

## Systemic amyloidosis and the gastrointestinal tract

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**Abstract** | Systemic amyloidosis is characterized by the extracellular deposition of protein in an abnormal fibrillar form. Several different types of amyloidosis exist, each defined by the identity of their respective fibril precursor protein. Among patients with systemic amyloidosis, histological involvement of the gastrointestinal tract is very common but is often subclinical. Conversely, primary diseases of the gastrointestinal tract can cause systemic amyloidosis; for example, AA amyloidosis can occur secondary to IBD. The presence and pattern of gastrointestinal symptoms varies substantially, not only between the different types of amyloidosis but also within them. Typical clinical presentations, most of which are nonspecific, include macroglossia, hemorrhage, motility disorders, disturbance of bowel habit and malabsorption. Endoscopic and radiological features are also nonspecific, with the small intestine most commonly affected. Currently, the aim of therapy for amyloidosis is to slow amyloid formation by reducing the abundance of the fibril precursor protein. No specific treatments for the gastrointestinal symptoms of systemic amyloidosis are available; however, case reports and small published series encourage nutritional support for patients with motility disorders and pharmacological agents for treatment of diarrhea. Surgical procedures should be contemplated only in an emergency setting because of the risk of decompensation of organs affected by amyloid deposition.

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### Introduction

Amyloidosis is a disorder characterized by abnormal folding of proteins; the deposition of these proteins as insoluble fibrils disrupts tissue structure and function. Over 20 different proteins are known to form amyloid fibrils *in vivo*, but not all of these cause overt disease.<sup>1</sup> Despite the heterogeneity of the proteins that form amyloid fibrils, the structure and properties of all amyloid fibrils are remarkably similar. Nonfibrillar constituents of amyloid deposits include glycosaminoglycans, proteoglycans and serum amyloid P component, which is a normal plasma glycoprotein. Amyloidosis can be acquired or hereditary, and the deposition of amyloid fibrils can be localized or systemic.

Classification of amyloidosis is based on the precursor protein that forms the amyloid fibril (Table 1). Deposition of amyloid fibrils can occur in several different situations—firstly, when persistently high concentrations of a structurally normal protein are present (for example, high levels of serum amyloid A protein in chronic inflammatory states,  $\beta_2$ -microglobulin in patients on long-term dialysis for end-stage renal disease); secondly, in association with the production of an abnormal protein with amyloidogenic propensity (for example, certain immunoglobulin light chains from plasma cell dyscrasias, genetic variants of some proteins); and finally, after prolonged exposure to a normal concentration of a structurally normal protein with weak

inherent amyloidogenic potential, for example, senile systemic amyloidosis associated with the accumulation of wild-type transthyretin as amyloid in the hearts of elderly patients.<sup>2</sup> The clinical features of amyloidosis are dependent on the organs involved and can sometimes suggest the presence of a particular type of amyloid (Table 1).

### Clinical syndromes

#### Systemic AL amyloidosis

Systemic AL amyloidosis is the most common form of amyloidosis in the developed world and, in this region, is thought to be the cause of approximately 1 in 2,000 deaths. This disease is associated with an underlying but usually subtle clonal dyscrasia of plasma cells or B lymphoid cells.<sup>3</sup> The amyloid fibrils form from the N-terminus of the variable region of monoclonal  $\kappa$  or  $\lambda$  immunoglobulin light chains and may deposit in all organs except for the brain. Systemic AL amyloidosis is a very heterogeneous disease in its presentation and clinical course. Kidney involvement presents as proteinuria or renal impairment. Cardiac amyloid deposition usually manifests as a restrictive cardiomyopathy and confers a poor prognosis with a median survival of 4–6 months after the appearance of congestive cardiac failure.<sup>4</sup> Amyloid deposition in the autonomic nervous system presents variably and can cause orthostatic hypotension, impotence, urinary retention and gastrointestinal dysfunction. In addition, peripheral neuropathy can occur and progresses from a distal sensory deficit to a motor neuropathy in advanced cases. A plethora of potential

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#### Competing interests

The authors declare no competing interests.

soft tissue features including pseudohypertrophy of skeletal muscle, cutaneous lesions, carpal tunnel syndrome, periorbital bruising, macroglossia and lymphadenopathy can also be present. Hepatomegaly is common and may result from infiltration of amyloid fibrils, arise secondary to congestive cardiac failure or involve a combination of both factors. The typical biochemical profile of hepatic amyloidosis is characterized by elevated liver function test results indicative of obstructive liver diseases and is related to sinusoidal infiltration.<sup>5</sup>

### Systemic AA amyloidosis

AA amyloidosis is associated with chronic inflammation. The protein that forms the amyloid fibril is the N-terminal fragment of the acute phase reactant, serum amyloid A protein (SAA), an apolipoprotein constituent of HDL. The concentration of SAA can rise 1,000-fold during inflammation and remains persistently elevated until the inflammation remits. The outcome of patients with AA amyloidosis is favorable when the concentration of SAA is maintained below 10 mg/l.<sup>6</sup> Rheumatoid arthritis is the most common cause of AA amyloidosis in the developed world,<sup>7</sup> but many other conditions are associated with this disorder (Box 1). The presentation of AA amyloidosis is usually renal, characterized by nephrotic syndrome and/or renal impairment. Liver involvement in AA amyloidosis is a feature of advanced disease,<sup>8</sup> and clinical amyloid cardiomyopathy and autonomic neuropathy are exceptionally rare.<sup>9</sup>

### $\beta_2$ -Microglobulin amyloidosis

$\beta_2$ -Microglobulin amyloidosis can occur in patients who have received long-term dialysis for end-stage renal failure, and predominantly affects bones and joints.  $\beta_2$ -Microglobulin is a nonglycosylated protein found in all nucleated cells that is normally metabolized in the kidney. The concentration of  $\beta_2$ -microglobulin is greatly increased in the blood of patients with renal failure, and the deposition of  $\beta_2$ -microglobulin amyloid is influenced by length of time on dialysis, type of dialyzer membrane and cleanliness of the dialysis fluid.

