CASE REPORT

Multisystem amyloidosis as the unifying diagnosis for constipation, collapse and cardiomyopathy

Michael McFarlane,¹ Alexander Bashford,¹ Shatrughan Sah,² Ben R Disney¹

¹Gastroenterology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

²Histopathology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Correspondence to

Dr Michael McFarlane, mmcf1982@doctors.org.uk

Accepted 22 June 2018

SUMMARY

Amyloidosis a rare disorder characterised by the deposition of amyloid protein aggregates in different organ systems throughout the body with resulting functional impairment of affected organs. It can present with localised or multisystemic deposits. Diagnosis is often delayed due to the non-specific nature of the symptoms. We present the case of a 59-year-old man with a 12-month history of non-specific symptoms. Investigations revealed *Helicobacter pylori* positive gastritis. Blood tests showed only a normocytic anaemia and thrombocytopaenia. CT scan showed proximal sigmoid thickening. Biopsies were unremarkable. Echocardiogram and cardiac MRI scan showed restrictive cardiomyopathy. Congo red staining of gastric biopsies showed amyloid deposition. The patient had elevated serum kappa light chains and a bone marrow biopsy confirmed multiple myeloma and he was subsequently diagnosed with systemic light chain (AL) amyloidosis secondary to this. He was started on chemotherapy and parenteral nutrition; however, he deteriorated rapidly and so was started on palliative treatment and discharged home.

BACKGROUND

Amyloidosis is a rare multisystem disorder characterised by the misfolding of precursor proteins resulting in the formation of unstable protein aggregates and amyloid fibril formation. These fibrils are subsequently deposited in different organs, causing progressive impairment of the organ's architecture and function.¹ The most frequently affected organs are the heart, kidneys, liver, gastrointestinal (GI) tract and the autonomic and peripheral nervous system. Systemic light chain (AL) amyloidosis is the most common form of amyloidosis, with the amyloid protein being a monoclonal light chain secreted by an underlying abnormally functioning (dyscrastic) clonal plasma cell, such as myeloma, or monoclonal gammopathy of undetermined significance.¹

Here we present the case of a 59-year-old man who presented with a 12-month history of non-specific symptoms, highlighting the diagnostic difficulty often faced with amyloidosis and its non-specific presentation.

CASE PRESENTATION

A 59-year-old man with a background of hypertension and ischaemic heart disease was referred to outpatient gastroenterology clinic for assessment.

He described a 12-month history of intermittent vomiting, constipation, weight loss and recurrent syncope. A recent oesophagogastroduodenoscopy (OGD) requested by his general practitioner had shown haemorrhagic gastritis and the presence of *Helicobacter pylori* on rapid urease testing, for which he received eradication therapy. Duodenal biopsies taken at the time of this OGD were normal. He had recently been reviewed in a 2 week wait colorectal clinic and had a colonoscopy performed which had been unremarkable, with random colonic biopsies showing a normal histological appearance.

After being assessed in gastroenterology outpatient clinic, he was admitted directly to the ward as he was unable to tolerate oral intake and had lost 20 kg in the preceding 6 months. His weight in clinic was 82.2 kg, with a body mass index of 23.5. He was experiencing marked postural symptoms and a painful peripheral neuropathy. He was subsequently found to have a postural blood pressure drop from 110 mm Hg systolic to 80 mm Hg. Blood tests revealed normocytic anaemia (Hb 117 g/dL) and thrombocytopenia (Platelets $128 \times 10^9/L$). Thyroid function, blood glucose, HIV serology, short synacthen test, coeliac serology and a vasculitic screen, including antinuclear antibodies, antinuclear cytoplasmic antibodies and double-stranded DNA antibodies were all normal. An abdominal X-ray showed faecal loading in the proximal colon. A repeat OGD showed persistent gastritis (figure 1A), which was biopsied but no evidence of ongoing *H. pylori* infection was found. CT imaging showed ground glass changes to the left upper lobe and circumferential proximal sigmoid wall thickening with fat stranding. A PET-CT showed no evidence of malignancy. N-terminal pro B-type Natriuretic Peptide (NT-proBNP) was elevated at 936 pmol/L (<32). An echocardiogram, and subsequent cardiac MRI, demonstrated a restrictive cardiomyopathy. The patient underwent a flexible sigmoidoscopy to the splenic flexure (figure 1B). Random biopsies from this sigmoidoscopy showed normal histological appearances.

