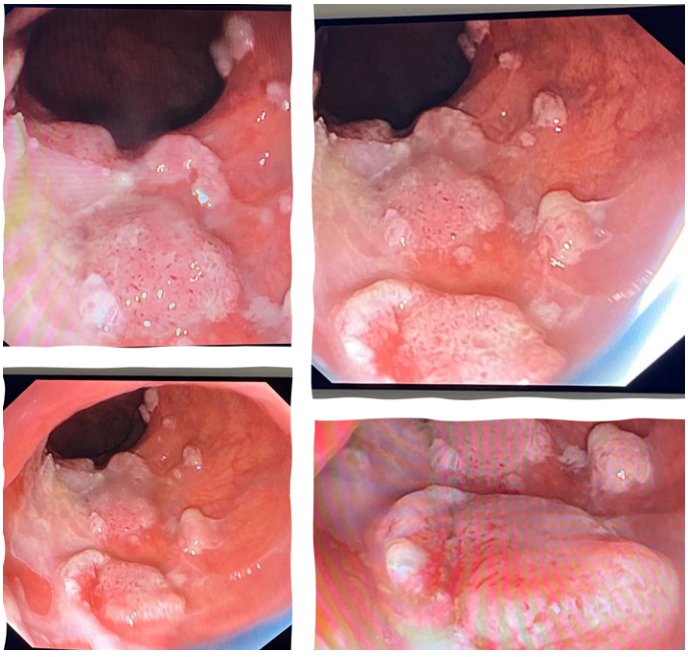

**Figure 1.** Polypoid ulcerovegetant lesion measuring approximately 3 cm, located on the anterior wall of the rectum, 5 cm from the anal verge, with additional smaller polyps—the largest measuring 0.5 cm.

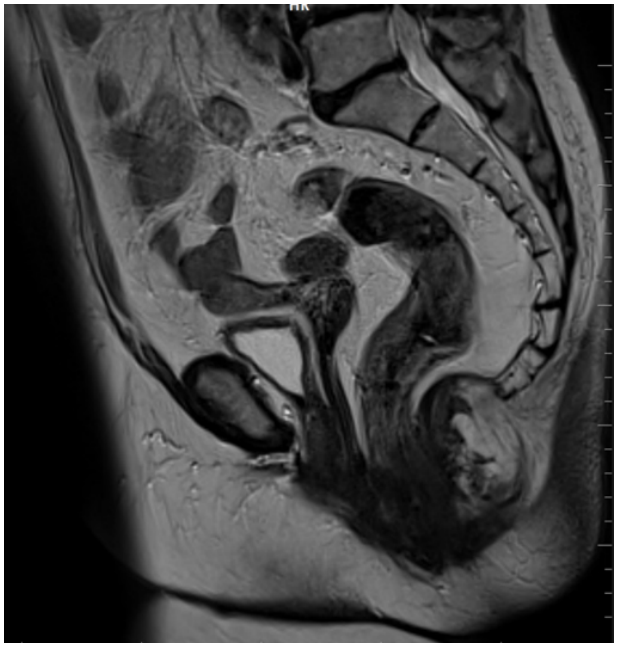

**Figure 2.** Thickening of the rectal wall, with the lesion located posteriorly and displaying a mildly polypoid intraluminal configuration. No evidence of diffuse inflammatory changes or infiltration into the surrounding fat tissue is observed, which is not suggestive of malignant infiltration.

