Isolated amyloidosis of the gastro-intestinal tract

S. Smeets[1], F. Dedeurwaerdere[2], E. Thomaere[3], B. Houthoofd[3], L. D'Hulst[4], P. Wilmes[5], F. Offner[6], S. De Coninck[7]

(1) Gastroenterologist in training, University hospital of Ghent; (2) Department of anatomopathology Sint-Andries hospital Tielt; (3) Department of radiology Sint-Andries hospital Tielt; (4) Department of nuclear medicine Sint-Andries hospital Tielt; (5) Department of oncology Sint-Andries hospital Tielt; (6) Department of hematology University hospital Ghent; (7) Department of gastroenterology Sint-Andries hospital Tielt.

Abstract

Amyloidosis is a very rare condition, which, due to its rarity, is often missed or diagnosed in an advanced stage of the disease, causing significant morbidity and mortality. In this review we describe the existing types of amyloidosis focusing on the gastro-intestinal tract. Amyloidosis occurs when abnormal protein fibrils (amyloid) deposit in the muscularis mucosae. This can cause an array of symptoms ranging from (in order of occurrence): gastro-intestinal bleeding, heartburn, unintentional weight loss, early satiety, constipation, diarrhea, nausea, vomiting and fecal incontinence (1). Treatment is focused on the underlying condition (if any) causing the production and deposition of the abnormal fibrils, in combination of symptomatic treatment. (Acta gastroenterol. belg., **2022,** 85, **80-84**).

Keywords: Amyloidosis, gastro-intestinal amyloid deposition.

Introduction

Amyloidosis is caused by the aggregation and deposition of insoluble extracellular proteins within a multitude of organs, which resist digestion due to an abnormal folding (2-4). All forms of amyloid deposits form sheets composed of protein fibrils with a remarkably similar structure: a diameter of 7-13nm and a similar core structure consisting of anti-parallel β-strands (parallel β-strands are less common) (5-8). This specific ordered ultrastructure of these amyloid fibrils gives them the characteristic property of binding congo-red dye in a manner that produces green birefringence when viewed under cross-polarized light. This birefringence is the gold standard for confirming the presence of amyloid in tissue samples (9).

Amyloid formation and its deposition can occur due to various reasons: firstly when an abnormal protein is present (eg. Hereditary amyloidosis and acquired systemic immunoglobulin light chain amyloidosis (AL). Secondly, in the presence of an exessive amount of a normal protein that's present for a long time (eg. Reactive systemic amyloidosis (AA) and β2-microglobulin dialysis-related amyloidosis (β2M)). Finally, the ageing process can sometimes, for unknown reasons, be accompanied with the deposition of a specific type of amyloidosis (eg. wild-type transthyretin amyloidosis (ATTRwt or senile systemic amyloidosis, SSA) and atrial natriuretic peptide amyloidosis).

Nomenclature

Amyloidosis is usually referred to as an abbreviation, which always begins with the letter A, which stands for amyloid. The second letter (or group of letters) delineates the specific type of amyloid that is formed by describing the precursor protein, the most prevalent types of amyloidosis are depicted in table 1 (10).

In case of primary or light chain associated amyloidosis (AL) there is a deposition of immuno-globulin light chains, this type of amyloidosis seems to have the most gastro-intestinal involvement and is usually associated with a multiple myeloma (11).

A second form of amyloidosis, the secondary form (AA), is caused by deposition of the acute-phase reactant serum amyloid A protein. This is associated with chronic infections, inflammatory disorders or, more seldomly, neoplastic disorders (12). AA amyloidosis is also known to affect the gastro-intestinal tract.

