Liver Biopsy-confirmed Primary Hepatic Amyloidosis with Only Jaundice As the Initial Symptom: An Autopsy Case Report

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Abstract:
Amyloidosis causes various symptoms in many organs of the body, but amyloidosis that presents with liver damage alone has never been reported. We treated an 83-year-old man with amyloidosis who presented with liver damage alone. The liver damage in this patient was histologically proven to be liver amyloidosis. The administration of bortezomib and dexamethasone was not effective, so he rapidly died of liver failure. An aggressive liver biopsy should be considered when unexplained jaundice is observed.

Key words: amyloidosis, jaundice, liver biopsy, bortezomib

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Introduction
Amyloidosis is a rare disease that causes various symptoms due to the deposition of amyloid protein, which forms insoluble fibrils derived from immunoglobulin light chains in many organs of the body (1, 2). Since amyloid deposits in various organs, the symptoms of amyloidosis are not specific. The liver is a common site of amyloid deposition in primary amyloidosis. However, the symptoms of hepatic amyloidosis are usually mild, with slight liver damage or hepatomegaly, and rarely include severe jaundice or hepatic failure (2-4).

We herein report a case of primary hepatic amyloidosis with slight jaundice that was confirmed by a liver biopsy and finally progressed to hepatic failure.

Case Report
An 83-year-old man presented with brown urine and general malaise that had persisted for 2 months. He was diagnosed with chronic liver disorder by his primary care doctor. Despite liver-supporting therapy, his jaundice became exacerbated. He was therefore referred to our hospital for a further evaluation and treatment. His first laboratory test (Table 1) showed a slight increase in total bilirubin (T.bil), direct bilirubin (D.bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (γ-GTP) levels. The levels of hepatic fibrosis markers, such as M2BPGi, type IV collagen 7S and hyaluronic acid, were elevated, but thrombocytopenia was not observed. Abdominal computed tomography showed no liver mass, liver swelling or splenomegaly (Fig. 1). Viral, alcoholic, drug-induced, and autoimmune hepatic disorders were not probable based on his history, blood sampling and imaging findings. Since his biliary enzymes and jaundice did not decrease for two weeks, we performed a liver biopsy for a histological evaluation.

Liver biopsy specimens stained with hematoxylin-eosin revealed diffuse amorphous substance deposits in the sinusoidal spaces. These cells were positively stained pink-red with Congo red and AL amyloid (Fig. 2). In contrast, AA amyloid staining was negative. Based on the hepatic findings above, we diagnosed the patient with hepatic amyloidosis. Additional examinations to evaluate systemic amyloidosis were therefore needed.

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Table 1. Characteristics of the Laboratory Data at the First.

| Hematology       | AST        | IgG       | 1,682 mg/dL |
|------------------|------------|-----------|-------------|
| WBC 4,800 μL     | ALT 26 IU/L| IgA 175 mg/dL |
| RBC 456×10^6 μL  | ALP 654 IU/L| IgM 194 mg/dL |
| Hb 14.4 g/dL     | γ-GTP 168 IU/L| Hbs-Ag 0.00 mg/dL |
| Plt 20.5×10^4 μL | Ch-E 317 U/L| HCV-Ag 0.49 IU/mL |
| Coagulation      | T.P 6.9 g/dL| Anti nuclear antibody 40 s/co |
| PT 13.8 s        | Alb 4.0 g/dL| Anti mitochondrial antibody Negative |
| PT % 74 %        | BUN 6.6 mg/dL| M2BPGi 8.5 C.O.I. |
| Chemistry        | Scr 0.91 mg/dL| Type IV collagen 7S 9.1 ng/mL |
| T.Bil 2.1 mg/dL  | eGFR 60.5 mL/min/1.73m^2| Hyaluronic acid 1.030 ng/mL |
| D.bil 1.0 mg/dL  | CRP 0.270 mg/dL|              |

Figure 1. Abdominal contrast-enhanced CT showed chronic hepatitis alone without hepatic tumor, bile duct dilatation, or splenomegaly.

