Introduction

Amyloidosis is characterized by abnormal deposition of aggregations of amyloid fibril proteins. The diagnosis of amyloidosis is often difficult because of a lack of specific symptoms, and still relies on biopsy and the pathological demonstration of typical deposits, with few other indicators available to suggest or support the diagnosis of this disease. Since biopsy is an invasive examination, a noninvasive and sensitive test for amyloidosis is needed [1].

Hepatocyte growth factor (HGF) was originally purified as a potent mitogen of cultured hepatocytes [2-4]. Some recently reports have demonstrated that HGF is a useful noninvasive marker for the early diagnosis and prediction of prognosis of cardiac amyloidosis [5, 6], but there are few reports about the relationship between serum HGF and primary systemic amyloidosis. We present here a case of primary systemic amyloidosis that was misdiagnosed as liver cirrhosis due to liver dysfunction, jaundice and severe ascites.

Case Report

A 75-year-old man showed initial findings of elevated hepatobiliary enzyme and was prescribed ursodeoxycholic acid (UDCA) at a local hospital. The hepatobiliary enzyme became further elevated the fol-
following year, and ascites appeared. He was diagnosed with decompensated liver cirrhosis, but its etiology was unknown. He was introduced to our hospital to identify the etiology.

The patient’s blood pressure on admission was 120/78 mmHg, his heart rate was 88 beats per minute, and his oxygen saturation by pulse oximetry was 100% in room air. A physical examination detected lucidity, mild conjunctive jaundice, severe abdominal distension and bilateral pitting edema in the lower extremities. The laboratory data, summarized in Table 1, showed elevation of alkaline phosphatase (ALP) and γ-glutamyltranspeptidase (γ-GTP) (1,982 U/l and 525 U/l, respectively), which are known to be common laboratory findings in patients with amyloidosis [7, 8]. Hyaluronic acid (531 ng/ml) and type IV collagen (1,612 ng/ml), alpha-fetoprotein (AFP) (21.9 ng/ml), and protein induced by vitamin K absence or antagonist (PIVKA)-II (6,170 mAU/ml) were also elevated. The serum HGF was very high (16.24 ng/ml). A urine test revealed that Bence-Jones protein and beta-2 microglobulin were negative.

Abdominal ultrasonography showed liver swelling and ascites, but did not show any space-occupying lesion in the liver (Figure 1). Contrast-enhanced computed tomography (CT) showed small bilateral pleural effusion, severe liver swelling, and ascites, but did not show any pathologic fractures, osteolysis, splenomegaly or liver tumors (Figure 2). Magnetic resonance imaging at a local hospital also showed no liver tumors (not shown). Thus, the mild elevation of AFP was thought to reflect hepatic regeneration after the liver damage. Because a previous report demonstrated that hepatic amyloidosis induced intrahepatic cholestasis [9], vitamin K deficiency was suspected to have induced the elevation of PIVKA-II. Echocardiography showed mild left ventricular myocardial hypertrophy, but cardiac output was maintained without pericardial effusion (not shown).

We were unable to identify a definite etiology of the liver dysfunction from the blood tests and imaging. Amyloidosis was considered to be a possible differential diagnosis, based on the findings of hepatomegaly and high serum HGF, but we didn’t perform liver biopsy due to the risk of bleeding. We performed esophagogastroduodenoscopy (EGD) on the 21st day of hospitalization and colonoscopy (CS) on the 27th day. The EGD demonstrated erosions in the greater curvature of the lower gastric body, but no esophageal or gastric varices (Figure 3). CS demonstrated that the vascular pattern had vanished, and there was intestinal edema from the rectum to the anus (Figure 4).

The histological results of biopsies from the mucosa of the gastric body, esophagus, duodenum and rectum demonstrated amyloid protein deposition in the mucosa of the stomach, duodenum, and rectum by Congo red staining (Figure 5). The samples were positive for immunoglobulin light-chain antibodies, but didn’t react to monoclonal amyloid A (AA) antibody or polyclonal transthyretin antibodies, so we diagnosed the patient with systemic amyloid light-chain (AL) amyloidosis.

The patient and his family rejected further detailed examinations, including head CT and bone marrow puncture, as well as additional treatments. Although we continued to administer blanched-chain amino acids, nonabsorbable disaccharide (lactulose), and V2 receptor antagonist (tolvaptan), his general condition and liver function got worse. Unfortunately, he died one month after the diagnosis.