β2- macroglobulin amyloidosis is usually caused by long term hemodialysis (prior to the introduction of

Table 1. — **Most common types of amyloidosis**
(Adapted from Palladini et al. (10))

Type of amyloidosis	Precursor protein	Portion of new cases	Organ involvement
AL	Monoclonal immunoglobulin light chains	78%	Heart (75%), kidney (65%), soft tissues (15%), liver (15%), nervous system (10%), GI tract (5%)
ATTRwt	Wild-type transthyretin	10%	Heart (up to 100%), ligaments, tenosynovium
ATTRm	Mutated transthyretin	7%	Nervous system, heart, eye
AA	Apolipoprotein	6%	Kidney (>95%), liver (15%), Heart (10%), GI tract (5%)
AapoA1	Mutated amolipoprotein A1	3%	Liver, kidney, testes, heart, peripheral nervous system

Correspondence to: Dr. Smeets Sander, Bloemstraat 32, 9050 Gentbrugge.
Email: sasmeets.smeets@ugent.be

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high flux membranes). β2- macroglobulin is a larger size molecule and is insufficiently filtered by older low flux membranes, this can cause accumulation of this molecule in various tissues (13-17).

Another type of amyloidosis, previously known as senile amyloidosis, is caused by the deposition of unmutated (wild-type, wt) transthyretin (TTR). This protein, predominantly produced by the liver, is a plasma transport protein for thyroxine and vitamin A. The deposition of ATTRwt usually occurs in the heart and nervous system, this can cause gastro-intestinal symptoms (diarrhea, weight loss, …) due to autonomic neuropathy (18). The vast majority of patients will, however, present with a cardiac phenotype, generally heart failure with preserved ejection fraction (HFpEF), depending on the author up to 100% of patients. There is no clear data about isolated ATTRwt amyloidosis of the gastro-intestinal tract.

Hereditary (also called familial) amyloidosis is very rare and can be caused by many different precursor proteins due to various genetic mutations. (19-21). For example, familial AApoA1 amyloidosis is caused by a single amino acid mutation (G26R) in human apolipoprotein A-I (apoA-IIowa). When the N-terminal fragments (amino acid residues 1-83) of apoA-I contain this mutation, they will deposit as amyloid fibrils in patients' tissues. However, the exact mechanisms of cellular degradation and cytotoxicity are currently not yet known (22). This type of amyloidosis (familial AApoA1) usually affects the liver, kidney, larynx, skin and myocardium, seldomly, amyloid can also be found in the testes and adrenal glands (23). Another type of a familial type of amyloidosis is the hereditary form of ATTR amyloidosis, also referred to as ATTRm. This is a rare condition caused by an autosomal dominant mutation of the gene coding for the transthyretin protein. Its presence can be found all over the world with a few endemic areas including Sweden, Portugal, Brazil and Japan (1).

Lastly, amyloid deposition can also be isolated to a single organ without systemic involvement, resulting in specific syndromes (e.g. Alzheimer's disease).

Epidemiology

Even if all types of amyloidosis are very rare, AL is the most common occurring subtype. A study performed by the UK National Health Service established the incidence of systemic AL amyloidosis between 0.3-0.8/100,000 of the general population, with a peak in the age group between 60 and 79 years (24). A Swedish study performed in 2012 reported an incidence of non-hereditary amyloidosis of about 8.29/1,000,000 person-years with a peak in the population of over 65 years of age. This study also revealed that secondary systemic amyloidosis (AA) was rarer (incidence of 2/1,000,000) (25).

An older study performed in Minnesota in the US, came to similar results (10).

Senile amyloidosis (ATTRwt) usually affects the heart in the elderly population and causes congestive heart failure (HFpEF) due to ventricular hypertrophy which progresses slowly. ATTRwt can also affect the gastro-intestinal tract, usually this is a histological diagnosis (on autopsy) and is seen in 40% of the general population who are more than 80 years of age, irrespective of GI complaints (26-27).

True population-based studies have not yet been performed on the prevalence of ATTRwt amyloidosis, so exact numbers are not yet known (28,35).

