Chronic Diarrhea as the Presenting Feature of Amyloidosis with Multiple Myeloma: A Case Report Diagnosed by a Myocardial Biopsy

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Abstract:
A 73-year-old woman with a history of diarrhea for one year and other various symptoms was admitted to our hospital. Gastrointestinal endoscopy that included enteroscopy with multiple biopsies was performed. However, no significant findings were observed. Electrocardiography showed low voltage in all limb leads, and an echocardiogram showed thickened cardiac walls with granular sparkling pattern. A myocardial biopsy revealed amyloidosis, and a bone marrow biopsy showed multiple myeloma. This case suggests that we should suspect the possibility of amyloidosis in a patient with diarrhea and various symptoms involving multiple organ systems. Additionally, electrocardiograms and echocardiograms should be performed even when gastrointestinal biopsies reveal negative results.

Key words: amyloidosis, bone marrow, chronic diarrhea, multiple myeloma, myocardial biopsy

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Introduction
Amyloidosis is a rare disease caused by the extracellular deposition of pathologic insoluble fibrillar proteins called amyloid in various organs and tissues (1). This deposition impairs both the structure and function of these affected organs (2). The gold standard for diagnosing amyloidosis is a tissue biopsy of the affected organs.

Multiple myeloma (MM) is an incurable, biologically heterogeneous form of plasma cell neoplasm. 10-15% of patients with MM develop amyloid light-chain (AL) amyloidosis during the myeloma course (3). AL amyloidosis affects the heart, kidneys, gastrointestinal (GI) tract, and liver as well as the peripheral and autonomic nervous systems (4). It has been reported that AL amyloidosis has GI tract involvement in 22% (164/741) of Japanese patients (5).

In this report, we present a patient with amyloidosis who presented with chronic diarrhea for one year. Although we could not diagnose her after an initial GI examination, a diagnosis of amyloidosis of the GI tract was eventually established based on the results of her heart examination and a myocardial biopsy. This is a first case report of comorbid amyloidosis and MM that presented with a chief complaint of chronic diarrhea of unknown origin, diagnosed based on a myocardial biopsy and bone marrow biopsy after negative results of biopsies from almost all sections of the GI tract.

Case Report
A 73-year-old woman was admitted to our hospital because of diarrhea of unknown origin that had lasted for one year. Six months prior to admission, she noticed a further worsening stool frequency of up to 10-20 times per day, prompting consultation with another gastroenterology hospital. Esophagogastroduodenoscopy (EGD) and colonoscopy

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with biopsies were performed. However, the cause of diarrhea could not be confirmed. Treatment of irritable bowel disease with loperamide was not effective. She also had parotid pain and headache that prompted a separate consultation with an otolaryngology and neurosurgery hospital. However, the etiology likewise remained unknown. On questioning, she noted other symptoms of lightheadedness, cough, and breathlessness. Because of these unexplained symptoms, she was referred to our institution and subsequently hospitalized.

