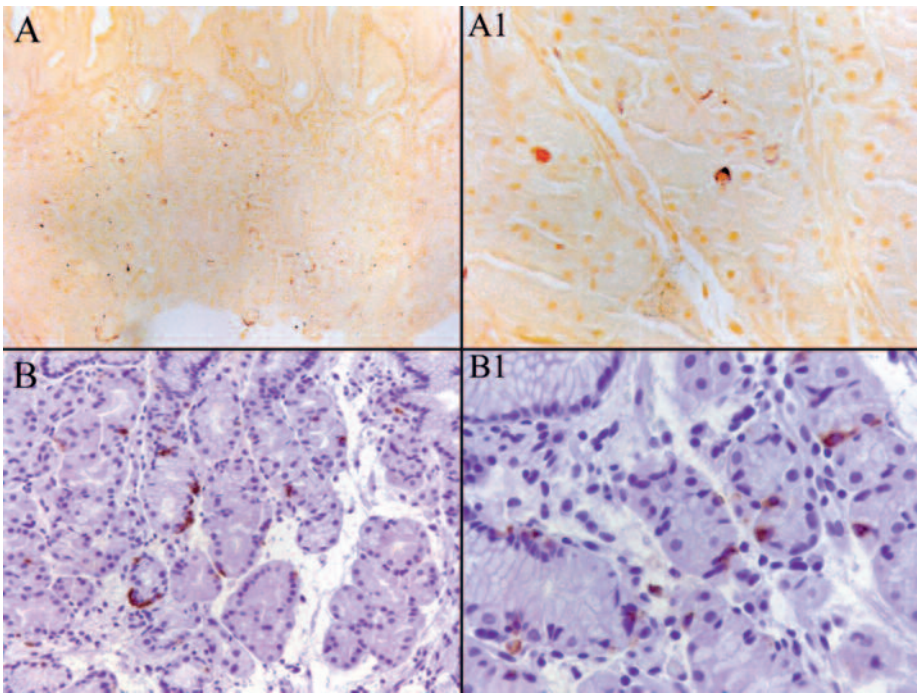

Fig. 3. — Argyrophilic endocrine cells in gastric body mucosa stained with Grimelius (A and A1, 25× and 100× magnification respectively) and (B and B1, 50× and 100× magnification respectively) scattered neuroendocrine cells within oxyntic mucosa showing immunoreactivity to anti-chromogranin antibody (hematoxylin counterstain).

inhibitors and prokinetic drugs) which resolved the symptoms.

Six month later symptoms recurred and the patient underwent to a control visit and EGDS. Culture of the duodenal fluid (double catheter technique) in the suspect of a small intestine bacterial overgrowth (SIBO), highly probable in case of intestinal reduced motility, resulted positive for *E. coli* and *Enterococcus species* : rifaximin and ciprofloxacin therapy was started with resolution of symptoms. We did not see the patient for three years.

In 2007 he was re-admitted to the hospital for dyspnea and lower leg edema. A severe cardiac dilatation was present at X-ray. The biopsy of the abdominal subcutaneous fat confirmed the diagnosis of amyloidosis (Fig. 2B) ; immunohistochemistry resulted positive for protein A (AA amyloidosis) and negative for λ chains (Fig. 2C). The patient died a month later for cardiac failure.

Discussion

It is well-known that also the gastrointestinal tract can be involved in systemic amyloidosis manifesting a wide variety of symptoms and signs, but this is the first description of an association with megaduodenum (25). Moreover, the clinical onset, limited to the upper gastrointestinal tract without any involvement of other organs as heart or kidneys, is quite unusual.