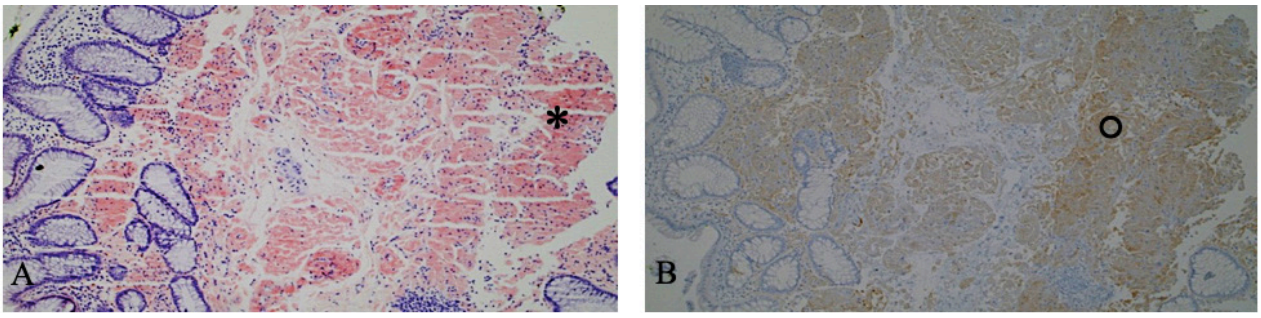
In a study performed in Kiel, Germany investigated 663 gastro-intestinal biopsies with amyloid (from 542 patients), it was found that ALλ (lambda light chain) was present in 52.8 %, ATTR in 16.2 %, ALκ (kappa light chain) in 13.7 %, and AA in 10.7 %, ApoAI amyloid in 0.7 %. The remaining cases were ALys (0.7 %), AL n.o.s. (2.6 %), and mixed type amyloidosis (0.6 %). 11 cases (2%) remained unclassified (29).

Gastro-intestinal manifestation of amyloidosis is usually found in the elderly population. Over 70% of patients were 60 years or older. In the case of ATTR amyloidosis the mean age of the patients was even higher (>70). If ATTRwt affects the gastro-intestinal tract, it is usually found in the colon and/or rectum, more precisely in the muscularis mucosa and submucosa. There is also a clear male preponderance in gastro-intestinal amyloidosis (61.7% vs 38.3%) (29).

Cowan et al. retrospectively reviewed data of 2334 patients with all types of amyloidosis referred to a tertiary center. 3.2% had proven amyloid involvement of the gastro-intestinal tract on biopsy. 79% had systemic amyloidosis with dominant gastro-intestinal involvement. In 21% there was a localized involvement of GI tract but these patients had no evidence of other underlying conditions (eg plasma cell dyscrasia) proven by a normal bone marrow biopsy (no evidence of clonality by immunohistochemistry or *in situ* hybridi-

Table 2. — **GI symptoms in ATTR amyloidosis**
(Adapted from Wixner et al. (1))

Symptoms	Percentage of patients with comfirmed ATTRwt	Percentage of patients with confirmed ATTRm
Any GI symptoms	15.3%	63%
Early satiety	3.6%	26.4%
Nausea	2.2%	17.1%
Vomiting	0%	13.4%
Constipation	3.6%	20.9%
Diarrhea/constipation	1.5%	24.3%
Diarrhea	3.6%	19.8%
Fecal incontenence	0%	6.2%
Unintentional weight loss	2.9%	31.5%



10 × enlarged Congo red staining: Salmon pink coloring of amyloid*

20 × enlarged prealbumin staining positive° (= transthyretin)

Figure 1.

zation) and a normal level and ratio of serum free light chains. In these patients there was also no clinical evidence of involvement of other organ systems and no amyloid deposition in a fat aspirate. Of these 16 patients with isolated gastrointestinal amyloidosis 11 had AL amyloidosis, the other 5 were unspecified (18).

The THAOS study, performed in 2014 found that gastro-intestinal disturbances are frequent in patients with ATTR amyloidosis (15.3% in ATTRwt and 63% in ATTRm) (table 2). These disturbances have an important effect on the survival rate of these patients, by malnutrition due to malabsorption and decreased functional capacity. However, in this study, GI symptoms were documented by a questionnaire and no biopsies were taken to confirm gastro-intestinal involvement (1).