Esophagogastroduodenoscopy, colonoscopy, and a gastrointestinal biopsy were performed, but amyloid protein was not found to have been deposited in the mucosa or submucosa of the alimentary tract. An electrocardiogram analysis showed a normal sinus rhythm without any findings of abnormal conduction. His renal function was normal without any evidence of albumin or Bence-Jones protein in the urine. A bone marrow biopsy revealed that the plasma cell count was 4.0%. Thus, the diagnostic criteria of multiple myeloma were not satisfied. The diagnosis based on the additional findings above, the patient was diagnosed with primary amyloidosis (AL type).

The diagnosis was confirmed, the T.bil level had increased to 9.7 mg/dL, and the ALP level had increased to 1,717 IU/L. Therefore, liver-supporting therapy and chemotherapy were started. We administered Ursodeoxycholic acid and glycyrrhizin, glycine, and cysteine combined drugs as liver-supporting therapy and bortezomib and dexamethasone as chemotherapy. However, his jaundice became significantly exacerbated, and he ultimately died of liver failure approximately three months after his first visit (Fig. 3).

Autopsy was performed the day after the patient’s death for the further evaluation of his amyloidosis status. Macroscopic findings revealed hepatomegaly and a liver volume of 1,650 g (Fig. 4). A microscopic analysis revealed that amyloid protein was deposited in the liver to a higher degree than at the time of the liver biopsy, and almost no normal hepatocytes were found. Amyloid proteins were abundantly deposited in the liver and spleen and slightly deposited in very small vessels of the kidney, heart, and alimentary tract. However, amyloid proteins were not found in the renal glomeruli, the myocardial muscle layer, or the gastrointestinal mucosal layer (Fig. 5).

Discussion

Amyloidosis is a systemic disorder caused by amyloid, which is an insoluble protein with a fibrous structure that causes dysfunction of various organs by its deposition. Amyloidosis with amyloid light chain, which is deposited in the organs throughout the body, is called amyloid light chain (AL) amyloidosis (5-8). The average survival time of AL amyloidosis is approximately 12-17 months (9, 10). Furthermore, the prognosis was particularly poor (approximately only 1 month) in patients with jaundice of T.bil ≥2.0 mg/dL at the time of the diagnosis (11). In the present case, since the T.bil level was over 2.1 mg/dL, the predicted prognosis was poor at the first visit. Most symptoms of hepatic amyloidosis are clinically unclear, and liver dysfunction is mild. Thus, it is very rare to observe jaundice or liver failure in these patients. The organs in which amyloid tends to deposit include the heart, kidneys, liver, spleen, and digestive tract, but there is no organ specificity, and the symptoms vary depending on the site of deposition.

Treatment for AL amyloidosis aims to support the organ function and suppress the production of M protein with large-scale chemotherapy in combination with autologous peripheral blood stem cell transplantation. Specific chemotherapy includes melphalan, prednisolone (MP) therapy; vincristine, doxorubicin, dexamethasone (VAD) therapy; small-dose oral melphalan therapy; thalidomide; bortezomib; lenalidomide; etc. However, no consensus has been obtained (10, 12-15). In the present case, we administered a
combination treatment of bortezomib and dexamethasone due to severe jaundice and his poor general condition, but the condition did not improve, and a rapid clinical course followed.

The clinical characteristics of the present case included persistent jaundice and liver dysfunction. In addition, since
there were few depositions in the heart and kidneys, where amyloid is often deposited, there were no symptoms of arrhythmias or nephrotic syndrome. The mechanisms underlying jaundice include (I) obstruction of intrahepatic bile ducts by amyloid protein, (II) hepatocellular disorders, (III) combination of cholestatic hepatitis, (IV) blockage of the gluteal duct stubble due to amyloid nodules, and (V) compression atrophy of hepatocytes due to a large amount and diffuse deposition of amyloid (16). In addition, in patients with advanced jaundice and liver failure, atrophy of the lobular bile duct and loss of hepatocellular cord structure are severe. The pathological mechanisms underlying jaundice in this case were pressure atrophy of hepatocytes and the loss of normal hepatocytes due to a large amount of amyloid deposition.