From the beginning, in our case the suspicion for amyloidosis was present, however some findings appeared extremely uncommon. In fact, even if the reduced motility and clearance capacity of the esophagus, and the LES atony may cause gastroesophageal acid reflux in patients affected by amyloidosis, the presence of severe esophagitis is rare and described only in patients with concomitant chronic renal failure (26). Dismotility of the stomach and, rarely, gastroparesis can be present but only 1% of patients affected by amyloidosis refer gastric symptoms (27) or develop small intestine bacterial overgrowth (28). The severe dilatation of the duodenum and the presence of a Barrett's esophagus suggest the long-lasting presence of motility disorders due to amyloidosis. Although we cannot exclude an involvement of the muscular layer of intestine, the altered motility of the upper gastrointestinal tract is often due to an underlying autonomic neuropathy, which, in the present case, seemed absent as there were no symptoms of autonomic neuropathy. El-Salhy *et al.* (29) reported in a cohort of 11 patients affected by familiar amyloidosis a reduction of intestinal neuroendocrine cells and suggested that this finding can be the cause of the altered motility. We performed microscopic re-evaluation of the mucosal samples, which were unremarkable except for some mild atrophic changes and focal, non-specific collections of small lymphoid cells within the lamina propria in the stomach. A panel of antibodies was applied to paraffin sections directed against several neuroendocrine markers including chromogranin, serotonin, calcitonin, synaptophysin and CD56. Chromogranin was positive in a few cells within the antral and fundal

mucosa glands. The Grimelius silver stain revealed similarly distributed argyrophilic cells. These findings were not consistent with a quantitative reduction of the number of neuroedocrine cells (Fig. 3).

In our patient immunohistochemistry analysis of the abdominal fat resulted positive for protein A suggesting an AA amyloidosis without an underlying disease, as happens in approximately 5% of subjects (30). Moreover, at the first admission amyloid deposits in the rectal biopsies were absent. The reported sensibility of rectal biopsies for the diagnosis of amyloidosis is 70-80%, comparable with the subcutaneous fat analysis (31). For this reason we think that only a full-thickness biopsy of the intestinal wall could have confirmed diagnosis allowing a treatment.

Stomach and small intestine are frequently involved (from 12% to 31%) in amyloidosis as shown by autopsy studies but rarely symptomatic (27,32). Main symptoms are nausea, vomiting, epigastric pain and hematemesis caused and alteration of motility and mucosal lesions (27). Gastric endoscopic pictures are very heterogeneous : irregular gastric folds (33), antral narrowing (34), ulcers, massive ulcerative gastritis or hematomas due to damaged mucosal vessels and/or vascular malformations (8,35,36), polyps, plaque or cancer-like lesions (9,37,38). Small intestine could be heavily damaged by the depositions of fibrils and findings range from diffuse mucosal alterations (erosions, granular appearance, friability or thickening of the Kerckring's folds (25,39,40)) to ulcers, polyps or tumor mimicking masses which could complicate with fistula, perforations or massive bleeding, pseudo-obstruction, pneumomatosis intestinalis and intussusception (8,15,41-44). Besides acute events occurring in patients with amyloidosis (mainly hemorrhagic), malabsorption could be present in 8% of cases, leading to protein loss and diarrhea caused by osmotic, motility and bacterial factors (45-48). To our knowledge this is the first case presenting a endoscopically proven megaduodenum in a patient affected by amyloidosis.

The prognosis of amyloidosis is usually severe, although recent data on the use of chemotherapic drugs suggest their efficacy in systemic amyloidosis (49). It is possible that an early diagnosis of a localized form could have a better outcome than the systemic form.

In conclusion, the unique characteristics and clinical presentation of this case pinpoint the heterogeneity of the possible presentations of amyloidosis which can involve the gastrointestinal tract with different types of lesions. In the light of the current therapeutic options, we suggest to be aware of this disorder which is probably widely underestimated.