On admission, she weighed 32.9 kg (body mass index: 15.7 kg/m²). The patient noted that she had lost 7.0 kg over a period of one year. Physical examination showed a low blood pressure (91/55 mmHg). Her heart rate was 84 beats per minutes and oxygen saturation was 99% at room air. She also had a rash on both the upper eyelids (Fig. 1). On physical examination, there were no abnormal lung sounds, abnormal abdominal findings or peripheral neuropathy. Blood tests revealed anemia, hypoalbuminemia, hypogammaglobulinemia, and folic acid deficiency (Table). Stool cultures and parasite testing were negative. Abdominal computed tomography (CT) showed thickening of the inner walls of the stomach and small intestine (Fig. 2a, b). No pathological fracture was observed on CT. We performed EGD and anal double-balloon enteroscopy. Food residue in the stomach, some erosions in the ileum, and erythema in the colon were observed (Fig. 2c, e, f). Biopsies from the stomach, duodenum, ileum, colon, and rectum did not show any specific findings (Fig. 3). However, electrocardiogram (ECG) revealed a low voltage abnormality in all limb leads (Fig. 4a) and an echocardiogram showed a thickened cardiac walls with a granular sparkling pattern (Fig. 4b), suggesting cardiac amyloidosis. The left ventricular ejection fraction was normal (62%) on echocardiogram. A chest X-ray showed mild pulmonary congestion and cardiomegaly (Fig. 4c). An abdominal fat biopsy was performed. However, the amyloid deposits were negatively stained. The patient finally underwent an endomyocardial biopsy that confirmed cardiac amyloid deposition (Fig. 5). Furthermore, the serum free light chain (FLC) kappa/lambda ratio was extremely low (Table), urine Bence-Jones protein was detected, and bone marrow plasma cell infiltration was 42.2% (Fig. 6). Based on these findings, she was diagnosed as having MM (Stage IIA according to the Durie-Salmon staging system and stage II according to the International Staging System criteria) with cardiac AL amyloidosis. She was discharged from our hospital 32 days after admission and admitted to another hospital to be treated with bortezomib and dexamethasone. At one week after being discharged, chemotherapy was initiated and the FLC kappa levels decreased. However, the severe diarrhea did not improve, and her general condition furtherly worsened. She was considered to be unable to continue chemotherapy after cycle 4. Finally, she died 6 months after the diagnosis.

**Figure 1. A rash on both eyelids.**

**Discussion**

Patients with amyloidosis have various symptoms because amyloid protein can be deposited in any organ. In our case, the patient had headache, lightheadedness, cough and breathlessness, and parotid pain; in addition to chronic diarrhea. Amyloid deposits were detected only in the heart. Therefore, headache and lightheadedness could be explained by hypotension caused by cardiac amyloidosis (6). Nevertheless, it is possible that other symptoms may be caused by amyloid deposition in the bronchi or lung (7) and the parotid gland (8), even though amyloid protein deposition was not detected in these organs. Furthermore, she had a rash on both eyelids. Agarwal et al. reported that key skin findings of amyloidosis include scattered, nontraumatic ecchymoses, and periorbital pinch purpura (9), which were consistent with the findings of our case. A possibility of amyloidosis should thus be considered in the differential diagnosis when examining a patient with chronic diarrhea and various concomitant symptoms involving other multiple organ systems.

GI amyloidosis manifests as a spectrum that includes abdominal pain, GI dysmotility, diarrhea, and GI bleeding (2, 10). In our patient, upper GI dysmotility and severe diarrhea were observed. Although there were no pathognomonic radiological findings for amyloidosis, it has been reported that CT scans show marked thickening of the stomach or small intestine walls in 17% of patients with GI amyloidosis (11). The CT images in our case matched this finding. Endoscopically, it has been reported that findings in the GI tract were non-specific and included erythema, erosions, ulcerations, granular mucosa or elevated lesions similar to submucosal tumors (12). In our case, erosions in the small intestine and erythema in the colon were observed.

A Japanese study reported the positive results rate of AL amyloidosis in a GI tract biopsy to be 72% (5). Any section along the GI tract can be affected by amyloidosis. However, the small bowel is the mostly commonly affected (2). Amyloid deposition from GI biopsies could not be detected, despite conducting biopsies from almost all sections of the GI tract. There may be two reasons to explain these negative results. The first possible reason is that chronic diarrhea might have occurred as GI autonomic neuropathy due to amyloid deposition. A similar case report by Pfleuecke et al. agrees with this explanation (13). The second possible reason could be the quality of biopsy specimens. The sensitivity of amyloid detection is higher when the submucosal layers are enclosed (14). However, our sampling did not contain the sub-
**Table. Laboratory Findings.**

| Blood test    | Result (Normal range) | Urinalysis          |
|---------------|-----------------------|---------------------|
| WBC           | 7,600 /mL (3,300-8,600) | Urine specific gravity 1.007 |
| Ly.           | 33.0 % (30.0-50.0)     | Urine protein (1+) (-) |
| Neu.          | 66.0 % (40.0-75.0)     | Urine occult blood (-) (-) |
| Mo.           | 0.0 % (0.0-8.0)        |                     |
| Eo.           | 1.0 % (0.0-6.0)        |                     |
| Baso.         | 0.0 % (0.0-2.0)        |                     |
| Hb            | 9.9 g/dL (11.6-14.8)   |                     |
| Plt           | 37.8×10^4 /mL (15.8-34.8×10^4) |                     |