### Hereditary systemic amyloidosis

The various types of hereditary amyloidosis are associated with genetically variant proteins, mostly comprising single amino acid substitutions. A common theme amongst these conditions is an autosomal dominant mode of inheritance, variable phenotype and expressivity. The different types of hereditary amyloidosis are diverse with respect to age of onset, mode of presentation, pattern of organ involvement and rate of progression, even within affected members of a single family, which suggests a contributory role of other factors. Familial amyloidotic polyneuropathy (FAP) is the most common type of hereditary systemic amyloidosis (Table 1) and is caused by mutations in the transthyretin gene, more than 100 of which have been described. Tetramers of transthyretin that contain amyloidogenic variants of transthyretin can

### Key points

- Amyloidosis is a multisystem disease caused by extracellular deposition of protein in an abnormal fibrillar form
- Gastrointestinal manifestations and malnutrition are common and multifactorial in etiology and have a negative impact on quality of life and survival
- Endoscopic and radiological features of gastrointestinal amyloid deposition are nonspecific
- Treatment of amyloidosis aims to reduce the abundance of the respective precursor protein that forms amyloid fibrils (for example, administration of anti-inflammatory drugs, chemotherapy or liver transplantation)
- Intensive nutritional support and nonspecific supportive measures are recommended for gastrointestinal complications

dissociate into monomers and form amyloid fibrils more readily than the wild-type protein can. Typical symptoms of FAP include progressive peripheral and autonomic neuropathy and the deposition of cardiac amyloid, which results in profound wasting and malnutrition that usually leads to death within 9–13 years.<sup>10</sup>

### Senile systemic amyloidosis

Senile systemic amyloidosis is caused by the deposition of amyloid fibrils derived from wild-type transthyretin.<sup>11</sup> The dominant clinical manifestations of this disorder are related to cardiac amyloid deposition (which presents as congestive cardiac failure or conduction disturbances), although carpal tunnel syndrome is common. Senile systemic amyloidosis is usually confined to individuals over 70 years of age and the cardiac features typically progress slowly. Subclinical involvement of the gastrointestinal tract is typically detected histologically within subserosal veins and is present in about 40% of individuals with senile systemic amyloidosis who are over 80 years of age.<sup>12</sup>

### Gastrointestinal manifestations

#### Oral manifestations

Macroglossia (Figure 1) is virtually pathognomonic of systemic AL amyloidosis and can cause numerous complications including dysphagia, dysarthria and, very occasionally, airway obstruction. Macroglossia is present in 10–23% of patients with systemic AL amyloidosis.<sup>3,13</sup> Other oral manifestations of systemic amyloidosis include bullous lesions, vesicles and ulcers. Involvement of the salivary glands can result in xerostomia, which mimics the symptoms of Sjögren syndrome.<sup>14</sup>

#### Esophageal manifestations

Patients with systemic amyloidosis that affects the esophagus can present with dyspepsia and dysphagia, which is usually caused by esophageal dysmotility. Hematemesis can also be a feature.<sup>15</sup> Esophageal manometry studies in patients with systemic AA amyloidosis, AL amyloidosis<sup>16</sup> or FAP<sup>17</sup> have shown abnormal manometric profiles, characterized by achalasia, aperistalsis in the esophageal body and abnormal lower esophageal sphincter relaxation.<sup>18</sup> In addition, portal hypertension

**Table 1** | Classification of amyloidosis

Type of amyloidosis	Abnormal amyloidogenic precursor protein	Clinical syndrome
AA	Serum amyloid A protein	Reactive systemic amyloidosis associated with chronic inflammatory diseases
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis associated with monoclonal plasma cell dyscrasias
A $\beta_2$ M	$\beta_2$ -microglobulin	Periarticular and, occasionally, systemic amyloidosis associated with long-term dialysis
ATTR	Normal plasma transthyretin	Senile systemic amyloidosis with prominent cardiac involvement
ATTR	Genetically variant transthyretin	Autosomal dominant systemic amyloidosis Familial amyloid polyneuropathy
ACys	Genetically variant cystatin C	Hereditary cerebral hemorrhage with cerebral and systemic amyloidosis
AGel	Genetically variant gelsolin	Autosomal dominant systemic amyloidosis Predominant cranial nerve involvement with lattice corneal dystrophy
ALys	Genetically variant lysozyme	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent visceral involvement
AApoAI	Genetically variant apolipoprotein AI	Autosomal dominant systemic amyloidosis Predominantly non-neuropathic with prominent visceral involvement
AApoAII	Genetically variant apolipoprotein AII	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
AFib	Genetically variant fibrinogen A $\alpha$ chain	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement

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and esophageal varices have been reported in individuals with extensive hepatic amyloid infiltration.<sup>19</sup>

**Gastric manifestations**

Patients with systemic amyloidosis that involves the stomach can present with early satiety, nausea, abdominal pain, vomiting or hematemesis. In one series of 769 patients with AL amyloidosis, 1% had symptomatic gastric amyloidosis.<sup>20</sup> Hemorrhage can occur in patients with lesions such as Dieulafoy type ulcers<sup>21</sup> and submucosal hematomas.<sup>22</sup> Gastric outlet obstruction can result from amyloid-induced peptic ulceration with benign pyloric stenosis.<sup>23</sup> Symptomatic gastroparesis is common in patients with FAP, which affects the autonomic nervous system,<sup>24</sup> but may also occur in patients with other types of amyloidosis.<sup>25</sup>

**Small intestine manifestations**

The small intestine is commonly affected in patients with systemic amyloidosis and the resultant symptoms are due either to intestinal dysmotility, which reflects predominantly neural involvement, or to the mechanical effects of direct mucosal infiltration by amyloid fibrils. The muscularis propria is more commonly involved in AL amyloidosis than in AA amyloidosis, which tends to affect the lamina propria.<sup>26</sup> Patients with FAP have a greater involvement of amyloid fibrils in and around the myenteric plexuses of the gastrointestinal tract than do patients with other forms of systemic amyloidosis.<sup>27</sup> One study of patients with FAP revealed a reduced number of endocrine cells that secrete serotonin, cholecystokinin, gastrin and secretin in the duodenum. The authors of

this study postulated that these changes contribute to dysmotility by inducing an imbalance in the neuro-endocrine regulation of intestinal motility. Interestingly, amyloid deposition in the intestinal lumen was not evident, providing further evidence that dysmotility is the dominant cause of gastrointestinal problems in these patients.<sup>28</sup> The differences in the histological presentation of the different types of amyloidosis have a bearing on the symptoms of the different diseases. The symptoms are also undoubtedly influenced by the portion of the gastrointestinal tract affected.