Clinical presentation

Systemic amyloidosis can present in many different forms, depending on the affected organ.

Whatever the underlying type of amyloidosis, GI amyloidosis can occur with symptoms including unintentional weight loss, diarrhea, abdominal pain, malabsorption, gastro-esophageal reflux, and GI bleeding (involving either upper or lower tract) (12,30-32). Cowan et al. found that the most frequent reported symptoms of localized GI amyloidosis were GI bleeding and heartburn, both occurring in about 50 % of patients (18).

These symptoms can be explained by the histological localization of the amyloid depositions, namely: in the muscularis mucosae, in the direct proximity of blood vessels, nerves and nerve plexuses (in lesser extent in the lamina propria and submucosa) (33).

This causes an increasing fragility of blood vessels (causing bleeding), hinders intrinsic peristalsis (causing acid reflux) and increases the stiffness of the gut wall (34). The endoscopic appearance is highly variable and, as of yet, there is no clear link between the endoscopic findings and specific types of amyloidosis.

The esophagus can become atonic and dilated, sometimes resembling an achalasia. In the stomach it can appear as polyps, enlarged gastric folds or ulcerations, sometimes only gastroparesis is present. In the small intestine amyloidosis can present as polyps, thickened folds or only a granular appearance of the mucosa is noticeable. Amyloidosis of the colon can present as a narrowing of the colonic lumen, ulcerations, loss of haustrations, thickened mucosal folds, nodules or pseudo-obstruction (2,12).

Diagnosis

Whatever the underlying type of amyloidosis, the clinical presentation of gastro-intestinal amyloidosis is non-specific, endoscopic and radiological features are also non-specific (mass formation, bleeding, motility disorders, pseudo-obstruction, …).

Due to the rarity of isolated amyloidosis of the GI tract, diagnosis is often delayed. Because of the variety of symptoms: unintentional weight loss, diarrhea, abdominal pain, malabsorption, gastro-esophageal reflux, and GI bleeding (involving either upper or lower tract) (12, 30-32), amyloidosis should be considered in all patients presenting with GI complaints after alternative diagnoses are excluded. The gold standard for diagnosing amyloidosis is Congo-red staining on a tissue sample of the affected organ (9). Different types of amyloid can be detected by different staining methods, for example ATTR deposition can be detected by pre-albumin staining (figure 1).

The study performed in Kiel found that if the GI tract is affected, the best diagnostic yield depends on the type of amyloidosis. ALλ can be present in every region of the gastrointestinal tract. Its prevalence increases slightly proximally to distally. ATTR showed a similar increase in its prevalence proximally to distally. ALκ- and AA however, are most commonly found in biopsies from stomach and duodenum. The distribution of amyloid deposition in the GI tract is depicted in figure 2 and 3 (29).

Whole-body 123I-labeled serum amyloid P (SAP) scintigraphy is a very sensitive test for the diagnosis of systemic AA amyloidosis (up to 90% sensitivity) and can report the extent of organ involvement. Its downsides however are: it is only usable for AA amyloidosis, and it is only available at the NAC in London and the University of Groningen in the Netherlands (2,9).

Since the 1980s technetium-labelled bone-seeking radiopharmaceuticals bone scintigraphy is used to differentiate cardiac ATTR from other forms of cardiac

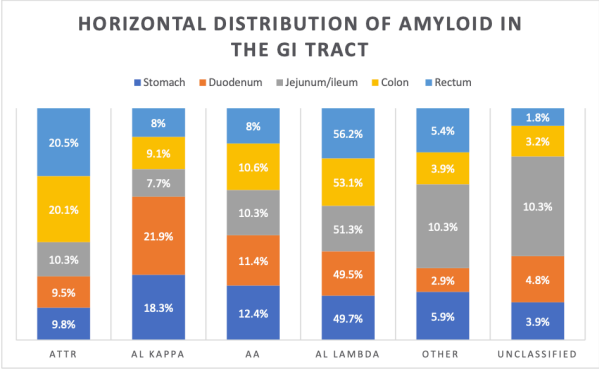


Figure 2. — Amyloid distribution in the gastrointestinal tract, horizontally. (Adapted from Freudenthaler et al. (29)).