**Laboratory results:**

- **WBC**: white blood cell, **Hb**: hemoglobin, **Plt**: platelet, **MCV**: mean corpuscular volume, **MCH**: mean corpuscular hemoglobin, **Alb**: albumin, **AST**: aspartate transaminase, **ALT**: alanine aminotransferase, **LDH**: lactate dehydrogenase, **ALP**: alkaline phosphatase, **γ-GTP**: γ-glutamyl transpeptidase, **CPK**: creatine phosphokinase, **BUN**: blood urea nitrogen, **Cre**: creatinine, **CRP**: C-reactive protein, **CMV**: cytomegalovirus, **BNP**: brain natriuretic peptide, **HIV**: human immunodeficiency virus, **ACTH**: adrenocorticotropic hormone, **TSH**: thyroid-stimulating hormone, **FLC**: free-light chains

mucosa (Fig. 3). Rochen et al. reported that GI biopsies from patients with amyloidosis, which do not contain submucosal layers, may result in a false negative in more than 60% of cases (15). Had GI tract biopsies been included the submucosa in our case, it may have been possible to note amyloid protein deposition in the GI tract of our patient.
We could not find any conclusive relationship between AL amyloidosis and chronic diarrhea. However, as her diarrhea occurred along with other symptoms that could be caused by amyloidosis, and as we excluded other diseases...
The findings of electrocardiograms (ECG), echocardiograms and chest X-rays. (a) ECG reveals low voltage in all limb leads. (b) An echocardiogram reveals a thick-walled heart and granular sparkling pattern. (c) A chest X-ray shows mild pulmonary congestion and cardiomegaly (the cardiothoracic ratio; 54%).

Pathologic findings of the myocardium. (a) On Hematoxylin and Eosin staining, perimyocyte interstitial deposition of an eosinophilic, amorphous substances are observed. (b) These substances are positive for direct fast scarlet staining. (c) Under electron microscopy (×1,500), deposition of moderate electron density materials surrounding individual myocardial fibers is observed. (d) A high-magnification image (×50,000) reveals fibril structures with a diameter of about 10 nm, and the fibrils extend straight without crossing. These findings are compatible with typical cardiac amyloidosis.

that may cause chronic diarrhea: cytomegalovirus enterocolitis, intestinal tuberculosis, pseudomembranous enterocolitis, parasitic infection, infectious enterocolitis, HIV infection, hyperthyroidism, Addison’s disease, inflammatory bowel disease, and eosinophilic gastroenteritis based on the laboratory data and pathologic findings of the GI tract, we concluded that her diarrhea was due to amyloidosis.

Cardiac involvement is the leading cause of morbidity and mortality in amyloidosis, and it occurs in approximately 50% of patients with AL amyloidosis (6). ECG is an easily
available and cost-effective modality that can provide invaluable information regarding the underlying disease. Because the thickening of ventricular walls in amyloidosis is due to myocardial amyloid deposition rather than hypertrophy, the ECG voltages tend to decrease as the disease progresses. Low voltage on ECG (defined as all limb leads <5 mm in height) is found in a high proportion of patients with AL amyloidosis (16). Thick-walled heart on echocardiogram but with a normal or low voltage ECG remains a diagnostic hallmark of amyloidosis, with high sensitivity (72-79%) and specificity (91-100%) (17). In addition, a granular sparkling appearance on 2D-echocardiograms was associated with high specificity rates (71-81%), although such sensitivity tended to be low (26-36%) in the diagnosis of cardiac-involving amyloidosis (17). In our case, the findings of ECG and echocardiogram were consistent with the literature regarding amyloidosis and provided the clinical basis for endomyocardial biopsy. We conclude that ECG and echocardiograms are important tools for the diagnosis of cardiac-involving amyloidosis. They are noninvasive, safe, and may show findings that justify using a more invasive but definitive endomyocardial biopsy.