Reanalysis of the gastric biopsies and sigmoid biopsies subsequently showed positive staining for amyloid using Congo red under polarised light, which confirmed the diagnosis of GI amyloidosis (figure 2A,B). The patient had a paraprotein on serum protein electrophoresis and elevated serum free kappa light chains, urinary Bence Jones protein was not tested for (see table 1). A bone marrow biopsy was performed after haematology review and this showed over 50% kappa restricted

© BMJ Publishing Group Limited. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: McFarlane M, Bashford A, Sah S, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225301

Figure 1 (A) Endoscopic appearance of gastric mucosa. (B) Endoscopic appearance of sigmoid mucosa.

plasma cells with evidence of amyloid deposition. The patient was subsequently diagnosed with AL amyloidosis secondary to multiple myeloma in keeping with the current guidelines on the diagnosis and investigation of AL amyloidosis.² A skeletal survey showed no evidence of bone lesions, and the patient reported no bone or back pain. He was discharged home pending referral to the National Amyloidosis Centre (NAC) having been started on Gabapentin for his painful neuropathy.

INVESTIGATIONS

A summary of the key serological investigations can be found in Table 1.

DIFFERENTIAL DIAGNOSIS

Gastrointestinal malignancy: unlikely given the recent endoscopic investigations which had not found any evidence of this.
Addison's: could account for postural symptoms, weight loss and neuropathy. However, the Synacthen test showed an appropriate cortisol rise to Adrenocorticotrophic Hormone (ACTH).
Diabetes mellitus: can cause non-specific GI symptoms and autonomic neuropathy. It usually causes a dilated cardiomyopathy. This patient had normal blood glucose, excluding it.

Figure 2 (A) Gastric biopsy with Congo red staining (without polarised light), magnification $\times 100$. Shows salmon pink coloured deposition in stroma and capillaries. (B) Gastric biopsy with Congo red staining (with polarised light), magnification $\times 100$. Shows apple green birefringence.

Vasculitis/Connective tissue disorders: a potential cause of the presentation seen here. However, a vasculitic screen was negative.

Table 1 Summary of key investigation results	
Investigation	Result (normal range)
Haemoglobin	116 g/dL (130–170)
Mean corpuscular volume	91.9 fL (80–100)
Platelet count	111×10^9 /L (140–400)
Creatinine	119 μ mol/L (70–120)
Albumin	36 g/L (34–48)
Calcium	2.47 mmol/L (2.22–2.58)
Serum protein electrophoresis	Paraprotein detected 19.9 g/L
Immunofixation	A monoclonal IgG Kappa paraprotein
Serum free light chains:	
Free Kappa light chains	480 mg/L (3.3–19.4)
Free Lambda light chains	9.12 mg/L (5.7–26.3)
Kappa/Lambda ratio	52.63 (0.26–1.65)

Sarcoidosis: can cause autonomic neuropathy, restrictive cardiomyopathy and GI symptoms. This would be an important differential if amyloidosis had not been identified.

Lymphoma: no widespread lymphadenopathy identified on normal CT scanning or PET-CT.

Paraneoplastic syndromes: no overt malignancy identified on normal CT scanning or PET-CT.

Amyloidosis: as discussed above.

TREATMENT

He was referred to the NAC for assessment; however, he became unwell and was readmitted with marked postural symptoms and reduced oral intake and deteriorating renal function. After discussion with the NAC, the decision was made to start chemotherapy locally with Bortezomib and Melphalan. He received 2 doses of Bortezomib before clinically deteriorating.

OUTCOME AND FOLLOW-UP

The patient remained unable to tolerate oral intake. He was started on first nasogastric and then nasojejunal feeding; however, he was unable to tolerate either due to vomiting and diarrhoea. It was unclear whether he had autonomic GI dysfunction as a result of AL amyloidosis or GI amyloid infiltration. The decision was made to undertake a trial of parenteral nutrition (PN). He continued to deteriorate despite this and so chemotherapy and PN were discontinued and he was started on palliative treatment and discharged home.