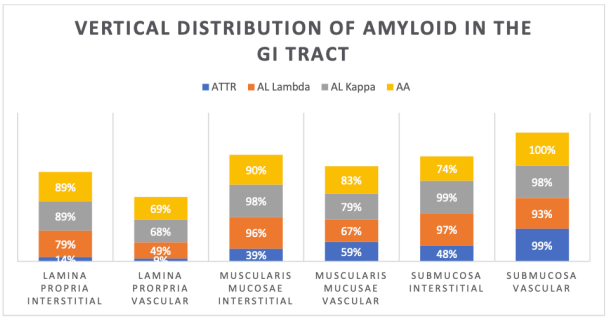


Figure 3. — Amyloid distribution in the gastrointestinal tract, vertically. (Adapted from Freudenthaler et al. (29)).

amyloidosis. How this mechanism works is not yet fully understood.

A meta-analysis performed by Treglia et al. in 2018 revealed that bone scintigraphy is up to 92% sensitive and 95% specific in detecting cardiac ATTR amyloid (both wild type and mutated) (40).

In all patients (irrespective of the type of amyloidosis) screening for cardiomyopathy, nephropathy and bone marrow malignancy should be undertaken and special attention must be given to complete family history and identifying conditions predisposing to amyloid formation (35).

When ATTR (wild type or mutated) amyloidosis is suspected (eg. Patient with new onset HFpEF) following steps should be undertaken:

– Physical examination for evidence of autonomic neuropathy/carpal tunnel syndrome
– Blood testing for serum immunofixation and immunoglobulin free LC assay. When these are normal it excludes LC amyloidosis
– Urine test to find evidence of nephrotic range proteinuria
– Tissue and strain Doppler echocardiography for evidence of left atrial dysfunction (lateral or septal) and biventricular hypertrophy
– Cardiac magnetic resonance imaging for evidence of severe atrial and ventricular amyloid infiltration
– Radionuclide imaging to detect myocardial amyloid deposition by tracer uptake
– Cardiac biomarkers for evidence of troponin and brain natriuretic peptide
– Evidence of Carpal tunnel syndrome
– Biopsy for the verification of amyloid deposits in fat, bone marrow, lip, skin, salivary gland, or gastrointestinal tract. If these less-invasive biopsies are negative a verification of amyloid deposits in the heart, kidney, or nerve are necessary.
– The last step is immunohistochemically/immune gold staining with electron microscopy or preferably mass spectroscopy because of its improved diagnostic accuracy from 77% to 94%. This to find evidence of the ATTR amyloid deposit type (excludes LC amyloidosis) (35).

Treatment

Treatment of acquired amyloidosis is treating the underlying disorder (malignancy, infection, auto-immune disorder).

In case of hereditary ATTR (which is caused by a mutation in genes coding for the protein transthyretin, causing the accumulation of this abnormal protein in several tissues), liver transplantation will remove the source of variant TTR and is in this case the treatment of choice in young and fit patients (41). Other treatment options have recently been investigated in small phase II and III trials, such as TTR tetramer stabilizers (tafamidis and diflunisal). These drugs prevent tetramer dissociation and misfolding of these proteins (35,36,41).

To date however, no specific treatment is approved for SSA, treatment is based solely on symptom control (cfr diuretics in case of symptomatic heart failure) (42,43).

In case of gastro-intestinal sequelae, due to the low incidence of this condition, there is little or no evidence about further treatment and only supportive/symptomatic management can be provided (2). For ATTRwt isolated to the colon we found no definitive therapeutic strategy in the literature.

Prognosis

Prognosis of systemic amyloidosis is largely dependent on the underlying disease which causes the amyloid production. Generally, AL amyloidosis has the worst outcome due to its link with malignancy. ATTRwt is usually a fatal disorder because it usually affects the nerves and heart (35). Mean survival in patients with ATTRwt (diagnosed based on new onset heartfailure) was 32 months, compared with 10 months in patients with AL cardiac amyloidosis (46). There is no data describing the prognosis of ATTRwt isolated to the colon.

Conclusion and prospects for future research

Amyloidosis is a very uncommon disease and can occur with a plethora of symptoms determined by the organ that is affected. Upon diagnosis, patients should be

checked for cardiomyopathy, bone marrow malignancy and nephropathy.

Treatment should focus on the underlying condition causing the deposition of amyloid, together with treating the symptoms.

Isolated amyloidosis of the GI tract is even more rare, has many different presentations and can often only be diagnosed on tissue samples containing submucosa. It is very important to exclude any underlying conditions.

References

1. WIXNER J., MUNDAYAT R., KARAYAL O., ANAN I., KARLING P., SURH O., *et al.* THAOS investigators. THAOS: Gastrointestinal manifestations of transthyretin amyloidosis – common complications of a rare disease. *Journal of Rare Diseases*., 2014, **9**: 6.
2. ROWE K.,PANKOW J., NEHME F., SALYERS W. Gastrointestinal Amyloidosis: Review of the Literature. *Cureus*., 2017, **9**(5): 1-6.
3. SIPE JD., BENSON MD., BUXBAUM JN., SHU-ICHI I., GIAMPAOLO M., MARIA J., *et al.* Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. *Amyloid*., 2014, **21**: 221-224.
4. WESTERMARK P. Aspects on human amyloid forms and their fibril polypeptides. *Febs j.*, 2005, **272**: 5942-5949.
5. SAWAYA MR., SAMBASHIVAN S., NELSON R., IVANOVA M., SIEVERS S., APOSTOL M., *et al.* Atomic structures of amyloid cross-beta spines reveal varied steric zippers. *Nature*., 2007, **447**: 453-457.
6. BONAR L., COHEN A., SKINNER M. Characterization of the amyloid fibril as a cross-beta protein. *Proc Soc Exp Biol Med*., 1969, **131**: 1373-1375.
7. GLENNER G., TERRY W. Characterization of amyloid. *Annu Rev Med*.,1974, **25**: 131-135.
8. SUNDE M., SERPELL L., BARTLAM M., FRASER P.,PEPYS M., BLAKE C. Common core structure of amyloid fibrils by synchrotron X-ray diffraction. *J Mol Biol.*, 1997, **273**: 729-739.
9. WECHALEKAR A., GILLMORE J., HAWKINS P. Systemic amyloidosis. *Lancet*., 2015, **387**: 2641-2654.
10. PALLADINI G, MERLINI G. What is new in diagnosis and management of light chain amyloidosis? *Blood*. 2016, **128**: 159-168.
11. KYLE R., GERTZ M. Primary systemic amyloidosis: Clinical and laboratory features in 474 cases. *Semin Hematol.*,1995, **32**: 45-59.
12. EBERT E., NAGARM. Gastrointestinal Manifestations of Amyloidosis. *American Journal of Gastroenterology*., 2008, **103**: 776-787.
13. CAMPISTOL J., ARGILES A. Dialysis-related amyloidosis: Visceral involvement and protein constituents. *Nephrol Dial Transplant*., 1996, **11**: 142-145.