Diarrhea is the most common gastrointestinal symptom of systemic amyloidosis and has many potential etiologies. Diarrhea can be caused by bacterial overgrowth within the small intestine, which might be associated with intestinal dysmotility in patients with nonhereditary amyloidosis<sup>29</sup> or FAP.<sup>30</sup> In patients with FAP, malabsorption of bile acids might also have a role in development of diarrhea.<sup>31</sup> Such malabsorption may occur because of impaired water absorption or altered colonic transit time via effects on motor propulsion. These effects may again be linked to dysmotility. Another potential cause of diarrhea in patients with systemic amyloidosis is the rapid intestinal transit of digested products and secretions related to autonomic neuropathy.<sup>32</sup>

Steatorrhea occurs in <5% of patients with AL amyloidosis<sup>33</sup> but in up to 98% of those affected by FAP.<sup>34</sup> Steatorrhea probably develops secondary to a combination of factors, including intestinal dysmotility, bacterial overgrowth and bile salt malabsorption. Protein-losing enteropathy can also be caused by intestinal infiltration by amyloid fibrils, which results in increased capillary

**Box 1** | Conditions that can cause systemic AA amyloidosis**Inflammatory arthritis**

Adult Still disease  
Ankylosing spondylitis  
Juvenile idiopathic arthritis

Psoriatic arthropathy  
Rheumatoid arthritis

**Chronic infections**

Bronchiectasis  
Osteomyelitis  
Tuberculosis  
Skin abscesses (usually from injected drug abuse)

**Immunodeficiency states**

Common variable immunodeficiency  
HIV or AIDS

**Hereditary periodic fevers**

Familial Mediterranean fever  
Hyperimmunoglobulin D syndrome  
Muckle–Wells syndrome  
TNF receptor-associated periodic syndrome

**IBD**

Crohn's disease  
Ulcerative colitis

**Neoplasia**

Castleman disease  
Renal cell carcinoma  
Adenocarcinoma of the lung, gut and urogenital tract

**Systemic vasculitis**

Behçet disease  
Systemic lupus erythematosus

permeability with exudation of plasma proteins through an inflamed mucosa.<sup>35</sup>

Intestinal bleeding can occur due to diffuse intestinal amyloid infiltration,<sup>26</sup> the presence of isolated amyloid lesions<sup>36</sup> or secondary to infarction of the bowel.<sup>37</sup> A potential risk factor for intestinal hemorrhage in patients with systemic amyloidosis is vascular fragility.<sup>38</sup> Several bleeding diatheses, such as factor X deficiency, have been described in patients with amyloidosis but they might not necessarily be present in patients with evidence of gastrointestinal hemorrhage.<sup>39</sup>

Weight loss and malnutrition are common features of systemic amyloidosis and are associated with poor survival in patients with AL amyloidosis<sup>33</sup> and FAP.<sup>10</sup> In patients with AL amyloidosis, malnutrition seems to influence functional capacity in terms of the Eastern



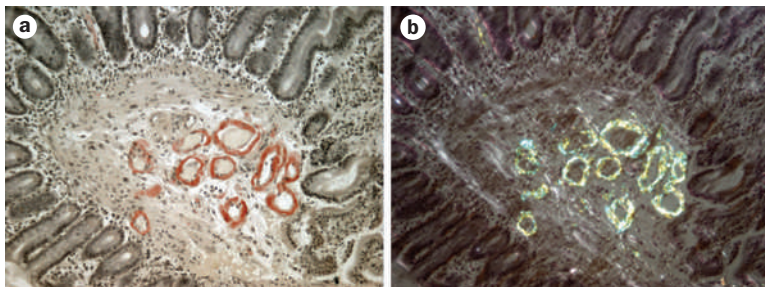
**Figure 1** | Massive macroglossia in a patient with systemic AL amyloidosis. Written consent for publication was obtained from the patient's responsible relative.

Cooperative Oncology Group (ECOG) performance status.<sup>40</sup> Gastrointestinal symptoms probably have a role in weight loss, but extraintestinal features of amyloidosis such as cardiac cachexia or liver infiltration might also contribute to weight loss in patients with systemic amyloidosis. Nutritional assessment and appropriate early intervention should be a high priority in patients with systemic amyloidosis.

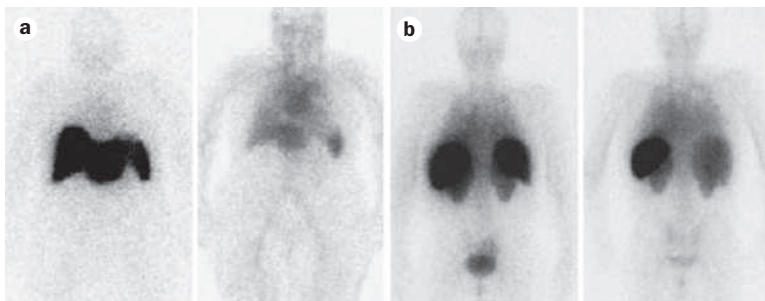
**Large intestine manifestations**

Amyloidosis of the large intestine can present in several ways. Complications related to mucosal infiltration by amyloid fibrils include bowel obstruction, perforation, hemorrhage and stricture formation. Motility disorders of the large intestine can initially present as constipation, which progresses to diarrhea and, in advanced stages, to fecal incontinence. In one study, constipation was attributed to an enteric neuropathy.<sup>41</sup> Analogous to amyloidosis of the small intestine, a decrease in the number of intestinal endocrine cells that secrete hormones, such as serotonin, has been proposed to alter the neuroendocrine milieu and intestinal motility, and thereby cause constipation.<sup>42</sup>

Pseudo-obstruction can affect any part of the intestine. Pseudo-obstruction in AA amyloidosis is typically acute or subacute and self-limiting but has a more chronic course in patients with AL amyloidosis, with a negative influence on survival.<sup>43</sup> These different outcomes may, in part, be explained by the different patterns of amyloid



**Figure 2** | Congo red staining of amyloid deposits in duodenal submucosal vessels **a** | viewed under brightfield microscopy and **b** | cross-polarized light, which reveals pathognomonic apple green birefringence.



**Figure 3** | Serum amyloid P component scintigraphy in patients with systemic amyloidosis. **a** | Anterior whole-body view in a patient with AL amyloidosis treated with chemotherapy. The pretreatment image (left) shows amyloid deposits in the liver and spleen, which obscure the kidneys, and the post-treatment image (right) shows regression of amyloid deposition from the liver and spleen. **b** | Posterior whole-body view in a patient with juvenile rheumatoid arthritis. Pretreatment image (left) shows amyloid deposition in the liver, spleen and kidney; follow-up image whilst in remission with well-controlled inflammation (right) shows regression predominantly from the liver. Permission obtained from Nature Publishing Group © Gillmore, J. D. & Hawkins, P. N. *Nat. Clin. Pract. Nephrol.* **2**, 263–270 (2006).

deposition, as assessed by histology. Involvement of the myenteric plexus in AA-type amyloidosis can be potentially compensated for by other enteric neurons. By contrast, AL-type amyloid infiltrates smooth muscle, the effects of which are more likely to be irreversible.<sup>43</sup>