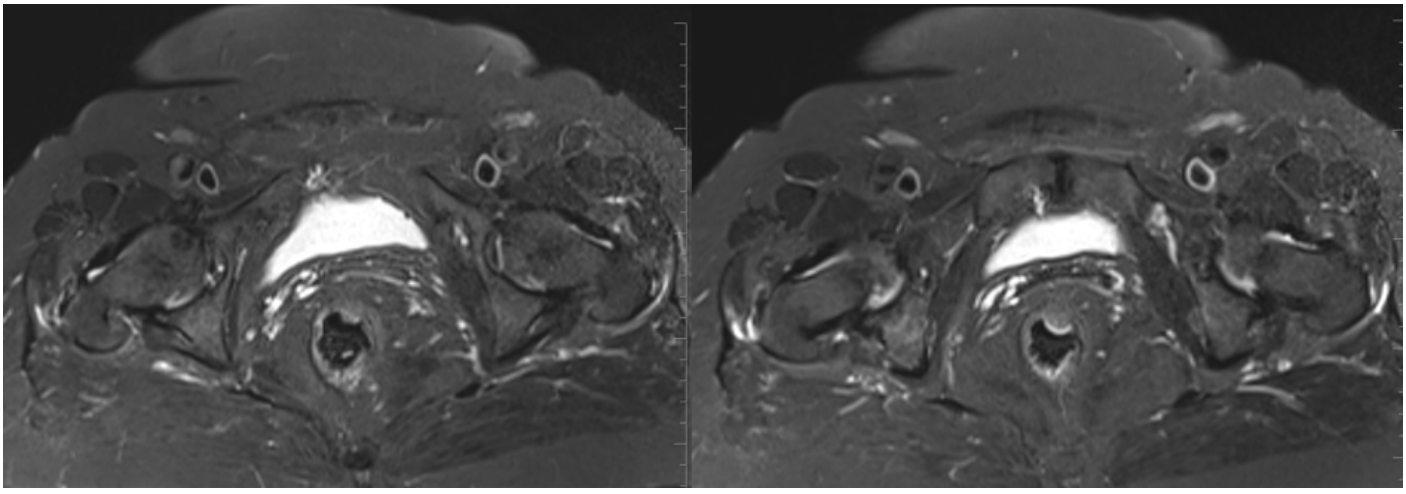

**Figure 3.** Axial T2-weighted sequences showing localized thickening of the posterior/lateral quadrant of the rectal wall. Signal intensity is pronounced at the submucosal level, with no significant infiltration into the surrounding fatty tissue. No diffuse inflammatory reaction or fistulous tract is observed. The mesorectal fat plane is preserved, and no significant perirectal pathological lymphadenopathy is noted.

The pathogenesis of SRUS is thought to involve rectal prolapse, pelvic floor dysfunction, and mucosal ischemia.[5,6] Habitual digital evacuation may exacerbate mucosal trauma, contributing to lesion development.[7] In our case, rectoanal dyssynergia, chronic constipation, and a history of digital maneuvers were all present.

Treatment options include behavioral modifications, biofeedback therapy, and topical mesalazine.[8,9] Biofeedback has been shown to improve pelvic floor coordination and alleviate symptoms.[9,10] Our patient experienced significant clinical and endoscopic improvement after three months of therapy.

## CONCLUSION

SRUS should always be considered in the differential diagnosis of rectal lesions mimicking malignancy. A thorough history, including inquiry about digital evacuation, is essential. Anorectal manometry and defecography should be performed when indicated to evaluate pelvic floor dysfunction. Successful outcomes can be achieved with biofeedback therapy and topical mesalazine.