14. DULGHERU E., BALOS L., BAER A. Gastrointestinal complications of β2-microglobulin amyloidosis: A case report and review of the literature. *Arthritis Rheum*., 2005, **53**: 142-145.
15. JIMENEZ R., PINKUS G., OWEN W., LAZARUS M., KAY J., TURNER J. Development of gastrointestinal β2-microglobulin amyloidosis correlates with time on dialysis. *Am J Surg Pathol*., 1998, **22**: 729-735.
16. FRIEDMAN S., JANOWITZ H., Systemic amyloidosis and the gastrointestinal tract. *Gastroenterol Clin North Am*., 1998, **27**: 595-614.
17. GAL R., KORZETS A., SCHWARTZ A., RATH-WOLFSON L., GAFTER U. Systemic distribution of β 2-microglobulin-derived amyloidosis in patients who undergo long-term hemodialysis. *Arch Pathol Lab Med*., 1994, **118**: 718-21.
18. COWAN A., SKINNER M., SELDIN C., BERK J., LICHTENSTEIN D., O'HARA C., *et al.* Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. *Haematologica*., 2013, **98**: 141-146.
19. OLSSON M., HELLAMN U., PLANTE-BORDENEUVE V., JONASSON J., LANG K ., SUHR O. Mitochondrial haplogroup is associated with the phenotype of familial amyloidosis with polyneuropathy in Swedish and French patients. *Clin Genet.*, 2009, **75**: 163-168.
20. ROCKEN C., SAEGER W., LINKE R. Gastrointestinal amyloid deposits in old age. Report on 110 consecutive autopsical patients and 98 retrospective bioptic specimens. *Pathol Res Pract*., 1994, **190**: 641-649.
21. MATSUTANI H., HOSHII Y., SETOGUCHI M., KAWANO H., GONDO T., TAKAHASHI M., *et al.* Vascular amyloid of unknown origin and senile transthyretin amyloid in the lung and gastrointestinal tract of old age: Histological and immunohistochemical studies. *Pathol Int.*, 2001, **51**: 326-332.
22. KAMEYAMA H., NAKAJIMA H., NISHITSUJI K., MIKAWA S., UCHIMURA K., KOBAYASHI N., *et all.* Iowa Mutant Apolipoprotein A-I (ApoA-IIowa) Fibrils Target Lysosomes. *Sci Rep.*, 2016, **6**: 30391.
23. ERIKSSON M., SCHÖNLAND S., YUMLU S., HEGENBART U., VON HUTTEN H., GIOEVA Z., *et al.* Hereditary Apolipoprotein AI-Associated Amyloidosis in Surgical Pathology Specimens. *J Mol Diagn*., 2009, **11**(3): 257-262.
24. PINNEY J., SMITH C., TAUBE J., LACHMAN H., VENNER C., GIBBS S., *et al.* Systemic amyloidosis in England: an epidemiological study. *Br. J. Haematol*., 2013, **161**: 525-532.
25. HEMMINKI K., LI X., FÖRSTI A., SUNDQUIST J., SUNDQUIST K. Incidence and survival in non-hereditary amyloidosis in Sweden. *BMC Public Health*., 2012, **12**: 974.
26. SYEDA U., CHING COMPANIONI R., ALKHAWAMA H., WALFISH A. Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. *European Journal of Gastroenterology & Hepatology.*, 2016, **28**: 1109-1121.
27. SATTIANAYAGAM P., HAWKINS P., GILLMORE J. Systemic amyloidosis and the gastrointestinal tract. *Nat Rev Gastroenterol Hepatol*., 2009, **6**: 608-617.
28. SEKIJIMA Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. *Journal of Neurology, Neurosurgery & Psychiatry*., 2015, **86**: 1036-1043.
29. FREUDENTHALER S., HEGENBART U., SCHÖNLAND S., BEHRENS H., KRÜGER S., RÖCKEN C. Amyloid in biopsies of the gastrointestinal tract-a retrospective observational study on 542 patients. *Virchows Arch.*, 2016, **5**: 468-569.