### Crohn's disease and AA amyloidosis

Systemic amyloidosis can cause an array of gastrointestinal complications but conversely, primary diseases of the gastrointestinal tract can also cause AA amyloidosis. This form of amyloidosis is a rare complication of IBD and occurs more commonly in patients with Crohn's disease (frequency 0.9%) than in patients with ulcerative colitis (frequency 0.07%).<sup>44</sup> The reason why Crohn's disease is more readily complicated by AA amyloidosis than ulcerative colitis is not known but could relate to the greater degree of systemic inflammation seen in patients with Crohn's disease, particularly in association with suppurative features, such as abscesses and fistulae.<sup>45</sup>

### Diagnosis and monitoring of amyloidosis

The diagnosis of amyloidosis is often made long after the onset of symptoms because of its nonspecific and varied

presentation, which can mimic many other conditions. Diagnosis requires confirmation of the presence of amyloid fibrils by histology and is achieved by staining suspected amyloidotic tissue with Congo red; in the presence of amyloid fibrils, apple green birefringence under cross-polarized light will be visualized by light microscopy (Figure 2).<sup>46</sup> Common biopsy sites include kidneys, liver, subcutaneous fat, bone marrow and the gastrointestinal tract. 'Screening' biopsies of the gastrointestinal tract and abdominal fat are diagnostic in most cases of systemic amyloidosis, whereas direct biopsy of an affected organ, such as the liver or kidney, has close to 100% sensitivity. Liver biopsy via the percutaneous route is not generally advised if amyloid deposition is suspected because of the risk of hemorrhage.<sup>8</sup> The precise identification of the amyloid fibril protein is critical in all cases of amyloidosis since treatment is type-specific. Immunohistochemistry should, therefore, be routinely performed in biopsy samples from any patient with amyloidosis, although in our experience, this technique may fail to diagnose the amyloid type in up to 50% of cases. Clinical manifestations and immunohistochemistry alone may, therefore, not be sufficient to distinguish between AL amyloidosis and hereditary amyloidosis, and screening for mutations in the genes that encode known variant proteins that can form amyloid fibrils may be necessary to exclude hereditary types.<sup>47</sup> Monoclonal gammopathies are not infrequent in the general population, and although the presence of a monoclonal gammopathy in a patient with systemic amyloidosis is suggestive of AL type, it does not prove that the amyloid fibrils are composed of the monoclonal immunoglobulin light chain. Immunohistochemistry and/or genetic sequencing is, therefore, required for a definitive diagnosis.<sup>47</sup>

Another diagnostic modality is SAP scintigraphy, which at present, is available in only two centers in the world. SAP binds to all amyloid fibrils and, when radio-labeled and intravenously injected, can be used to identify and quantify visceral amyloid deposits. Serial SAP scans can be used to monitor the regression or accumulation of amyloid deposits (Figure 3).<sup>48</sup> In patients with AA amyloidosis, hepatic involvement is associated with a poor prognosis.<sup>8</sup> In patients with AL amyloidosis, total body amyloid load as assessed by SAP scintigraphy is useful for evaluating the risk of potential treatments such as stem cell transplantation.<sup>1</sup>

Treatment of amyloidosis aims to reduce the abundance of the protein that forms the amyloid fibrils. Monitoring the concentration of amyloidogenic precursors, such as monoclonal immunoglobulin light chains in AL amyloidosis and SAA in AA amyloidosis, might be helpful diagnostically and is critical to determine response of the patient to treatment.

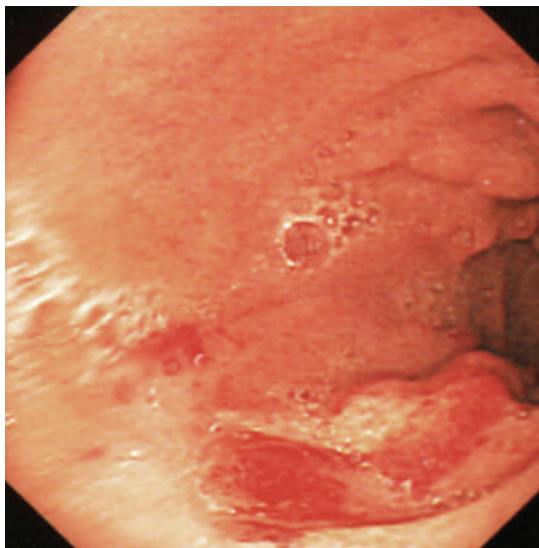
### Endoscopy and histology

Mucosal abnormalities of the gastrointestinal tract as observed by endoscopy or histologically are

common but nonspecific in patients with amyloidosis. Involvement of the small intestine is especially common.<sup>26</sup> In one study of 37 patients with systemic amyloidosis, abnormal endoscopy findings were most marked in the duodenum and correlated with the extent of amyloid deposition. Amyloid fibrils were identified in 100% of biopsy samples from the duodenum, 95% of samples from the stomach, 91% of colorectal samples and in 72% of esophageal samples.<sup>49</sup> However, the rectum remains the most common site of the gastrointestinal tract for biopsy for histological diagnosis of amyloidosis because of the ease of access and an acceptable sensitivity of histological analysis of 75–94%.<sup>50</sup> Submucosal vessels should be included in the biopsy sample to increase sensitivity since diffuse vascular involvement of amyloid fibrils is very common in systemic amyloidosis.<sup>51</sup>

A variety of abnormalities can be observed in the small intestine of patients with systemic amyloidosis. One endoscopic study of the jejunum noted a fine granular appearance of the mucosa, erosions, mucosal friability, shallow ulcers, thickening of the valvulae conniventes and polypoid protrusions. Valvulae conniventes and polypoid protrusions were seen only in patients with AL amyloidosis while the fine granular appearance of the mucosa was more frequently observed in AA amyloidosis than in patients with other types of this disease.<sup>52</sup> Histological assessment of the jejunal biopsy samples demonstrated diffuse deposition of amyloid fibrils within the muscularis mucosa, submucosa and muscularis propria in patients with AL amyloidosis, whereas isolated deposits of granular amyloid fibrils in the propria mucosa were seen more often in those with AA amyloidosis. These patterns were observed with statistical significance in both amyloidosis types. Consistent with these different histological appearances, diarrhea, malabsorption and fecal occult blood was common in patients with AA amyloidosis, whereas mechanical obstruction and chronic intestinal pseudo-obstruction were only apparent in patients with AL and  $\beta_2$ -microglobulin amyloidosis.<sup>52</sup> New endoscopic techniques, such as enteroscopy and capsule endoscopy, have also been used to aid diagnosis of amyloidosis in the small intestine.<sup>53,54</sup> An endoscopist should be open to the possibility of systemic amyloidosis on visualization of nonspecific lesions in the gastrointestinal tract, which are especially prominent in the upper gastrointestinal tract (Figure 4).