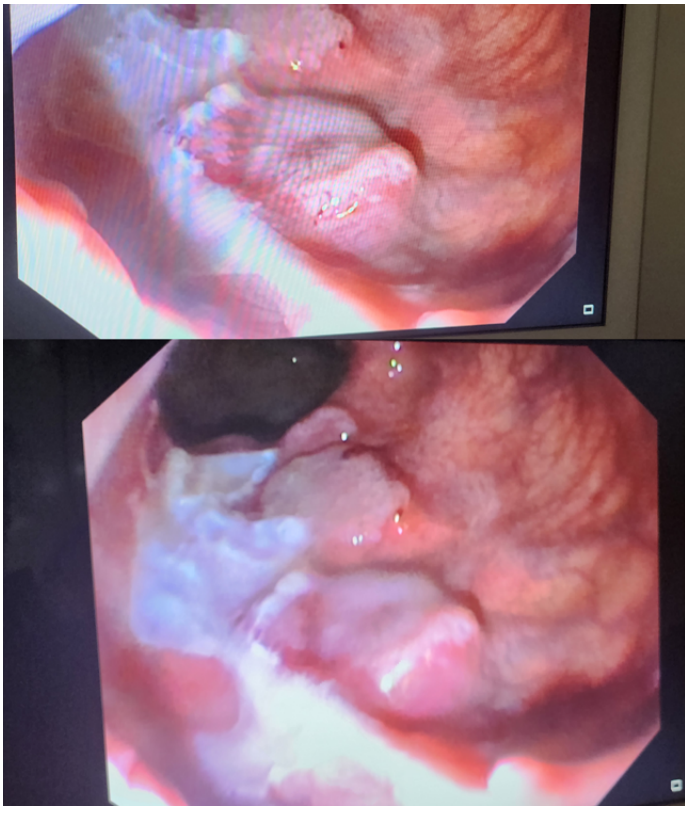

**Figure 4.** Polypoid lesion on the anterior wall of the rectum, 5 cm from the anal verge, displaying erythematous mucosal patches and superficial ulcerations.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent was obtained from the patients participating in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contribution**: Concept – R.E; Design – R.E.; Supervision – R.E., M.A.; Resource – R.E.; Materials – R.E., M.A.; Data Collection and/or Processing – R.E.; Analysis and/or Interpretation – R.E., M.A..; Literature Review – R.E., M.A.; Writing – R.E.; Critical Review –R.E., M.A.

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# A Rare and Overlooked Cause of Chronic Diarrhea: Hereditary Transthyretin Amyloidosis

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**Abstract**

Hereditary transthyretin amyloidosis is a rare, rapidly progressive, and fatal disease caused by pathogenic variants in the transthyretin gene. It is inherited in an autosomal dominant manner. The disease is characterized by the accumulation of amyloid fibrils in various organs, particularly the peripheral nerves, heart, kidneys, eyes, and gastrointestinal tract. We present a rare case of transthyretin amyloidosis manifested by chronic diarrhea.
**Keywords:** Amyloidosis, diarrhea, hereditary

## INTRODUCTION

Amyloidosis is a heterogeneous group of diseases caused by the extracellular deposition of insoluble fibrillar proteins, leading to multiple organ dysfunction and a shortened lifespan.[1] Various systems can be affected by amyloid deposition, with the digestive tract being one of the organs involved, potentially causing chronic diarrhea.[2] Gastrointestinal involvement in amyloidosis can present with a variety of clinical symptoms, including weight loss, fatigue, nausea, vomiting, bleeding, and abnormal bowel habits.[3] The onset of gastrointestinal tract involvement is often insidious, and the nonspecific nature of the symptoms makes diagnosis challenging, often resulting in diagnostic delays. Endoscopic biopsy plays a crucial role in diagnosing amyloidosis, determining the subtype, and ruling out other potential diagnoses. While many endoscopic findings have been described, they are generally nonspecific and include edema, erythema, submucosal hematoma, or even normal findings.[4] We present a rare case of transthyretin (TTR) amyloidosis manifesting as chronic diarrhea.

## CASE REPORT

A 63-year-old woman presented with a 2-year history of watery diarrhea and a 30 kg weight loss over the same period. She had no significant medical history and was not on any medications. She did not smoke or consume alcohol. On physical examination, the patient appeared dehydrated. Stool tests were negative for polymorphonuclear leukocytes, starch, and fat. Microbiological cultures were also negative. The patient had normocytic anemia, while iron, vitamin B12, and folic acid levels were normal. Liver and kidney function tests were within normal limits, and celiac antibodies were negative. Protein electrophoresis revealed an M-band (Figure 1). Her IgG level was 1681 mg/dL (normal range: 700–1600 mg/dL), while IgA and IgM levels were normal. Serum and urine immunofixation electrophoresis showed IgG lambda and lambda light chain. Magnetic resonance enteroclysis revealed no significant intestinal pathology (Figure 2). Both gastroscopy and colonoscopy, including examination of the terminal ileum, were unremarkable, and biopsies were taken from all segments. Jejunal aspirate was negative. Biopsies from the antrum, corpus (Figure 3), duodenum (Figure 4), and transverse colon showed deposits consistent with amyloidosis. PET-CT imaging revealed several hypermetabolic lymph nodes (SUVmax: 10.4) with effaced fatty hilums in the left inguinal area, the largest measuring 16x14 mm (Figure 5). Lymph node excision was performed, and pathology confirmed lambda amyloid deposition in the vessel walls. A bone marrow biopsy revealed hypercellular bone marrow with a minimal plasma cell population and lambda light chain monopathy. Echocardiography showed concentrically increased cardiac wall thickness, with a normal ejection fraction. ProBNP levels were elevated at 2395 pg/mL (normal range: 0–125). Cardiac magnetic resonance imaging (Figure 6) revealed an interventricular septum thickness of 18 mm and an increased lateral wall thickness of 18 mm. Concentric hypertrophy of the left ventricle was observed, along with thickening of the interatrial septum. Subendocardial ring enhancement, more prominent in the basal segments, suggested cardiac amyloidosis. Genetic testing confirmed the presence of a transthyretin amyloidosis gene variant, and the patient was diagnosed with hereditary transthyretin amyloidosis.

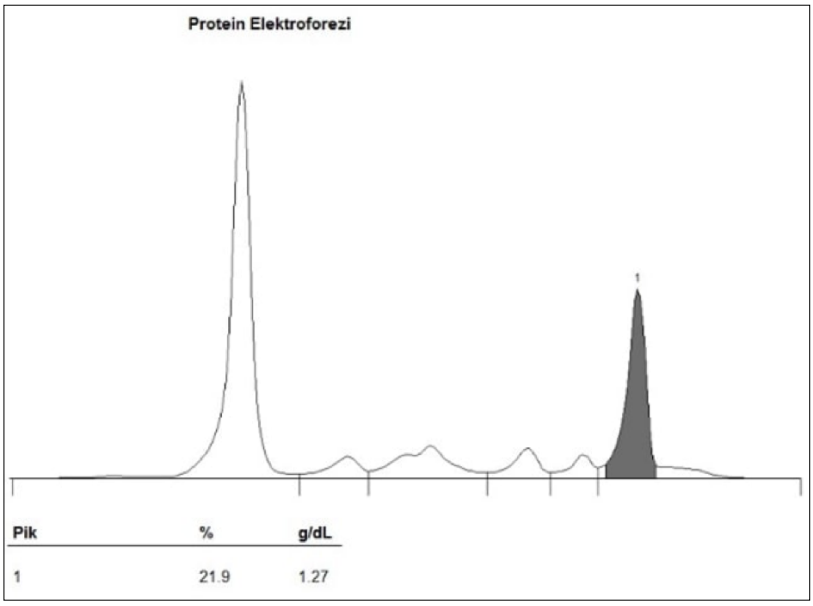


**Figure 1.** M-band in protein electrophoresis.

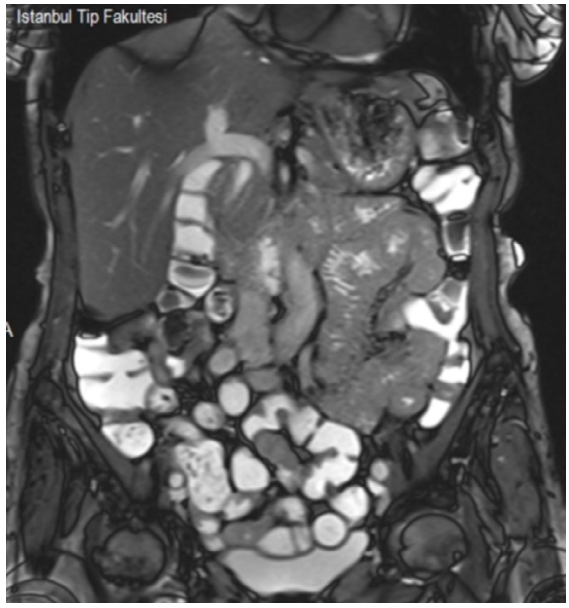


**Figure 2.** Magnetic resonance enteroclysis findings.

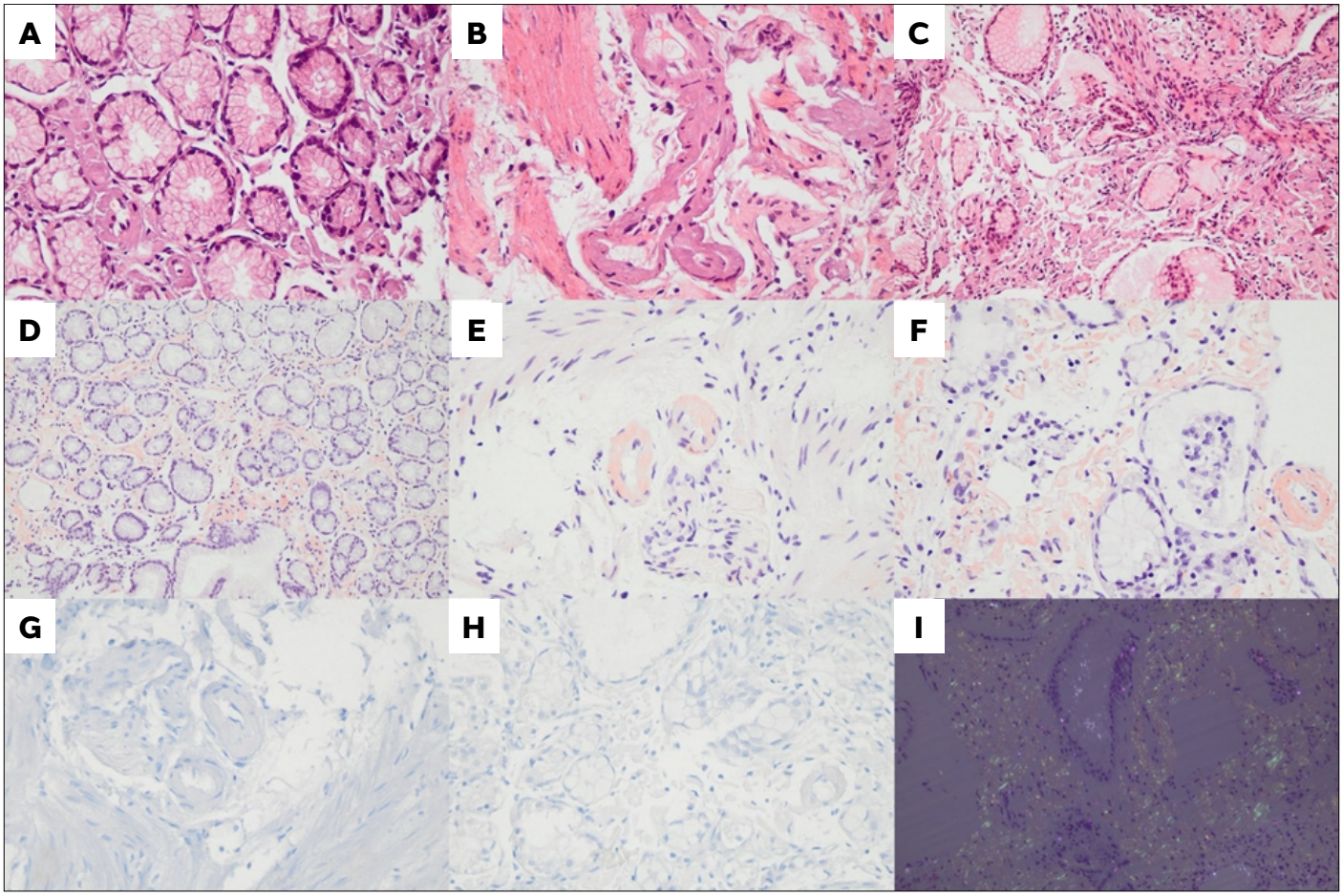


**Figure 3.** Amyloid deposition in gastric biopsies taken from the antrum and corpus: **(A)** Antrum mucosa showing homogeneous eosinophilic thickening of the vessel walls and eosinophilic droplets in the lamina propria, suspicious for amyloid deposition (H&E, ×400); **(B)** Antrum submucosal vessel walls