The sensitivity of abdominal fat biopsy in the diagnosis of amyloidosis has been reported ranging from 13 to 73% (2). The same report indicated that amyloidosis may also be detected in other organs like the kidney, bone marrow, and thyroid gland. Finally, the sensitivity of endomyocardial biopsy for the diagnosis of amyloidosis has been reported to be 100% (6). Thus, when amyloidosis in the GI tract cannot be detected, we may consider performing biopsies from other organs, including myocardial biopsy if deemed necessary. We considered trying to perform a re-biopsy from the GI tract including submucosal layers, but we prioritized biopsies from other organs since abnormalities on ECG and echocardiogram were detected.

MM is a neoplastic disease affecting plasma cells that is characterized by the clonal proliferation of malignant plasma cells within the bone marrow (18). The typical clinical manifestations of MM are hypercalcemia, renal insufficiency, anemia, and bone lesions (19). In the present case, anemia was observed, and we considered it a result of MM and folic acid deficiency. It has been reported that 12-15% of the patients diagnosed with MM were found to have co-existing active AL amyloidosis (20). Although further investigation into the subtype of amyloidosis in our patient was not done, we highly suspected AL amyloidosis due to comorbidity in MM.

Based on the National Comprehensive Cancer Network (NCCN) guidelines for MM, bortezomib and dexamethasone therapy is recommended for non-transplant candidates in certain circumstances (21). As her general condition was frail, this therapy was chosen for her. Bortezomib is an anticancer medication that induces a rapid decrease in serum FLC concentration in patients with MM and AL amyloidosis (22). It has been reported that a favorable response rate to bortezomib and dexamethasone as therapy for MM ranges from 66-90% (23). However, in patients with AL amyloidosis, once symptoms of heart failure occur, the prognosis is dismal with a median survival of <6 months if the patients remain untreated (24). Moreover, the severe diarrhea did not

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Figure 6. The urine immunoelectrophoretic findings and pathological findings of the bone marrow. (a) Immunoelectrophoresis of urine proteins reveals an anti-lambda precipitation line (arrow). HWS: human whole serum. (b) The bone marrow smear reveals plasma cell infiltration and a plasma cell with a double nucleus is observed (arrow). (c) On Hematoxylin and Eosin staining of the bone marrow tissue, the marrow is relatively hypercellular. (d) On CD138 immunohistochemical staining, a large number of CD138-positive cells form aggregates. These neoplastic plasma cells are negative for kappa light chain (e) and positive for lambda light chain (f).
improve after chemotherapy initiation in the present case. It has been reported that a late diagnosis results in approximately 30% of patients presenting with advanced, irreversible organ involvement and most end up dying within a few months despite recent advances in treatments (25). Therefore, both early diagnosis and treatment are very important for improving the prognosis.

In conclusion, we herein reported a case of comorbid amyloidosis and MM that presented with a chief complaint of chronic diarrhea of unknown origin. However, other symptoms involving multiple organ systems including the heart led to an established diagnosis of amyloidosis by myocardial biopsy and MM by bone marrow biopsy. We propose that we may suspect the possibility of amyloidosis when we encounter a patient with chronic diarrhea with the presence of various symptoms involving multiple organ systems. ECG and echocardiograms remain highly useful modalities in patients with suspected cardiac-involving amyloidosis even in the setting of negative GI biopsy results. Although comorbid amyloidosis and MM may be rare, a prompt diagnosis is necessary as timely treatment is known to show favorable recovery rates. Thus, including amyloidosis in the differential diagnosis in such cases greatly benefits patients with multisystem-involved complaints.

The authors state that they have no Conflict of Interest (COI).

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