References

1. PICKEN M.M. New insights into systemic amyloidosis : the importance of diagnosis of specific type. *Curr. Opin. Nephrol. Hypertens.*, 2007, **16** : 196-203.
2. LACHMANN H.J., HAWKINS P.N. Systemic amyloidosis. *Curr. Opin. Pharmacol.*, 2006, **6** : 214-220.
3. MERLINI G., BELLOTTI V. Molecular mechanisms of amyloidosis. *N. Engl. J. Med.*, 2003, **349** : 583-596.
4. LOVAT L.B., PEPYS M.B., HAWKINS P.N. Amyloid and the gut. *Dig. Dis.*, 1997, **15** : 155-171.
5. HEMMER P.R., TOPAZIAN M.D., GERTZ M.A., ABRAHAM S.C. Globular amyloid deposits isolated to the small bowel : a rare association with AL amyloidosis. *Am. J. Surg. Pathol.*, 2007, **31** : 141-145.
6. AKAMATSU T., WATANABE N., CHIBA T. Primary localized amyloidosis of the duodenum. *Clin. Gastroenterol. Hepatol.*, 2007, **5** : e4-5.
7. DENIZ K., SARI I., TORUN E., PATIROGLU T.E. Localized gastric amyloidosis : A case report. *Turk. J. Gastroenterol.*, 2006, **17** : 116-119.
8. IIJIMA-DOHI N., SHINJI A., SHIMIZU T., ISHIKAWA SZ., MUKAWA K., NAKAMURA T., MARUYAMA K., HOSHII Y., IKEDA S. Recurrent gastric hemorrhaging with large submucosal hematomas in a patient with primary AL systemic amyloidosis : endoscopic and histopathological findings. *Intern. Med.*, 2004, **43** : 468-472.
9. CHANG H.S., MYUNG S.J., YANG S.K., JUNG H.Y., LEE G.H., HONG W.S., KIM J.H., MIN Y.I., KIM H.C., HA H.K., KIM J.S. Massive small bowel bleeding in a patient with amyloidosis. *Gastrointest. Endosc.*, 2004, **59** : 126-129.
10. HOKAMA A., KINJO F., KINJO N. Image of the month : primary amyloidosis of the duodenum. *Gastroenterology*, 2003, 125 : 1302, 1565.
11. JAYANTHI V., VIMALA R. Duodenal amyloidosis. *Indian J. Gastroenterol.*, 2002, **21** : 157.
12. GONO T., MATSUDA M., DOHI N., SEKIJIMA Y., TADA T., SAKASHITA K., KOIKE K., KADOSAKA S., IKEDA S. Gastroduodenal lesions in primary AL amyloidosis. *Gastrointest. Endosc.*, 2002, **56** : 563.
13. CHEN J.H., LAI S.J., TSAI P.P., CHEN Y.F. Localized amyloidosis mimicking carcinoma of the colon. *AJR Am. J. Roentgenol.*, 2002, **179** : 536-537.
14. SISK C.M., CHAMBERLIN W., RHOLL V.L., RHOLL J.C. Acute recurring pancreatitis : a manifestation of duodenal amyloid deposition. Case report and review. *Gastrointest. Endosc.*, 2001, **53** : 656-657.
15. DEGUCHI M., SHIRAKI K., OKANO H., YAMANAKA T., ITO N., TAKASE K., NAKANO T. Primary localized amyloidosis of the small intestine presenting as an intestinal pseudo-obstruction : report of a case. *Surg. Today*, 2001, **31** : 1091-1093.