with homogeneous eosinophilic thickening, suspicious for amyloid (H&E, ×400); **(C)** Corpus mucosa showing similar eosinophilic thickening of the vessel walls and droplets in the lamina propria (H&E, ×200); **(D-F)** Congo red staining showing amyloid deposition at ×200 **(D)** and ×400 **(E)** in the antrum, and at ×400 **(F)** in the corpus; **(G-H)** Negative immunostaining with the anti–Amyloid-A antibody at ×400 in the antrum **(G)** and corpus **(H)**; **(I)** Congo red stain under polarized light demonstrating apple-green birefringence in the corpus (×200).

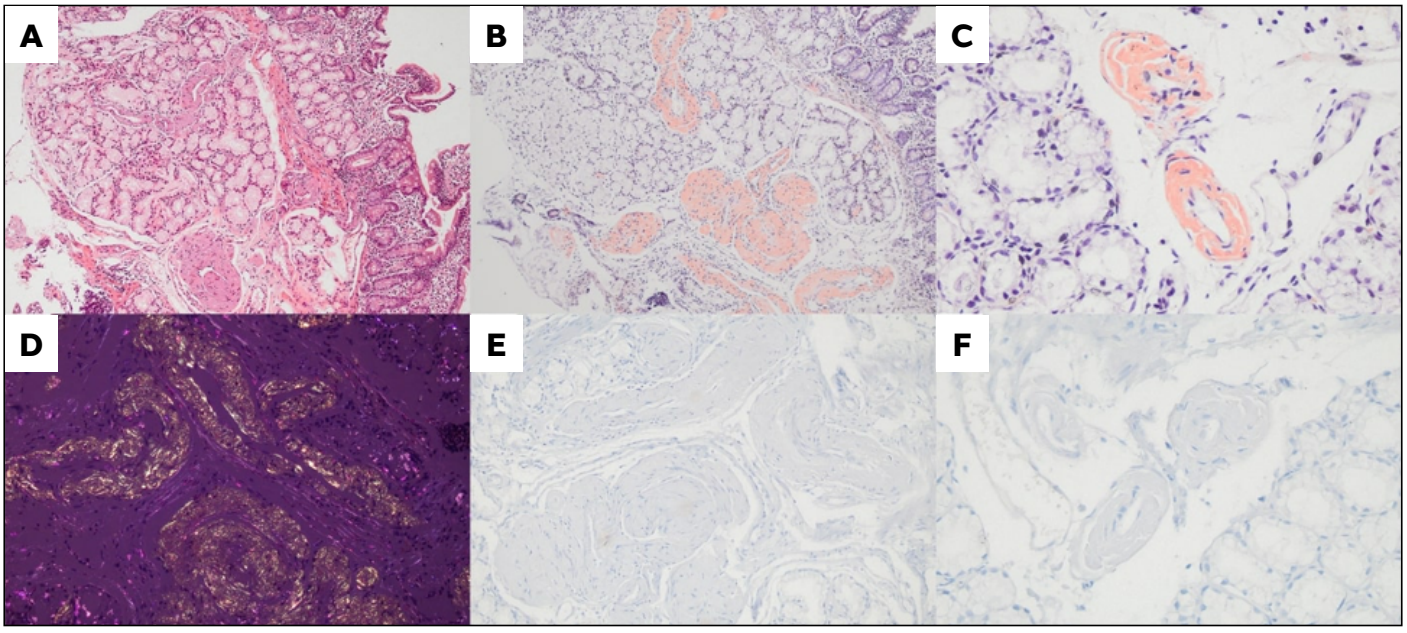


**Figure 4.** Amyloid deposition in the duodenum endoscopic biopsy specimen: **(A)** Submucosal vessel walls with homogeneous eosinophilic thickening, suspicious for amyloid (H&E, ×100); **(B-C)** Congo red staining showing amyloid deposition at ×100 **(B)** and ×400 **(C)**; **(D)** Congo red stain under polarized light demonstrating apple-green birefringence (×200); **(E-F)** Negative immunostaining with the anti–Amyloid-A antibody at ×200 **(E)** and ×400 **(F)**.

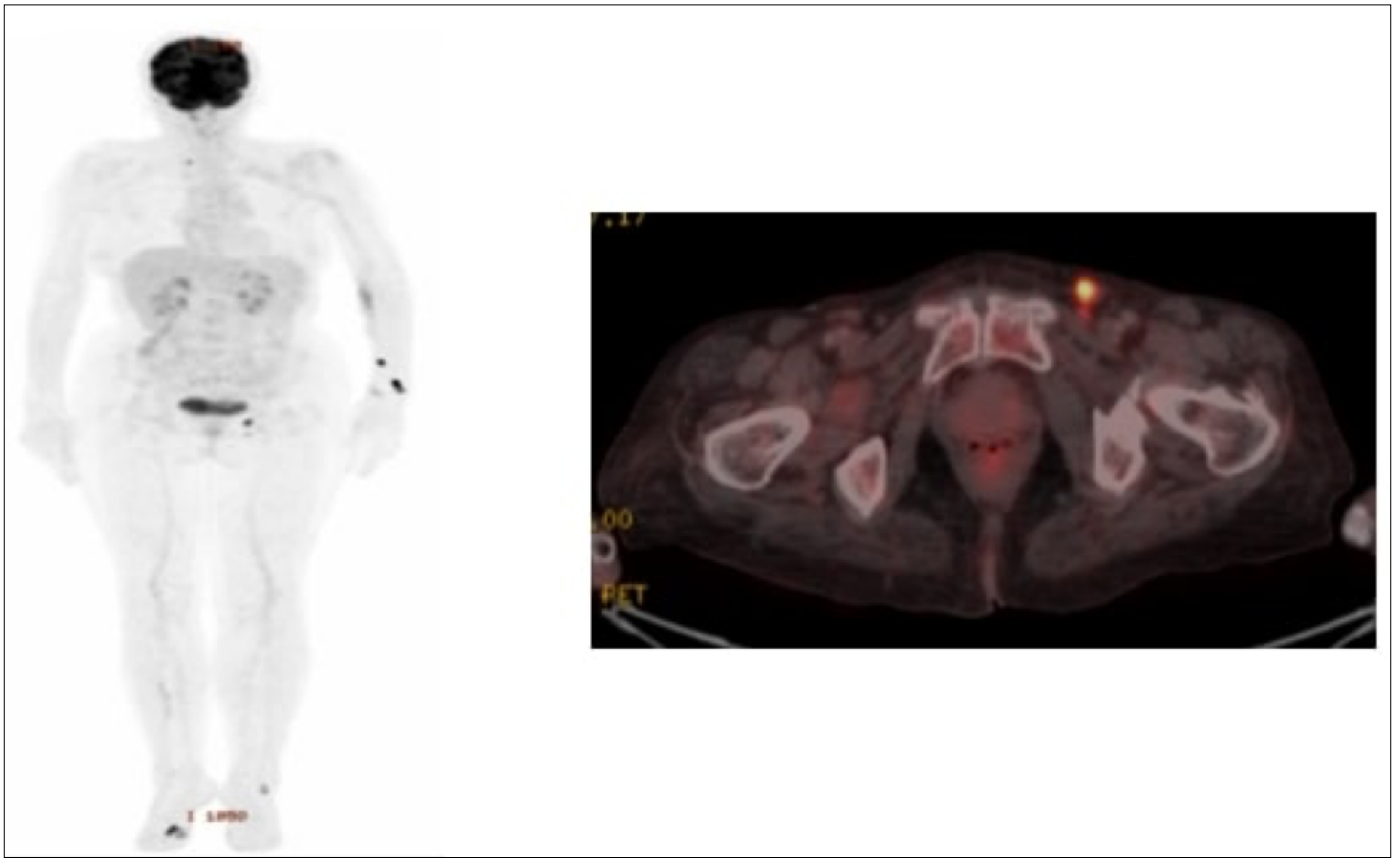


**Figure 5.** PET-CT findings.

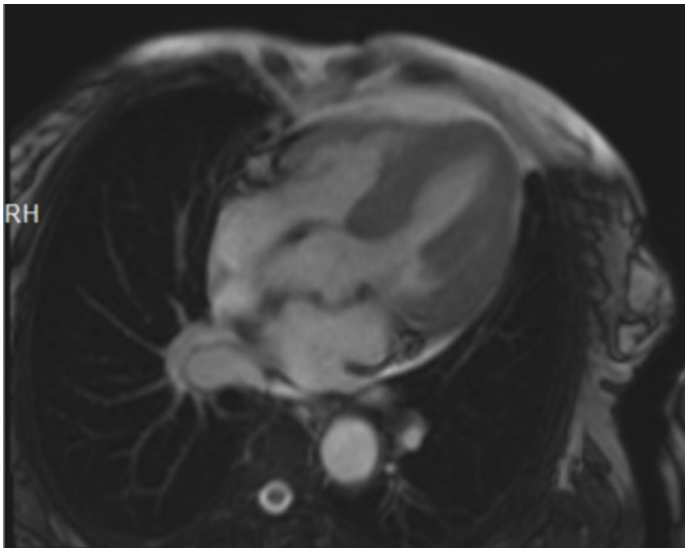


**Figure 6.** Cardiac magnetic resonance imaging findings.

## DISCUSSION

Amyloidosis refers to a heterogeneous group of disorders, which can be classified into two main subtypes: systemic and localized amyloidosis.[5] The most common subtype is systemic amyloidosis, which can be due to either acquired or hereditary conditions. The most well-known hereditary condition is caused by mutations in the TTR gene.[6]

Hereditary TTR amyloidosis is a rare, systemic, autosomal dominant disease caused by mutations in the gene encoding the transthyretin transport protein.[7,8] It is characterized by progressive peripheral sensorimotor and/or autonomic neuropathy, typically beginning in the 3rd to 5th decades of life. The disease often involves the heart, central nervous system, eyes, and kidneys.[9] Hereditary transthyretin amyloidosis should be suspected in adults with cardiac conduction blocks, restrictive cardiomyopathy, and nephropathy. Gastrointestinal manifestations can significantly impact a patient's quality of life, primarily due to damage to the autonomic nervous system, which affects motility and secretory functions in the gastrointestinal tract. Nearly 70% of individuals with transthyretin amyloidosis report gastrointestinal manifestations.[10] In some cases, gastrointestinal symptoms, especially diarrhea, may be the first symptom to appear.[11]