DISCUSSION

AL amyloidosis can occur in 10%–15% of patients with myeloma and is the most common cause of amyloid-associated GI tract involvement.³ It results from deposition of the protein in the submucosa and muscularis propria. Common symptoms include reflux, constipation, nausea, abdominal pain and weight loss.⁴ Other symptoms such as diarrhoea and early satiety may be as a result of concomitant autonomic neuropathy.⁴ Erosions, ulcers, mucosal ischaemia or vascular friability may present as GI bleeding. In contrast, Amyloid A amyloidosis occurs in the presence of chronic inflammatory conditions, with amyloid deposition in the mucosa causing a fine granular appearance with erosions and often presenting with malabsorption and diarrhoea.⁵

Other than the GI tract, potential systems which can be affected by AL amyloidosis include cardiac, renal, neurological, lung and soft tissues such as the tongue (macroglossia) and muscles, with myopathy and pseudohypertrophy.⁶ Cardiac involvement results in a restrictive cardiomyopathy via amyloid deposition in the myocardium, leading to thickening of the atrial and ventricular walls, demonstrated on echocardiography and cardiac MRI as described above. This can sometimes cause conduction defects due to disruption of the normal conductive processes.⁷ Renal involvement usually results in proteinuria, which unless myeloma is the underlying cause, does not contain Bence-Jones Protein. Neurological involvement is usually autonomic dysfunction and symmetrical lower limb sensorimotor neuropathy, as seen here. Pulmonary amyloidosis is rare and usually involves typical respiratory symptoms of dyspnoea and cough.⁶

Amyloidosis has a poor prognosis with cardiac and renal involvement being the main causes of mortality. Median survival of patients with AL amyloidosis in the early 1990s was 13 months, and this improved dramatically with the advent of more sophisticated chemotherapy regimens.⁸ Disease staging and associated prognosis is mainly based around cardiac markers, with a raised troponin and NT-proBNP resulting in a prognosis of 3–5 months.^{2,9,10}

The most effective available treatment is autologous bone marrow transplants. However, many patients have become too weak by the time of diagnosis to tolerate this approach. Other available treatments revolve around chemotherapy regimens similar to those used in myeloma, such as Melphalan, thalidomide and bortezomib.¹

Early diagnosis and treatment are required which relies on a high level of clinical suspicion given the often non-specific presentation.

Learning points

- ▶ Amyloidosis is a rare condition, which can cause non-specific symptoms, requiring heightened clinical vigilance.
- ▶ Diagnosis is by positive staining with Congo red stain which shows apple green birefringence under polarised light.
- ▶ Cardiac involvement in amyloidosis carries a poor prognosis of 3–5 months.
- ▶ Gastrointestinal involvement causes non-specific symptoms including nausea, reflux, constipation/diarrhoea, abdominal pain and weight loss.

Contributors MM, AB: wrote manuscript. SS: wrote manuscript, provided histopathology images. BRD: wrote manuscript, project co-ordination.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Mahmood S, Palladini G, Santhorawala V, *et al.* Update on treatment of light chain amyloidosis. *Haematologica* 2014;99:209–21.
- 2 Gillmore JD, Wechalekar A, Bird J, *et al.* Guidelines on the diagnosis and investigation of AL amyloidosis. *Br J Haematol* 2015;168:207–18.
- 3 Madan S, Dispenzieri A, Lacy MQ, *et al.* Clinical features and treatment response of light chain (AL) amyloidosis diagnosed in patients with previous diagnosis of multiple myeloma. *Mayo Clin Proc* 2010;85:232–8.
- 4 Cowan AJ, Skinner M, Seldin DC, *et al.* Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. *Haematologica* 2013;98:141–.
- 5 Hokama A, Kishimoto K, Nakamoto M, *et al.* Endoscopic and histopathological features of gastrointestinal amyloidosis. *World J Gastrointest Endosc* 2011;3:157–61.
- 6 Gertz MA, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. *Amyloid* 2010;17(Suppl 1):48–9.
- 7 Desport E, Bridoux F, Sirac C, *et al.* AL amyloidosis. *Orphanet J Rare Dis* 2012;7:54.
- 8 Wechalekar AD, Gillmore JD, Bird J, *et al.* Guidelines on the management of AL amyloidosis. *Br J Haematol* 2015;168:186–206.
- 9 Dispenzieri A, Gertz MA, Kyle RA, *et al.* Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004;22:3751–7.
- 10 Wechalekar AD, Schonland SO, Kastritis E, *et al.* A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood* 2013;121:3420–7.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow