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Severe chronic diarrhoea caused by hereditary transthyretin amyloidosis

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SUMMARY

Amyloidosis includes a heterogeneous group of diseases caused by the extracellular deposition of insoluble fibrillar proteins, leading to multiple organ dysfunction and a poor life expectancy. In the early stages of amyloidosis, gastrointestinal (GI) symptoms are uncommon. We describe a rare case of hereditary transthyretin amyloidosis (ATTRv) with involvement of the heart, nervous system and GI tract. A man in his 60s was hospitalised due to chronic diarrhoea, orthostatic hypotension, malabsorption and weight loss. An organic origin for the diarrhoea was suspected, but the most common causes were ruled out. The review of GI biopsies and an abdominal fat aspirate confirmed the diagnosis of amyloidosis. The diagnosis of ATTRv amyloidosis with GI presentation is challenging, especially in the early stages, and misdiagnosis is common. The recent approval of therapies emphasises the importance of early diagnosis to prevent irreversible organ damage.

BACKGROUND

Amyloidosis is characterised by the extracellular deposition of various abnormal fibrillar proteins, which disrupt tissue structure and function. It can occur as an acquired or hereditary condition and can affect either the entire body or specific localised areas. The kidneys, heart, nervous system and digestive tract are the organs most commonly affected by this condition.[1]

Several proteins have the ability to form amyloid fibrils, including immunoglobulin light chain (AL), transthyretin (ATTR), serum amyloid A (AA) and A2 amyloid (which causes haemodialysis-associated amyloidosis).[2–4] ATTR amyloidosis, which is less common, can be either hereditary (ATTRv), resulting from a mutation in the transthyretin gene, or acquired in the elderly as wild-type transthyretin amyloidosis (ATTRwt).[5]

Transthyretin (TTR) is a serum protein responsible for transporting thyroxine and retinol (vitamin A) into the plasma. The majority of TTR protein is produced by the liver and the choroid plexus in the central nervous system, encoded by the TTR gene on chromosome 18. The most prevalent mutations in ATTRv amyloidosis are Val30Met, Glu89Gln, Ser77Phe and Ser52Pro.[6] These mutations cause monomers to aggregate into beta-structured fibrils, leading to the formation of extracellular amyloid deposits, degenerative changes and impaired organ function.[7]

In ATTR amyloidosis, a TTR protein mutation accounts for 16% of the subtype affecting the gastrointestinal (GI) tract. This subtype is associated with peripheral neuropathy accompanied by autonomic symptoms, cardiomyopathy or a mixed phenotype.[8] Early-onset ATTRv amyloidosis from endemic areas typically exhibits severe autonomic dysfunction right from the outset, including conditions like orthostatic hypotension and diarrhoea. Instead, late-onset ATTRv amyloidosis (with clinical onset after the age of 50) in non-endemic regions shows initial symptoms of sensorimotor manifestations, commencing in the distal lower extremities, and less prominent autonomic manifestations.[9] In this report, we present a case of late-onset ATTRv amyloidosis with autonomic manifestation, specifically chronic diarrhoea, as the presenting symptom.

CASE PRESENTATION

A man in his 60s presented with watery diarrhoea that had been ongoing for 3 years. The diarrhoea episodes occurred at night as well, with five to ten bowel movements per day. The patient also experienced symptoms of nausea, vomiting and weight loss. His medical history included a partial prostatectomy for obstructive prostatic hypertrophy, inguinal hernioplasty and non-steroidal anti-inflammatory drugs (NSAIDs) abuse until 4 years prior. Due to the severity of his symptoms, the patient was admitted to the hospital.

INVESTIGATION

Routine laboratory evaluations showed normal results, and microbiological cultures ruled out *Clostridium difficile* and other enteropathogenic bacteria. However, faecal calprotectin levels were slightly elevated (100 µg, reference range <50 µg), indicating mild intestinal inflammation. Ileocolonoscopy revealed normal findings both endoscopically and histologically. An abdominal CT scan showed a 7 mm intramural nodule in the third portion of the duodenum, but subsequent CT-PET results were normal. Entero-MRI findings showed accelerated gastrointestinal transit, thickening of the small intestinal plica with collapsed loops and morphological changes and thickening of the terminal ileum plica with retrodilation. The patient was treated at the hospital and discharged with instructions to take loperamide, Gelsectan and diosmectite.

Two years later, the patient returned with persistent watery diarrhoea (five to ten bowel movements per day), stomach discomfort, asthenia, orthostatic hypotension and significant weight loss (20 kg since the onset). Supportive care was provided to address dehydration and sarcopenia. Laboratory analysis revealed normal C reactive protein levels

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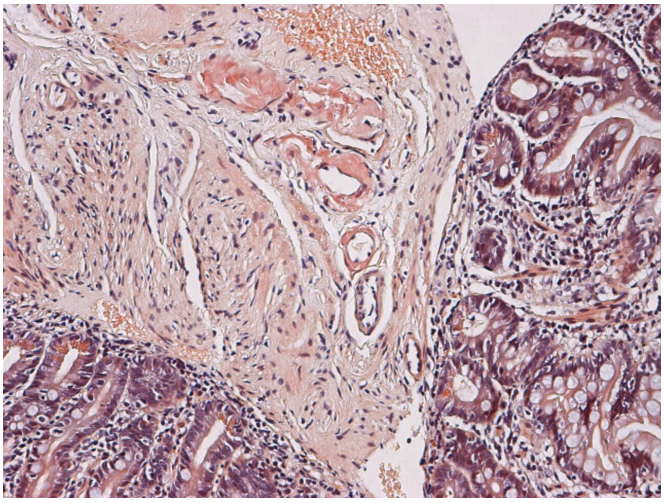

Figure 1 Duodenum biopsy: Congo red-stained hyaline perivascular deposits.

and moderate microcytic anaemia (haemoglobin ranging from 98 to 109 g/L, normal value >142 g/L). Low prealbumin levels (0.09 g/L, reference range >0.02 g/L) indicated malnutrition. An abdominal CT scan confirmed the previous findings of bowel and abdomen ultrasounds, showing a thin perihepatic fluid layer with hyperechogenicity of the mesentery and perihepatic parietal peritoneum. Video capsule endoscopy showed slow stomach transit and rapid small intestinal transit. Cholestyramine treatment was attempted for suspected bile acid diarrhoea but only resulted in mild improvement. Another intestinal ultrasound revealed resolution of the abdominal fluid. As an incidental finding, a thin (7 mm) pericardial effusion was discovered. This finding, along with orthostatic hypotension, prompted a transthoracic echocardiography, which revealed features resembling cardiomyopathy, including slight concentric hypertrophy and minimal pericardial effusion without haemodynamic significance (figure 1). Cardiac cine MRI was performed to further evaluate the concentric hypertrophy, showing thickened walls of the left ventricle, a distinct restrictive filling pattern, preserved systolic function (ejection fraction 65%), areas of intramural and "patchy" oedema and difficulty in myocardial signal washout in the sequences for late gadolinium enhancement (figure 2). These findings were consistent with storage cardiomyopathy. An elevated level of NT-proBNP (five times the upper normal range) indicated cardiac involvement in amyloidosis.

Intestinal samples were re-examined with Congo red staining, which confirmed the presence of amyloid (figure 3). The

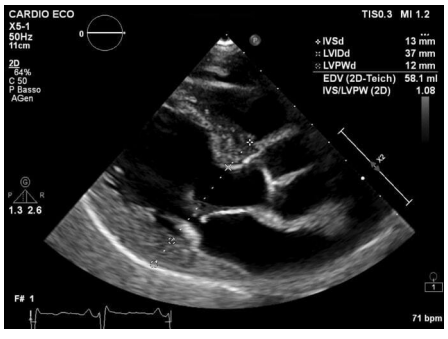

Figure 2 Transthoracic echocardiography: cardiomyopathy-like picture of the left ventricle with slight concentric hypertrophy

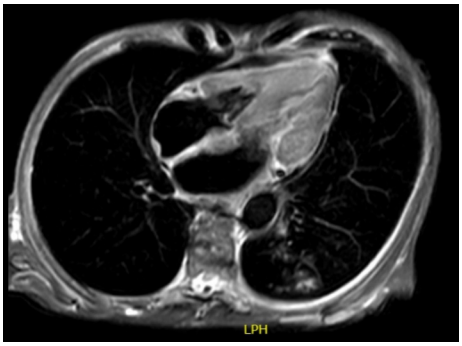

Figure 3 Cardiac cine MRI of a left ventricle with thickened walls from hypertrophy, a distinct restrictive filling pattern and difficult myocardial signal washout in the sequences for late gadolinium enhancement

diagnosis of amyloidosis was further confirmed by positive Congo red staining of the abdominal fat aspirate. The amyloid typing was performed using immunohistochemistry, which revealed deposits of TTR. Furthermore, salivary genetic testing identified a TTR gene mutation, and direct gene sequencing of exons 2, 3 and 4 revealed a heterozygous mutation of the Phe64Leu variant (also known as Phe84Leu according to HGVS nomenclature). The patient was subsequently discharged and referred to a tertiary centre for the initiation of appropriate therapy for amyloidosis.

Considering the above findings, our case represents a rare instance of hereditary transthyretin amyloidosis involving the autonomic nervous system and the heart.

DIFFERENTIAL DIAGNOSIS

The patient's symptoms had started 3 years prior, leading to the consideration of both functional and organic causes in the differential diagnosis of chronic diarrhoea. However, organic causes were promptly suspected due to red flag signs such as weight loss and nocturnal diarrhoea. The lactulose breath test was normal, ruling out the possibility of small intestinal bacterial overgrowth. The patient denied the use of medications known to affect gastrointestinal motility, such as opioids, anticholinergics, antipsychotics and calcium channel blockers. Diabetes, hypothyroidism and hypoparathyroidism were ruled out based on normal blood glucose levels, thyroid-stimulating hormone levels and serum calcium levels, respectively. Pancreatic exocrine insufficiency was considered, but faecal elastase levels were normal.

Infectious causes of chronic diarrhoea were also considered. Bacterial stool cultures for *Shigella*, *Salmonella* and *Campylobacter* were negative, as were interferon gamma release assay and serological tests for HIV, Epstein-Barr virus, cytomegalovirus, *Borrelia burgdorferi*, *Toxocara* and *Strongyloides stercoralis*. Antigen detection tests for *Giardia* and *Cryptosporidium* in stool samples also yielded negative results.

The possibility of microscopic colitis and inflammatory diseases such as ulcerative colitis and Crohn's disease was ruled out based on the mildly elevated faecal calprotectin levels and normal findings on ileocolonoscopy with biopsies. Esophagogastroduodenoscopy with biopsies excluded coeliac disease and Whipple's disease.

Neuroendocrine tumours were ruled out as well, as the levels of calcitonin, indole acetic acid, chromogranin A and gastrin were all within normal limits.

OUTCOME AND FOLLOW-UP

A few weeks after being discharged, the patient experienced walking instability. Neurological examination results indicated sensory polyneuropathy of the axonal type, which is characteristic of familial amyloid polyneuropathy (FAP) stage II. Apart from a small amount of proteinuria, renal function was normal. Gene silencing therapy is the most recommended treatment for FAP II. In cases where proteinuria is present, patisiran is the suggested treatment. Patisiran is an RNA interference drug that inhibits the liver's production of transthyretin. It has shown efficacy in improving clinical symptoms of ATTRv amyloidosis.[10] Additionally, the salivary test revealed the same mutation in three of the patient's brothers and his daughter.

DISCUSSION

ATTRv amyloidosis can be difficult to diagnose in its early stages, and distinguishing it from other gastrointestinal disorders can be challenging due to the wide range of symptoms. In some cases, GI symptoms may appear before peripheral polyneuropathy becomes apparent. Diarrhoea can be the initial manifestation of the disease, which then progresses to become persistent and severe, accompanied by malnutrition.[11 12] The exact pathophysiology of GI symptoms in ATTRv amyloidosis is not fully understood, but it is believed that autonomic neuron denervation may contribute to motility issues.

In line with the chronic diarrhoea guidelines of the British Society of Gastroenterology, we ruled out the most common and uncommon causes of chronic diarrhoea.[13] It is worth noting that amyloidosis is not specifically mentioned as a cause of chronic diarrhoea in these guidelines.

Apart from inflammatory bowel disease, there are no specific endoscopic findings that can be used to identify diarrhoeal diseases. Endoscopic findings in amyloidosis may include a fine granular appearance, erosions, ulcerations, mucosal friability and protrusions or lesions resembling tumours, although these findings are not pathognomonic.[14] Definitive diagnosis is made through pathological examination, which involves Congo red staining and the observation of apple-green birefringence in positive samples. Alternatively, mass spectrometry is also a highly useful method for amyloid typing, being more specific and sensitive than immunohistochemistry. However, it is a costly approach, and regrettably, it is not available in every hospital. The conventional methods (antigen-antibody-based typing methods, such as immunohistochemistry, immunofluorescence and immunoelectron microscopy) serve as acceptable alternative typing approaches, particularly when executed in proficient laboratories. Meanwhile, mass spectrometry can be considered for typing purposes when other methods prove ineffective or yield inconclusive results.[15] Performing a biopsy is crucial for the accurate detection of TTR deposits, as some non-invasive diagnostic techniques for amyloid transthyretin cardiac amyloidosis (ATTR-CA), such as Technetium Tc 99m pyrophosphate (99mTc-PYP) scanning, often yield false-negative results for the Phe64Leu variant.[16]

Radiological examinations are non-specific, although abdominal CT scans may reveal oedematous wall thickening in the small bowel and colon.[17]

Gastrointestinal involvement may be the sole symptom of amyloidosis, or more commonly, it is part of systemic amyloidosis that affects multiple organs. Intestinal amyloidosis can lead to weight loss, prolonged diarrhoea, abdominal pain, intestinal bleeding or pseudo-obstruction. Accumulation of amyloid in various organ systems causes gastrointestinal dysfunction, cardiomyopathy, nephropathy and progressive peripheral polyneuropathy.[18 19] Without treatment, the typical life expectancy after symptom onset ranges from 3 to 15 years, with worse prognosis associated with the development of cardiomyopathy. Cachexia, renal failure, cardiac disease and sudden death are common causes of mortality. Gastroenterologists should consider amyloidosis as a potential differential diagnosis for diarrhoea and be aware of previously published cases, such as ours, that have been reported in the literature.[20] However, we did not find the same genetic mutation associated with bowel involvement.

The approval of novel medications underscores the importance of early detection in ATTRv amyloidosis, a disease that is inevitably fatal if left untreated, in order to halt disease progression, stabilise the condition and reduce mortality. Tafamidis is recommended for patients primarily affected by cardiac symptoms, while inotersen or patisiran is recommended for those with neurological manifestations.[8 21] Accurate diagnosis is equally important for family members. Through this report, we advise clinicians to maintain a high level of suspicion when evaluating potential causes of chronic diarrhoea.

Patient's perspective

In my opinion, there are only two factors that should be taken into consideration: early diagnosis and therapy. Regarding diagnosis, the medical community should adopt a more open-minded approach and involve more specialists to identify the disease as soon as possible in order to minimise the damage caused by the illness. As for treatment, the key lies in research. The healthcare system has its limitations, and it is crucial to remember that individuals with rare diseases may not always have access to the assistance they require.

Learning points

- Clinical presentation of amyloidosis may mimic several multiorgan conditions, thus making diagnosis often challenging.
- Amyloidosis should be considered in the differential diagnosis of chronic diarrhoea.
- Cooperation between clinicians and pathologists is key to achieving an early diagnosis.

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