30. MENKE D., KYLE R., FLEMMING C., WOLFE J., KURTIN P., OLDENBURG W. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. *Mayo Clin Proc.*, 1993, **68**: 763-767.
31. FONNESU C., GIOVINALE M., VERRECCHIA E., DE SOCCIO G., CERQUAGLIA C., CURIGLIANO V., *et al.* Gastrointestinal amyloidosis: a case of chronic diarrhoea. *Eur Rev Med Pharmacol Sci*., 2009, **13**: 45-50.
32. KIM S., KANG E., PARK J., JO J., KIM S., CHO J., *et al.* Gastrointestinal amyloidosis presenting with multiple episodes of gastrointestinal bleeding. *Cardiovasc Intervent Radiol.*, 2009, **32**: 577-580.
33. KAISERLING E., KROBER S. Massive intestinal hemorrhage associated with intestinal amyloidosis. An investigation of underlying pathologic processes. *Gen Diagn Pathol.*, 1995, **141**: 147-154.
34. HIRSCHFIELD G. Amyloidosis: a clinico-pathophysiological synopsis. *Semin Cell Dev Biol.*, 2004, **15**: 39-44.
35. GERTZ M., BENSON M., DYCK P., GROGAN M., COELHO T., CRUZ M., *et al.* Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. *Journal of the American College of Cardiology.*, 2015, **66**: 2451-2466.
36. OBICI L., SUHR O. Diagnosis and treatment of gastrointestinal dysfunction in hereditary TTR amyloidosis. *Clinical Autonomic Research*., 2019, **29**(Suppl 1): S55-S63.
37. DISPENZIERI A., BUADI F., KUMAR S., REEDER C., SHER T., LACY M., *et al.* Treatment of immunoglobulin light chain amyloidosis: mayo stratification of myeloma and risk-adapted therapy (msmart) consensus statement. *Mayo Clin Proc.*, 2015, **90**: 1054-1081.
38. TOSCA CUQUERELLA J., BOSCA-WATTS M., ANTON AUSEJO R., ALONSO S., DE MIGUEL F, PEREZ M. Amyloidosis in inflammatory bowel disease: a systematic review of epidemiology, clinical features, and treatment. *J Crohns Colitis*., 2016, **10**: 1245-1253.
39. POULLOS P., STOLLMAN N. Gastrointestinal Amyloidosis: Approach to Treatment. *Curr Treat Options Gastroenterol.*, 2003, **6**: 17-25.
40. TREGLIA G., GLAUDEMANS A., BERTAGNA F., HAZENBERG B., ERBA P., GIUBBINI R., *et al.* Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. *European Journal of Nuclear Medicine and Molecular Imaging*., 2018, **45**: 1945-1955.
41. MARTINEZ-NAHARRO A., HAWKINS P., FONTANA M. Cardiac amyloidosis. Clin Med (Lond)., 2018, **18**(Suppl 2): s30-s35.
42. MANSO M., MARQUES D., ROCHA S., RODEIA S., DOMINGOS R. Senile Systemic Amyloidosis: An Underdiagnosed Disease. *Eur J Case Rep Intern Med*., 2017, **4**(9): 000725.
43. IHNE S., MORBACH C., SOMMER C., GEIER A., KNOPS., STÖRK S. Amyloidosis - the diagnosis and treatment of an underdiagnosed disease. *Dtsch Artzebl int*., 2020, **117**: 159-166.
44. HWAN KWON Y., YEON KIM J., HUN KIM J., WOO PARK H., MIN YANG H., WOO JEON S., *et al.* A case of primary colon amyloidosis presenting as hematochezia. *Korean J Gastroenterol*., 2012, **59**(1): 44-47.
45. RACANELLI V., D'AMORE F. Localized AL amyloidosis of the colon and clinical features of intestinal obstruction. A case report. *Ann Ital Med Int*., 1999, **14**: 58-60.
46. PINNEY J., WHELAN C., PETRIE A., DINGU J., BANYPERSAD S., SATTIANAYAGAM P., *et al.* Senile Systemic Amyloidosis: Clinical Features at Presentation and Outcome. *J Am Heart Assoc*., 2013, **2**: e000098.