16. HIRATA K., SASAGURI T., KUNOH M., SHIBAO K., NAGATA N., ITOH H. Solitary "amyloid ulcer" localized in the sigmoid colon without evidence of systemic amyloidosis. *Am. J. Gastroenterol.*, 1997, **92** : 356-357.
17. HAUBEN E., FIERENS H., HEYLEN H., VAN MARCK E. Localized amyloid tumour of the duodenum : a case report. *Acta Gastroenterol. Belg.*, 1997, 60 : 304-305.
18. BASILISCO G. Hereditary megaduodenum. *Am. J. Gastroenterol.*, 1997, **92** : 150-153.
19. MONCAYO A., ORTIZ YANINE M.I. An update on Chagas disease (human American trypanosomiasis). *Ann. Trop. Med. Parasitol.*, 2006, **100** : 663-677.
20. MUNGAN Z., AKYUZ F., BUGRA Z., YONALL O., OZTURK S., ACAR A., CEVIKBAS U. Familial visceral myopathy with pseudo-obstruction, megaduodenum, Barrett's esophagus, and cardiac abnormalities. *Am. J. Gastroenterol.*, 2003, **98** : 2556-2560.
21. KUDOH K., SHIBATA C., FUNAYAMA Y., FUKUSHIMA K., TAKAHASHI K., OGAWA H., SAGAMI Y., HIRABAYASHI Y., MORIYA T., SASAKI I. Gastrojejunostomy and duodenojejunostomy for megaduodenum in systemic sclerosis sine scleroderma : report of a case. *Dig. Dis. Sci.*, 2007, **52** : 2257-2260.
22. WESTON S., THUMSHIRN M., WISTE J., CAMILLERI M. Clinical and upper gastrointestinal motility features in systemic sclerosis and related disorders. *Am. J. Gastroenterol.*, 1998, **93** : 1085-1089.
23. CAMILLERI M. Disorders of gastrointestinal motility in neurologic diseases. *Mayo Clin. Proc.*, 1990, **65** : 825-846.
24. CAMILLERI M., PHILLIPS S.F. Disorders of small intestinal motility. *Gastroenterol. Clin. North Am.*, 1989, **18** : 405-424.
25. EBERT E.C., NAGAR M. Gastrointestinal manifestations of amyloidosis. *Am. J. Gastroenterol.*, 2008, **103** : 776-787.
26. CEKIN A.H., BOYACIOGLU S., GURSOY M., BILEZIKCI B., GUR G., AKIN E.D., OZDEMIR N., YILMAZ U. Gastroesophageal reflux disease in chronic renal failure patients with upper GI symptoms : multivariate analysis of pathogenetic factors. *Am. J. Gastroenterol.*, 2002, **97** : 1352-1356.
27. MENKE D.M., KYLE R.A., FLEMING C.R., WOLFE J.T. 3RD, KURTIN P.J., OLDENBURG W.A. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. *Mayo Clin. Proc.*, 1993, **68** : 763-767.
28. LIN H.C. Small intestinal bacterial overgrowth : a framework for understanding irritable bowel syndrome. *JAMA*, 2004, **292** : 852-858.