Discussion

Amyloidosis is a rare group of diseases that results from extracellular deposition of amyloid, a fibrillar material derived from various precursor proteins that self-assemble with highly ordered abnormal cross β-sheet conformation [10]. More than 30 proteins have been identified to form amyloid in humans [11]. The two major forms of amyloidosis are the AL (primary) and AA (secondary) types. AL amyloidosis is due to deposition of protein derived from immunoglobulin light-chain fragments. AA amyloidosis may complicate chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The clinical presentations in AL amyloidosis depend on the number and nature of the organs affected, and non-specific clinical presentations, including fatigue and unintentional weight loss, are common in patients with AL amyloidosis [12]. Other common clinical presentations of AL amyloidosis include hepatomegaly, restrictive cardiomyopathy, nephrotic syndrome, peripheral neuropathy.
Table 1. Laboratory findings of this patient on admission

| Hematology                  | Serology         | Coagulation       | Immunology          | Tumor markers | Virus markers | Urinalysis      |
|-----------------------------|------------------|-------------------|---------------------|---------------|---------------|----------------|
| WBC 1.3×10^4 /µl            | CRP 1.3 mg/dl    | PT 15.7 sec       | ANA <40             | AFP 21.9 ng/ml| HBs Ag (+)    | Protein (2+)   |
| Neut 82%                    |                  |                   | AMA <20             |               |               | Glucose (4+)   |
| Eosino 0.2%                 |                  |                   |                     |               |               | BNP 1,759 pg/d|
| RBC 3.9×10^4 /µl            |                  |                   |                     |               |               |                |
| Hb 12.8 g/dl                |                  |                   |                     |               |               |                |
| Hct 36.8%                   |                  |                   |                     |               |               |                |
| Plt 46.7 /µl                |                  |                   |                     |               |               |                |
| Hematology                  |                  |                   |                     |               |               |                |
| Biochemistry                |                  |                   |                     |               |               |                |
| TP 5.5 g/dl                 |                  |                   |                     |               |               |                |
| Alb 2.4 g/dl                |                  |                   |                     |               |               |                |
| T-Bil 2.3 mg/dl             |                  |                   |                     |               |               |                |
| D-Bil 1.7 mg/dl             |                  |                   |                     |               |               |                |
| AST 123 U/l                 |                  |                   |                     |               |               |                |
| ALT 58 U/l                  |                  |                   |                     |               |               |                |
| LDH 346 U/l                 |                  |                   |                     |               |               |                |
| ALP 1,982 U/l               |                  |                   |                     |               |               |                |
| γ-GTP 525 U/l               |                  |                   |                     |               |               |                |
| BUN 14 mg/dl                |                  |                   |                     |               |               |                |
| Cre 0.8 mg/dl               |                  |                   |                     |               |               |                |
| Na 132 mmol/l               |                  |                   |                     |               |               |                |
| K 4.6 mmol/l                |                  |                   |                     |               |               |                |
| Cl 99 mmol/l                |                  |                   |                     |               |               |                |
| Ca 8.7 mg/dl                |                  |                   |                     |               |               |                |
| Cu 205 µg/dl                |                  |                   |                     |               |               |                |
| Ceruloplasmin               |                  |                   |                     |               |               |                |
| FPG 465 mg/dl               |                  |                   |                     |               |               |                |
| NH₃ 89 µg/dl                |                  |                   |                     |               |               |                |
| BNP 1,759 pg/dl             |                  |                   |                     |               |               |                |
| HGF 16.24 ng/ml             |                  |                   |                     |               |               |                |
| sIL-2R 810 U/ml             | Protein (2+)      |                   |                     |               |               |                |
| SAA 6.6 µg/dl               |                  |                   |                     |               |               |                |
| Hyaluronic acid             |                  |                   |                     |               |               |                |
| Type IV collagen            |                  |                   |                     |               |               |                |
| WBC : White blood cell count, RBC: Red blood cell count, Hb: Hemoglobin, Hct: Hematocrit, Plt: Platelet count, TP: Thyroid peroxidase antibodies, Alb: Albumin, T-Bil: Total bilirubin, D-Bil: Direct bilirubin, AST: Alanine aminotransferase, ALT: Alanine transaminase, LDH: lactate dehydrogenase, ALP: Alkaline phosphatase, γ-GTP: γ-Glutamyl transpeptidase, BUN: Blood urea nitrogen, Cre: Creatinine, Na: Sodium, K: Potassium, Cl: Chloride, Ca: Calcium, Cu: Copper, FPG: Fasting plasma glucose, NH₃: Ammonia, BNP: Beta natriuretic peptide, HGF: Hepatocyte growth factor, sIL-2R: Soluble interleukin-2 receptor, SAA: Serum amyloid A, CRP: Cold reactive protein, PT: Prothrombin time, PT-INR: Prothrombin time, APTT: Activated partial thromboplastin time, FDP: Fibrin/fibrinogen degradation products, ANA: Anti-nuclear antibody, AMA: Anti-mitochondrial antibody, IgG: Immunoglobulin G, IgM: Immunoglobulin M, IgA: Immunoglobulin A, AFP: α-fetoprotein, PIVKA-II: Protein induced by vitamin K absence or antagonist-II, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, HBs Ag: Hepatitis B virus antigen, HBe Ab: Hepatitis B virus antibody, HBV DNA: Hepatitis B Virus DNA, HCV Ab: Hepatitis C virus antibody, BJP: Bence-Jones protein, β2-MG: β2-Microglobulin.
Figure 1. The findings of abdominal ultrasonography. Abdominal ultrasonography showed liver swelling and ascites, but not space-occupying lesion in the liver.