In addition, amyloidosis of the large intestine is associated with an array of mucosal abnormalities such as a hemorrhagic bullous colitis, in which amyloid deposition leads to cleavage between the submucosa and muscularis mucosa,<sup>55</sup> and petechial mucosal suffusion, in which the mucosal petechiae are thought to occur secondary to vascular infiltration by amyloid fibrils.<sup>56</sup> Another endoscopic technique used to diagnose amyloidosis of the large intestine is narrow-band imaging, which uses optical filters to enhance mucosal morphology



**Figure 4** | Endoscopic appearance of gastric ulceration secondary to hereditary lysozyme amyloidosis. This disorder frequently causes lesions that can lead to gastrointestinal hemorrhage.

without the need for dye spraying. When combined with high-resolution endoscopy, this technique can help differentiate between rectal amyloid deposits and neoplastic lesions.<sup>57</sup>

#### Radiology

No specific radiological features of gastrointestinal tract amyloidosis exist. The prevalence of radiological abnormalities in patients with systemic amyloidosis is highest in the small intestine, which corroborates the histological findings. One study that examined the correlation between radiological abnormalities and histological findings of amyloidosis reported that a coarse mucosal pattern with fine granular elevations by radiological barium examination were typically associated with AA amyloid deposits in the lamina propria. Findings of polypoid protrusions and variable fold thickening by barium examination were indicative of AL amyloid deposition in the muscularis mucosa and submucosa.<sup>58</sup> The presence of  $\beta_2$ -microglobulin amyloidosis was associated with delayed intestinal transit and bowel dilatation, which was secondary to amyloid deposition in the muscularis propria.<sup>58</sup> Other investigative techniques for evaluation of amyloid deposition within the small intestine include ultrasonography, CT imaging<sup>59</sup> and endoscopic ultrasonography.<sup>60</sup>

Assessment of amyloid deposition in the lower gastrointestinal tract by barium enema has shown luminal narrowing, loss of colonic haustration, thickened mucosal folds and a nodular mucosal pattern.<sup>61</sup> CT<sup>62</sup> and rectal endoscopic ultrasonography<sup>63</sup> have also been used to assess the presence of amyloid fibrils in the lower gastrointestinal tract and have demonstrated features such as thickened walls and bowel dilatation.

**Table 2** | Treatment of systemic amyloidosis

Disease	Aim of treatment	Example of treatment
AA amyloidosis	Suppress the acute phase response and, thereby, reduce the production of serum amyloid A protein	Anti-inflammatory and immunosuppressive therapy in patients with rheumatoid arthritis and Crohn's disease (e.g. anti-TNF antibodies) Colchicine for patients with familial Mediterranean fever Surgery for patients with osteomyelitis and rare cytokine-producing tumors
AL amyloidosis	Suppress production of monoclonal immunoglobulin light chains	Chemotherapy directed at plasma cell dyscrasia
Hereditary amyloidosis	Eliminate source of genetically variant protein	Orthotopic liver transplantation for patients with familial amyloid polyneuropathy secondary to variant transthyretin or renal amyloidosis secondary to variant fibrinogen A $\alpha$ -chain
$\beta_2$ -Microglobulin amyloidosis	Reduce plasma concentration of $\beta_2$ -microglobulin	Renal transplantation

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### Treatment of systemic amyloidosis

The prognosis of systemic amyloidosis has improved markedly over the past few decades. In the absence of specific anti-amyloid therapy, the principle of treatment is to reduce the abundance of the amyloidogenic precursor protein (Table 2). This approach can lead to regression of amyloid deposition and result in stabilization or improvement of organ function. Initial therapeutic efficacy is indicated by a reduced concentration of the relevant precursor protein, which may then be followed by regression of amyloidosis (Figure 3) and improvement in amyloidotic organ dysfunction.

Treatment of AL amyloidosis is with hematological stem cell transplantation or with myeloma-type chemotherapy, although important differences in treatment of myeloma and AL amyloidosis exist. The plasma cell dyscrasias that are usually present in patients with AL amyloidosis tend to be subtle and low grade. A complete hematological response is not the universal goal in the treatment of AL amyloidosis, since a partial response can be sufficient to lead to improvement in organ function. Toxicity of therapy is often substantial in patients with amyloidosis, particularly in those whose affected organs might have reduced functional reserve.<sup>64</sup>

The aim of therapy for patients with AA amyloidosis is to reduce the production of SAA. Survival of the patient, amyloidotic organ survival and change in amyloid load are directly influenced by SAA concentration.<sup>6</sup> In addition to specific anti-inflammatory or immunosuppressive therapies for any given underlying inflammatory condition, biological agents that target pivotal inflammatory cytokines, such as tumor necrosis factor, have had an immense effect on the treatment of a variety of conditions that underlie AA amyloidosis.

For patients with hereditary systemic amyloidosis in whom the amyloidogenic precursor protein is produced solely by the liver, treatment has been revolutionized by liver transplantation as a form of 'surgical gene therapy'. Liver transplantation has been used most successfully for treatment of FAP.<sup>65</sup> The mainstay of therapy for patients with  $\beta_2$ -microglobulin amyloidosis is supportive, but kidney transplantation

is associated with very rapid and marked relief of musculoskeletal symptoms.<sup>66</sup>

### Treatment of gastrointestinal manifestations

No specific treatments for the gastrointestinal complications of amyloidosis are available. Supportive measures are universally employed; however, anecdotal reports of clinical benefit with several pharmacological agents and surgery exist. Dimethyl sulfoxide may provide relief of gastrointestinal symptoms, such as diarrhea and protein-losing enteropathy, in patients with AA amyloidosis, which correlates with an improvement in endoscopic findings.<sup>67</sup> The somatostatin analog octreotide has been successfully used in combination with steroids to treat refractory diarrhea in patients with AA amyloidosis. Octreotide is thought to work by suppressing the secretion of gastrointestinal hormones, such as serotonin and vasoactive intestinal peptide, which increase vascular permeability and intestinal motility.<sup>68</sup> Biological agents such as tocilizumab, an anti-interleukin-6 receptor antibody, have been used to successfully reduce inflammation and SAA levels and to subsequently induce regression of amyloidosis in the gastrointestinal tract as assessed by histology.<sup>69</sup>

Gastrointestinal hemorrhage is a potentially life-threatening consequence of amyloid deposition in the gastrointestinal tract. Arterial embolization of intestinal vessels that are extravasating blood on visualization by angiography has been used with beneficial effect.<sup>70</sup> The role of endoscopic therapy in situations of gastrointestinal bleeding for patients with systemic amyloidosis has not been clearly defined and reports of success with endoscopic hemostasis in studies or case series are lacking. Endoscopy has been used with success for dilatation of amyloid-associated achalasia in the esophagus<sup>71</sup> and for treatment of gastric outflow obstruction secondary to amyloid-induced peptic ulceration.<sup>23</sup>