There are no published papers that discuss the frequency of deposition in other organs. Table 2 describes the organs in the body that are subject to amyloid deposition (2-4, 17-25). Our patient is the only known patient with clinical symptoms of liver failure alone. However, since amyloid was deposited in small vessels throughout the body, symptoms of renal impairment and arrhythmia may have developed in the future.

Thus far, liver biopsies in amyloidosis patient have generally been considered to carry a risk of bleeding. However, Park et al. reported that none of their patients experienced hepatic rupture or death due to a liver biopsy, and only 4 (4%) of 98 patients with primary systemic amyloidosis experienced bleeding (11). In addition, Gertz et al. made a point that bleeding was infrequent, and a liver biopsy carried a slightly increased risk (26). Their patients who experienced bleeding following a liver biopsy were managed conservatively with blood transfusion therapy. Therefore, the indication of a liver biopsy for systemic amyloidosis should be defined circumspectly, but it is not always necessary to avoid a liver biopsy.

In conclusion, this was a rare case and the first time that jaundice alone has been reported as a clinical symptom of amyloidosis. Since it was diagnosed for the first time by a liver biopsy, we should consider amyloidosis as a differential diagnosis if unexplained jaundice is observed.

Table 2. Regions with Amyloid Protein Deposition in Patients with Primary Amyloidosis.

| Case No. | Age | Sex | Chief complaint | T-bil (mg/dL) | ALP (IU/L) | Deposited organs | Survival time | Reference No. |
|---------|-----|-----|-----------------|--------------|-----------|-----------------|--------------|---------------|
| 1       | 73  | M   | General malaise | 11.6         | 1,046     | Liver, heart, kidney, spleen, lung, brain, digestive canals | 5 months | 17            |
| 2       | 47  | F   | Respiratory discomfort leg edema | normal       | normal    | Liver, kidney, digestive tract | 42 months | 18            |
| 3       | 70  | M   | Fever up general malaise | 2.6         | 4,164     | ? | 4 months | 19            |
| 4       | 60  | F   | Anorexia general malaise | 2.5         | 1,385     | Liver, heart, kidney, spleen adrenal gland, digestive tract, thyroid | 4 months | 20            |
| 5       | 61  | M   | Abdominal swelling | 0.9          | 1,050     | Liver, heart, kidney, digestive tract | ? | 21            |
| 6       | 72  | M   | No complaint | 1.2          | 844       | Liver, heart, kidney, spleen digestive tract | 3 months | 3             |
| 7       | 57  | M   | Jaundice hemorrhetic | 3.2         | 310       | Liver, digestive tract | 4 months | 3             |
| 8       | 38  | M   | Leg edema weight loss | ?           | 3,900     | Liver, heart, kidney | 3 months | 22            |
| 9       | 71  | F   | Jaundice, cardiac failure | 7.73         | ?         | Liver, heart, kidney, digestive tract | 1 week | 23            |
| 10      | 60  | M   | Jaundice, weight loss, ascites | 2.9         | 1,223     | Liver, kidney, digestive tract, bone marrow | 2 months | 2             |
| 11      | 39  | M   | Weight loss abdominal swelling | 0.5         | 938       | Liver, kidney, spleen, bone marrow | 2 months | 24            |
| 12      | 54  | M   | Jaundice weight loss | 5.7          | ?         | Liver, bone marrow, skin | ? | 25            |
| Our case | 83  | M   | Jaundice | 2.1         | 654       | Liver, spleen, small vessels | 5 months |               |
The authors state that they have no Conflict of Interest (COI).

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