Figure 2. The findings of computed tomography. Computed tomography showed small bilateral pleural effusion, severe hepatomegaly and ascites, but no splenomegaly. (A) Axial image and (B) coronal image.

Figure 3. The findings of esophagogastroduodenoscopy. Esophagogastroduodenoscopy demonstrated erosions in the greater curvature of the lower gastric body (arrows), but no esophageal or gastric varices.

Figure 4. The findings of colonoscopy. Colonoscopy showed the vanished vascular pattern and intestinal edema from the rectum to the anus.
and bleeding diathesis. Hepatomegaly has been found in 81%, proteinuria has been found in 89%, and elevated serum ALP level has found in 86% of patients with AL amyloidosis [13]. Cardiac involvement occurs in about 50% of patients with AL amyloidosis [14], and it is the leading cause of morbidity and mortality [15]. Clinical gastrointestinal involvement appears to be less common than in the other forms of amyloidosis, with clinically apparent disease occurring in only 1% of patients with AL amyloidosis [16].

Due to the lack of specific symptoms, the duration between the onset of symptoms and the diagnosis of AL amyloidosis is usually long. The duration in previous reports was 6–10 months [17-19]. Early diagnosis is crucial, because early intervention may prevent irreversible organ damage and improve the prognosis [17]. One study, however, reported that only 7.6% of patients received a diagnosis of amyloidosis after visiting one physician, and that 31.8% visited more than 5 physicians before receiving the correct diagnosis [20].

Clinical and imaging presentations of amyloidosis are often non-specific, hence histological examination is always required to confirm the diagnosis [21]. Histological confirmation of the amyloid deposits and of the fibril type following Congo red staining of biopsied tissue remains the gold standard for diagnosis, but liver biopsy carries a high risk of bleeding [22]. Because amyloidosis is a systemic disease, rates of positive gastrointestinal biopsies are known to be much higher [23], and the sensitivity of rectal biopsy in one large series composed predominantly of patients with systemic amyloidosis was estimated at 84% [24].

The patient in our case was misdiagnosed with liver cirrhosis because the serum hyaluronic acid and type IV collagen were very high. Hyaluronic acid is a very useful non-invasive marker of liver fibrosis, it increases not only in liver cirrhosis but also in non-liver diseases such as rheumatoid arthritis, systemic sclerosis and malignant diseases. Measurement of serum hyaluronic acid level has also been proposed as a useful non-invasive supplementary marker for the diagnosis of amyloidosis. Although the precise mechanisms of elevated hyaluronic acid in systemic amyloidosis are unclear, it has been hypothesized that a marked deposition of amyloid protein in the hepatic perisinusoidal spaces may inhibit the uptake of hyaluronic acid, and its degradation via the hepatic sinusoidal endothelial cells may be reduced in patients with amyloidosis [7].

We should consider the possibility of systemic amyloidosis in patients with liver injury and high serum hyaluronic acid. On the other hand, elevated serum HGF has been observed in patients with fulminant hepatic failure and reflects the degree of liver injury. Thus, the degree of HGF elevation is useful for predicting the prognosis in patients with fulminant hepatic failure [25]. HGF is a pro-angiogenic cytokine activated by tissue-type plasminogen activator [26]. It has been reported in recent years that serum HGF level was significantly increased in patients with systemic amyloidosis (the serum HGF ≥ 0.39 ng/ml), but no significant differences were found between AL and AA amyloidosis, and the serum HGF level in patients...
with amyloidosis who died within one year of measurement was significantly higher than that in patients who lived for more than one year (2.83 ± 2.85 ng/ml versus 0.49 ± 0.26 ng/ml, \( P < 0.01 \)) [27]. Thus, the measurement of serum HGF level is considered to be a valuable predictor of the prognosis of amyloidosis patients [28].

Furthermore, the serum HGF levels measured at diagnosis in patients with biopsy-proven systemic AL amyloidosis were significantly higher than in patients with monoclonal gammopathy (MG) without AL amyloidosis [26]. Although the detailed mechanisms of elevated HGF in patients with systemic amyloidosis remain unclear, HGF may increase as a result of extracellular amyloid deposition leading to the stimulation of macrophages and mesenchymal cells, and elevated serum HGF may correlate with the amount and/or extension of amyloid [27]. In the present case, the HGF was 12.5 ng/ml and the patient died one month after the diagnosis. This result was similar to that in previous reports, and the imaging examinations showed severe hepatomegaly, so we suspected that large amounts of amyloid protein deposition in the liver had induced the elevation of HGF.

In conclusion, we consider that HGF could be a useful noninvasive supplementary marker to diagnose and predict the prognosis of primary systemic amyloidosis. We suggest that physicians should consider the possibility of primary systemic amyloidosis in all patients with high serum HGF. Further studies are needed to understand the detailed mechanisms of the elevation of HGF in primary systemic amyloidosis.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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Hepatocyte Growth Factor and Primary Systemic Amyloidosis

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