Anecdotal reports suggest that prokinetic agents such as metoclopramide<sup>72</sup> and erythromycin<sup>25</sup> may benefit dysmotility-related symptoms. Nausea can be managed with antiemetic agents such as ondansetron. For patients with AA amyloidosis-related pseudo-obstruction,

conservative therapy such as total parenteral nutrition can be beneficial by bridging the period needed for recovery of bowel function. This recovery occurs after neuronal compensation by unaffected neurons within the large network of the myenteric plexus.<sup>43</sup>

Amyloid-associated diarrhea and malabsorption are problematic and are often difficult to treat. Antimicrobial therapy can be of benefit for patients with intestinal bacterial overgrowth,<sup>30</sup> and antidiarrheal agents such as loperamide or codeine phosphate may ameliorate symptoms. Use of bile acid sequestrants has not formally been assessed, but little published evidence of benefit with such agents exists.<sup>32</sup>

Gastrointestinal surgery should not be performed in patients with amyloidosis without careful preoperative assessment and an awareness of the associated risks. Amyloid involvement in the heart or kidneys may substantially increase the risks associated with general anesthesia or surgery as amyloidotic organs may decompensate, for example with sepsis or hypotension, because of lack of functional reserve. Patients with systemic amyloidosis also have a high risk of hemorrhage and poor wound healing following surgery.<sup>73</sup> Anastomotic dehiscence is a risk for patients with amyloidosis who undergo bowel surgery; this complication may be related to the presence of amyloid deposits in resection margins.<sup>74</sup> Our own anecdotal experience of surgery for severe macroglossia in patients who are frequently malnourished with a compromised aerodigestive system has not been favorable. Difficulties arise with the practicalities of airway management for anesthesia and considerable hemorrhagic risk is involved with surgery for an amyloidotic tongue.

Liver transplantation has been used with success in patients with FAP but requires a thorough pretransplant assessment. Liver transplantation results in improvement in gastrointestinal symptoms and nutritional indices in up to 50% of patients with FAP,<sup>75</sup> particularly if transplantation is performed early in the course of disease. Poor nutritional state and malabsorption before surgery confer poor survival in patients with FAP<sup>76</sup> and, in such patients, these indices rarely improve after transplantation.<sup>77</sup>

### Future treatments

Other potential treatments for systemic amyloidosis include fibril precursor protein stabilizers, immunotherapy and inhibitors of fibrillogenesis. In our own center we have focused on SAP as a therapeutic target and developed a small-molecule drug with the aim to

inhibit binding of SAP to amyloid fibrils. This inhibitor, R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC),<sup>78</sup> depletes levels of circulating SAP and shows promise in its ability to arrest amyloid deposition.<sup>79</sup> Furthermore, combined administration of CPHPC and anti-SAP antibodies potentially clears established amyloid deposits in mice.<sup>80</sup> This approach is now being developed for human use.

### Conclusions

The systemic amyloidosis syndromes constitute a diverse group of disorders characterized by the deposition of fibrillar protein within organs. The pattern of organ involvement and dysfunction varies substantially, not only between different amyloid types, but also within each type. The relative rarity of these diseases, along with their protean clinical presentations and requirement for precise immunohistochemical staining of biopsy specimens makes the diagnosis of amyloidosis challenging. The possibility of systemic amyloidosis is thus often overlooked, resulting in substantial delays in diagnosis. A high index of suspicion is, therefore, required.

Current treatment of the systemic amyloidosis syndromes aims to reduce the abundance of the fibril precursor protein, specific to the amyloidosis type, and can substantially benefit patients. Considerable advances have been made in our understanding of the pathophysiology of amyloidosis, accompanied by developments in treatment that result in improved organ function, quality of life and survival of patients. Future treatments for systemic amyloidosis include fibril precursor protein stabilizers, inhibitors of fibrillogenesis and immunotherapy.

Gastrointestinal symptoms and malnutrition are common in patients with systemic amyloidosis, are often multifactorial in etiology and have a negative influence on quality of life and overall survival of patients. These features should, therefore, be actively sought and treated in all individuals with systemic amyloidosis.

### Review criteria

References were obtained from papers that have appeared in the medical literature and have reported on the pathogenesis of amyloidosis and/or the investigation and management of gastrointestinal amyloidosis. The main source was PubMed. Terms used to search PubMed were "amyloid", "amyloidosis", "gastrointestinal amyloidosis", "histology amyloidosis", "radiology amyloidosis" and "endoscopy amyloidosis". All articles were searched with no restriction in terms of dates or language.

1. Pepys, M. B. Amyloidosis. *Annu. Rev. Med.* **57**, 223–241 (2006).
2. Pepys, M. B. Pathogenesis, diagnosis and treatment of systemic amyloidosis. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **356**, 203–210 (2001).
3. Kyle, R. A. & Gertz, M. A. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin. Hematol.* **32**, 45–59 (1995).
4. Dubrey, S. W. *et al.* The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM* **91**, 141–157 (1998).
5. Park, M. A. *et al.* Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. *Medicine (Baltimore)* **82**, 291–298 (2003).
6. Gillmore, J. D., Lovat, L. B., Persey, M. R., Pepys, M. B. & Hawkins, P. N. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* **358**, 24–29 (2001).
7. Gertz, M. A. & Kyle, R. A. Secondary systemic amyloidosis: response and survival in 64