29. EL-SALHY M., SUHR O., STENLING R., WILANDER E., GRIMELIUS L. Impact of familial amyloid associated polyneuropathy on duodenal endocrine cells. *Gut*, 1994, **35** : 1413-1418.
30. ROCKEN C., SHAKESPEARE A. Pathology, diagnosis and pathogenesis of AA amyloidosis. *Virchows Arch.*, 2002, **440** : 111-122.
31. FENTEM P.H., TURNBERG L.A., WORMSLEY K.G. Biopsy of the rectum as an aid to the diagnosis of amyloidosis. *Br. Med. J.*, 1962, **1** : 364-367.
32. BRIGGS G.W. Amyloidosis. *Ann. Intern. Med.*, 1961, **55** : 943-957.
33. BJORNSSON S., JOHANNSSON J.H., SIGURJONSSON F. Localized primary amyloidosis of the stomach presenting with gastric hemorrhage. *Acta Med. Scand.*, 1987, **221** : 115-119.
34. KLINGENBERG P.H. Amyloidosis of gastrointestinal tract simulating gastric carcinoma. *Am. J. Surg.*, 1958, **96** : 713-715.
35. MURAKI M., KANNO Y., HIGUCHI K., SHIROTORI K., OGUCHI T., HORA K., KIYOSAWA K. Laceration of gastric mucosa associated with dialysis-related amyloidosis. *Clin. Nephrol.*, 2005, **64** : 448-451.
36. SATAPATHY S.K., KURTZ L.E., SHEIKH-FAYYAZ S., BANK S., YANG S.S. Gastric amyloidosis presenting as massive upper gastrointestinal bleeding. *Am. J. Gastroenterol.*, 2009, **104** : 2113-2115.
37. LAU C.F., FOK K.O., HUI P.K., TAM C.M., TUNG Y.M., WONG M.C., LOO C.K., LAM K.M. Intestinal obstruction and gastrointestinal bleeding due to systemic amyloidosis in a woman with occult plasma cell dyscrasia. *Eur. J. Gastroenterol. Hepatol.*, 1999, **11** : 681-685.
38. JANCZEWSKA I., MEJHERT M., HAST R., RUNARSSON G., SANDSTEDT B. Primary AL-amyloidosis, ulcerative colitis and collagenous colitis in a 57-year-old woman : a case study. *Scand. J. Gastroenterol.*, 2004, **39** : 1306-1309.
39. TADA S., IIDA M., IWASHITA A., MATSUI T., FUCHIGAMI T., YAMAMOTO T., YAO T., FUJISHIMA M. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. *Gastrointest. Endosc.*, 1990, **36** : 10-14.
40. TADA S., IIDA M., YAO T., KAWAKUBO K., YAO T., OKADA M., FUJISHIMA M. Endoscopic features in amyloidosis of the small intestine : clinical and morphologic differences between chemical types of amyloid protein. *Gastrointest. Endosc.*, 1994, **40** : 45-50.
41. BROWN S.J., SHACKLETON M., SALEM H., SCHMIDT G. Gastro-colic fistula complicating primary (Al) amyloidosis. *J. Gastroenterol. Hepatol.*, 2002, **17** : 110-111.
42. YOUSUF M., AKAMATSU T., MATSUZAWA K., KATSUYAMA T., SUGIYAMA A., IKEDA S., KIYOSAWA K., FURUTA S. Al-type generalized amyloidosis showing a solitary duodenal tumor. *Hepatogastroenterology*, 1992, **39** : 267-269.
43. PEARSON D.C., PRICE L.M., URBANSKI S. Pneumatosis cystoides intestinalis : an unusual complication of systemic amyloidosis. *J. Clin. Gastroenterol.*, 1996, **22** : 74-76.
44. BALDEWIJNS M., ECTORS N., VERBEECK G., JANSSENS J., DE SCHEPPER J., PONETTE E., GEBOES K., DESMET V. Intermittent subobstruction and cholestasis as complications of duodenal amyloid tumours. *Gastroenterol. Clin. Biol.*, 1995, **19** : 218-221.
45. ECTORS N.L., GEBOES K.J., RUTGEERTS P.J. Malabsorption and motor dysfunction in patients with small bowel amyloidosis. *Gut*, 1994, **35** : 864.
46. HERSKOVIC T., BARTHOLOMEW L.G, GREEN P.A. Amyloidosis and Malabsorption Syndrome. *Arch. Intern. Med.*, 1964, **114** : 629-633.
47. JEONG Y.S., JUN J.B., KIM T.H., LEE I.H., BAE S.C., YOO D.H., PARK M.H., KIM S.Y. Successful treatment of protein-losing enteropathy due to AA amyloidosis with somatostatin analogue and high dose steroid in ankylosing spondylitis. *Clin. Exp. Rheumatol.*, 2000, **18** : 619-621.
48. MATSUMOTO T., IIDA M., HIRAKAWA M., HIRAKAWA K., KUROKI F., LEE S., NANBU T., FUJISHIMA M. Breath hydrogen test using water-diluted lactulose in patients with gastrointestinal amyloidosis. *Dig. Dis. Sci.*, 1991, **36** : 1756-1760.
49. MERLINI G., PALLADINI G. Amyloidosis : is a cure possible ? *Ann. Oncol.*, 2008, **19** Suppl 4 : iv63-66.