The most common gastrointestinal symptoms, in order of frequency, include unintentional weight loss, early satiety, alternating constipation and diarrhea, constipation, chronic diarrhea, nausea, vomiting, and fecal incontinence.[12] Changes in bowel habits may be the only symptom in some patients, and if not considered in the differential diagnosis, these patients may undergo multiple endoscopic examinations.[13]

Gastrointestinal manifestations in hereditary TTR amyloidosis often present insidiously and nonspecifically. These symptoms are poorly specific, leading to misdiagnosis with more common conditions such as irritable bowel syndrome and functional dyspepsia. Gastroenterologists play a critical role in both the diagnosis and management of this disease. Early diagnosis and treatment are essential for improving the patient's quality of life. Therefore, hereditary TTR amyloidosis should be considered in the differential diagnosis, especially as a rare cause of chronic diarrhea.

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**Peer-review:** Externally peer-reviewed.

**Author Contribution**: Concept – Z.İ., A.O.Ç.; Design – Z.İ., A.O.Ç.; Supervision – B.Ç., F.A.; Materials – Z.İ., A.O.Ç., B.Ç., F.A.; Data Collection and/or Processing - Z.İ., A.O.Ç., B.Ç., F.A.; Analysis and/or Interpretation - Z.İ., B.Ç., F.A.; Literature Review – Z.İ., A.O.Ç., N.B., B.Ç., F.A.; Writing – Z.İ., B.Ç., F.A.; Critical Review – Z.İ., B.Ç., F.A.

**Declaration of Interests:** The authors declare that they have no competing interest.

**Funding:** Authors declare that this study have not received any financial support.

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