- patients. *Medicine (Baltimore)* **70**, 246–256 (1991).
8. Lovat, L. B., Persey, M. R., Madhoo, S., Pepys, M. B. & Hawkins, P. N. The liver in systemic amyloidosis: insights from <sup>123</sup>I serum amyloid P component scintigraphy in 484 patients. *Gut* **42**, 727–734 (1998).
  9. Lachmann, H. J. et al. Natural history and outcome in systemic AA amyloidosis. *N. Engl. J. Med.* **356**, 2361–2371 (2007).
  10. Suhr, O., Danielsson, A., Holmgren, G. & Steen, L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J. Intern. Med.* **235**, 479–485 (1994).
  11. Westermark, P., Sletten, K., Johansson, B. & Cornwell, G. G. 3rd. Fibril in senile systemic amyloidosis is derived from normal transthyretin. *Proc. Natl Acad. Sci. USA* **87**, 2843–2845 (1990).
  12. Matsutani, H. 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.* **51**, 326–332 (2001).
  13. Prokaveva, T. et al. Soft tissue, joint and bone manifestations of AL amyloidosis: clinical presentation, molecular features and survival. *Arthritis Rheum.* **56**, 3858–3868 (2007).
  14. Gogel, H. K., Searles, R. P., Volpicelli, N. A. & Cornwell, G. G. 3rd. Primary amyloidosis presenting as Sjögren's syndrome. *Arch. Intern. Med.* **143**, 2325–2326 (1983).
  15. Khan, G. A., Lewis, F. I. & Dasgupta, M.  $\beta_2$ -microglobulin amyloidosis presenting as esophageal perforation in a hemodialysis patient. *Am. J. Nephrol.* **17**, 524–527 (1997).
  16. Rubinow, A., Burakoff, R. & Cohen, A. S. & Harris, L. D. Esophageal manometry in systemic amyloidosis: a study of 30 patients. *Am. J. Med.* **75**, 951–956 (1983).
  17. Bjerle, P., Ek, B., Linderholm, H. & Steen, L. Oesophageal dysfunction in familial amyloidosis with polyneuropathy. *Clin. Physiol.* **13**, 57–69 (1993).
  18. Battle, W. M., Rubin, M. R., Cohen, S. & Snape, W. J. Jr. Gastrointestinal-motility dysfunction in amyloidosis. *N. Engl. J. Med.* **301**, 24–25 (1979).
  19. Melkebeke, P., Vandepitte, J., Hannon, R. & Fevery, J. Huge hepatomegaly, jaundice and portal hypertension due to amyloidosis of the liver. *Digestion* **20**, 351–357 (1980).
  20. Menke, D. M. et al. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. *Mayo Clin. Proc.* **68**, 763–767 (1993).
  21. Youssef, N. et al. Fatal Dieulafoy's type ulcer in a case of AL amyloidosis [French]. *Ann. Pathol.* **24**, 256–258 (2004).
  22. Muraki, M. et al. Laceration of gastric mucosa associated with dialysis-related amyloidosis. *Clin. Nephrol.* **64**, 448–451 (2005).
  23. Hizawa, K. et al. Endoscopic hydrostatic balloon dilatation of ulcer-induced pyloric stenosis in rheumatoid arthritis and secondary amyloidosis. *Surg. Endosc.* **11**, 673–675 (1997).
  24. Suhr, O. B., Anan, I., Ahlström, K. R. & Rydh, A. Gastric emptying before and after liver transplantation for familial amyloidotic polyneuropathy: Portuguese type (Val30Met). *Amyloid* **10**, 121–126 (2003).
  25. Saglam, F. et al. A renal transplant recipient with delayed gastric emptying in amyloidosis due to familial Mediterranean fever improved with erythromycin: a case report. *Transplant. Proc.* **40**, 308–309 (2008).
  26. Gilat, T. & Spiro, H. M. Amyloidosis and the gut. *Am. J. Dig. Dis.* **13**, 619–633 (1968).
  27. Yoshimatsu, S. et al. Endoscopic and pathological manifestations of the gastrointestinal tract in familial amyloidotic polyneuropathy type I (Met30). *J. Intern. Med.* **243**, 65–72 (1998).
  28. El-Salhy, M., Suhr, O., Stenling, R., Wilander, E. & Grimelius, L. Impact of familial amyloid associated polyneuropathy on duodenal endocrine cells. *Gut* **35**, 1413–1418 (1994).
  29. Matsumoto, T. et al. Breath hydrogen test using water-diluted lactulose in patients with gastrointestinal amyloidosis. *Dig. Dis. Sci.* **36**, 1756–1760 (1991).
  30. Feurle, G. E. Pathophysiology of diarrhea in patients with familial amyloid neuropathy. *Digestion* **36**, 13–17 (1987).
  31. Suhr, O., Danielsson, A. & Steen, L. Bile acid malabsorption caused by gastrointestinal motility dysfunction? An investigation of gastrointestinal disturbances in familial amyloidosis with polyneuropathy. *Scand. J. Gastroenterol.* **27**, 201–207 (1992).
  32. Guiril, M. J. et al. Rapid intestinal transit as a primary cause of severe chronic diarrhea in patients with amyloidosis. *Am. J. Gastroenterol.* **98**, 2219–2225 (2003).
  33. Hayman, S. R., Lacy, M. Q., Kyle, R. A. & Gertz, M. A. Primary systemic amyloidosis: a cause of malabsorption syndrome. *Am. J. Med.* **111**, 535–540 (2001).
  34. Steen, L. & Ek, B. Familial amyloidosis with polyneuropathy: a long term follow up of 21 patients with special reference to gastrointestinal symptoms. *Acta Med. Scand.* **214**, 387–397 (1983).
  35. Kawaguchi, M., Koizumi, F., Shimao, M. & Hirose, S. Protein-losing enteropathy due to secondary amyloidosis of the gastrointestinal tract. *Acta Pathol. Jpn* **43**, 333–339 (1993).
  36. Chang, H. S. et al. Massive small bowel bleeding in a patient with amyloidosis. *Gastrointest. Endosc.* **59**, 126–129 (2004).
  37. Mallory, A., Struthers, J. E. Jr & Kern, F. Jr. Persistent hypotension and intestinal infarction in a patient with primary amyloidosis. *Gastroenterology* **68**, 1587–1592 (1975).
  38. Rapoport, M., Yona, R., Kaufman, S., Segal, M. & Kornberg, A. Unusual bleeding manifestations of amyloidosis in patients with multiple myeloma. *Clin. Lab. Haematol.* **16**, 349–353 (1994).
  39. Yood, R. A., Skinner, M., Rubinow, A., Talarico, L. & Cohen, A. S. Bleeding manifestations in 100 patients with amyloidosis. *JAMA* **249**, 1322–1324 (1983).
  40. Caccialanza, R. et al. Nutritional status of outpatients with systemic immunoglobulin light-chain amyloidosis. *Am. J. Clin. Nutr.* **83**, 350–354 (2006).
  41. Ito, T. et al. Mechanism of constipation in familial amyloid polyneuropathy: a case report. *Intern. Med.* **45**, 1173–1175 (2006).
  42. El-Salhy, M. & Suhr, O. Endocrine cells in rectal biopsy specimens from patients with familial amyloidotic polyneuropathy. *Scand. J. Gastroenterol.* **31**, 68–73 (1996).
  43. Tada, S., Iida, M., Yao, T., Kitamoto, T., Yao, T. & Fujishima, M. Intestinal pseudo-obstruction in patients with amyloidosis: clinicopathologic differences between chemical types of amyloid protein. *Gut* **34**, 1412–1417 (1993).
  44. Greenstein, A. J. et al. Amyloidosis and inflammatory bowel disease: a 50 year experience with 25 patients. *Medicine (Baltimore)* **71**, 261–270 (1992).
  45. Wester, A. L., Vatn, M. H. & Fausa, O. Secondary amyloidosis in inflammatory bowel disease: a study of 18 patients admitted to Rikshospitalet University Hospital, Oslo, from 1962–1998. *Inflamm. Bowel Dis.* **7**, 295–300 (2001).
  46. Puchtler, H., Sweat, F. & Levine, M. On the binding of Congo red by amyloid. *J. Histochem. Cytochem.* **10**, 355–364 (1962).
  47. Lachmann, H. J. et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N. Engl. J. Med.* **346**, 1786–1791 (2002).
  48. Hawkins, P. N. Studies with radiolabelled serum amyloid P component provide evidence for turnover and regression of amyloid deposits *in vivo*. *Clin. Sci. (Lond.)* **87**, 289–295 (1994).
  49. Tada, S. et al. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. *Gastrointest. Endosc.* **36**, 10–14 (1990).
  50. Ebert, E. C. & Nagar, M. Gastrointestinal manifestations of amyloidosis. *Am. J. Gastroenterol.* **103**, 776–787 (2008).
  51. Yamada, M., Hatakeyama, S. & Tsukagoshi, H. Gastrointestinal amyloid deposition in AL (primary or myeloma-associated) and AA (secondary) amyloidosis: diagnostic value of gastric biopsy. *Hum. Pathol.* **16**, 1206–1211 (1985).
  52. Tada, S. et al. Endoscopic features in amyloidosis of the small intestine: clinical and morphologic differences between chemical types of amyloid protein. *Gastrointest. Endosc.* **40**, 45–50 (1994).
  53. Michael, H. et al. Congo-red negative colonic amyloid with scalloping of the valvulae conniventes. *Gastrointest. Endosc.* **53**, 653–655 (2001).
  54. Pollack, M. J. & Isenberg, G. A. Isolated small bowel amyloidosis seen with capsule endoscopy. *Gastrointest. Endosc.* **66**, 829–830 (2007).
  55. Dray, X. et al. Hemorrhagic bullous colitis as a primary manifestation of AL amyloidosis. *Endoscopy* **38**, E15–E16 (2006).
  56. Schmidt, H., Frühmorgen, P., Riemann, J. F. & Becker, V. Mucosal saggillation in the colon in secondary amyloidosis. *Endoscopy* **13**, 181–183 (1981).
  57. Hui, Y. T., Lam, T. W., Yee Lam, P. W., Yan Wu, W. H. & Lam, W. M. Narrow-band imaging system with magnifying endoscopy for rectal amyloidosis. *Gastrointest. Endosc.* **68**, 400–401 (2008).
  58. Tada, S. et al. Gastrointestinal amyloidosis: radiologic features by chemical types. *Radiology* **190**, 37–42 (1994).
  59. Kala, Z., Válek, V. & Kysela, P. Amyloidosis of the small intestine. *Eur. J. Radiol.* **63**, 105–109 (2007).
  60. Goulding, C., O'Hanlon, D. M., Clarke, E., Kennedy, M. & Lennon, J. Primary amyloidosis of the stomach: EUS appearances. *Gastrointest. Endosc.* **56**, 305–306 (2002).
  61. Trinh, T. D., Jones, B. & Fishman, E. K. Amyloidosis of the colon presenting as ischemic colitis: a case report and review of the literature. *Gastrointest. Radiol.* **16**, 133–136 (1991).
  62. Araoz, P. A., Batts, K. P. & MacCarty, R. L. Amyloidosis of the alimentary canal: radiologic-pathologic correlation of CT findings. *Abdom. Imaging* **25**, 38–44 (2000).

63. Gandolfi, L. *et al.* Endoscopic ultrasonography in the diagnosis of gastrointestinal amyloid deposits: clinical case report. *Endoscopy* **27**, 132–134 (1995).
64. Wechalekar, A. D., Hawkins, P.N. & Gillmore, J. D. Perspectives in treatment of AL amyloidosis. *Br. J. Haematol.* **140**, 365–377 (2008).
65. Holmgren, G. *et al.* Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. *Lancet* **341**, 1113–1116 (1993).
66. Tan, S. Y. *et al.* Long term effect of renal transplantation on dialysis-related amyloid deposits and symptomatology. *Kidney Int.* **50**, 282–289 (1996).
67. Amemori, S. *et al.* Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. *J. Gastroenterol.* **41**, 444–449 (2006).
68. Fushimi, T. *et al.* Severe protein losing enteropathy with intractable diarrhea due to systemic AA amyloidosis, successfully treated with corticosteroid and octreotide. *Amyloid* **12**, 48–53 (2005).
69. Okuda, Y. & Takasugi, K. Successful use of humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. *Arthritis Rheum.* **54**, 2997–3000 (2006).
70. Maeshima, E., Yamada, Y. & Yukawa, S. Massive gastrointestinal hemorrhage in a case of amyloidosis secondary to rheumatoid arthritis. *Scand. J. Rheumatol.* **28**, 262–264 (1999).
71. Costigan, D. J. & Clouse, R. E. Achalasia-like esophagus from amyloidosis. Successful treatment with pneumatic bag dilatation. *Dig. Dis. Sci.* **28**, 763–765 (1983).
72. Reddy, A. B., Wright, R. A., Wheeler, G. E. & Nazer, H. Nonobstructive gastroparesis in amyloidosis with metoclopramide. *Arch. Intern. Med.* **143**, 247–248 (1983).
73. Mardinger, O., Rotenberg, I., Chaushu, G. & Taicher, S. Surgical management of macroglossia due to primary amyloidosis. *Int. J. Oral Maxillofac. Surg.* **28**, 129–131 (1999).
74. Johnson, D. H., Guthrie, T. H., Tedesco, F. J., Griffin, J. W. & Anthony, H. F. Jr. Amyloidosis masquerading as inflammatory bowel disease with a mass lesion stimulating a malignancy. *Am. J. Gastroenterol.* **77**, 141–145 (1982).
75. Herlenius, G., Wilczek, H. E., Larsson, M. & Ericzon, B. G. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation* **77**, 64–71 (2004).
76. Suhr, O. *et al.* Impact of gastrointestinal dysfunction on survival after liver transplantation for familial amyloidotic polyneuropathy. *Dig. Dis. Sci.* **41**, 1909–1914 (1996).
77. Lång, K., Wikström, L., Danielsson, A., Tashima, K. & Suhr, O. B. Outcome of gastrointestinal complications after liver transplantation for familial amyloidotic polyneuropathy. *Scand. J. Gastroenterol.* **35**, 985–989 (2000).
78. Pepys, M. B. *et al.* Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* **417**, 254–259 (2002).
79. Pepys, M. B. in *Amyloid and Amyloidosis* (eds Grateau, G. *et al.*) 488–490 (CRC, Boca Raton, 2005).
80. Pepys, M. B. Science and serendipity. *Clin. Med.* **7**, 562–578 (2007).