**Case Report**

**AL amyloidosis that presented with marked hepatomegaly and polyclonal hypergammaglobulinemia**

Hitoshi Ohno¹*, Yusuke Toda¹, Yoshimasa Kamoda¹, Makoto Okabe², Gen Honjo³

¹Department of Hematology, Tenri Hospital; ²Department of Gastroenterology, Tenri Hospital; ³Department of Diagnostic Pathology, Tenri Hospital

Received 2017/4/22; accepted 2017/5/16; released online 2017/7/1

A 65-year-old woman presented with marked hepatomegaly and polyclonal hypergammaglobulinemia. Her total serum protein was 8.9 g/dL with 35.6% albumin and 40.2% (35.8 mg/mL) γ globulin. Alkaline phosphatase was 730 IU/L. The cranio-caudal liver span measured on computed tomography was 24.2 cm. A biopsy of the liver revealed replacement of the liver parenchyma with amorphous eosinophilic materials that were stained positive with Congo red and showed the apple-green birefringence of amyloid; amyloid deposits were also observed in the gastric mucosa and bone marrow (BM). Although immunofixation of the serum and urine detected no monoclonal component, the serum free light chain (FLC) assay revealed an excess of FLC-κ (FLC-κ, 1,290 mg/L; FLC-λ, 86 mg/L). The BM contained 10.4% clonal plasma cells carrying the CCND1-immunoglobulin heavy chain fusion gene. She was diagnosed with AL amyloidosis and treated with bortezomib-based chemotherapy, readily leading to the hematological response fulfilling the criteria of very good partial response. The hepatomegaly was steadily resolved in response to persistent administration of bortezomib for >2 years. It is possible that the hypergammaglobulinemia reflected a reactive process against amyloid deposits in the liver. This report suggests that plasma cell-targeting therapy can reduce the amyloid deposits from the involved organs, potentially reversing their dysfunction.

**Keywords:** AL amyloidosis, hepatic amyloidosis, serum free light chain, polyclonal hypergammaglobulinemia, bortezomib-based chemotherapy

**INTRODUCTION**

Immunoglobulin light chain (AL) amyloidosis is a clonal plasma cell disorder characterized by tissue deposits of light chain protein, leading to dysfunction of vital organs.¹,² Cardiac and renal involvements of AL amyloidosis are well recognized, and the disease is considered in the differential diagnosis when a patient presents with cardiomegaly or nephrotic syndrome.²,⁴ In contrast, dominant hepatic involvement as the presenting sign or symptom is unusual.⁴ Nevertheless, the liver is palpable in 25 to 30% of patients with AL amyloidosis and the most frequently abnormal test of hepatic function is an elevated serum alkaline phosphatase (ALP) level;¹,³,⁴ the criterion of hepatic involvement is a liver span >15 cm in the absence of heart failure or ALP >1.5-times the institutional upper limit of normal.⁵ The outcome of patients with hepatic amyloidosis was reported to be dismal; the median survivals of the 80
and 98 patients in the Mayo clinic series were 9 and 8.5 months, respectively. A literature review found that patients may present with severe hepatomegaly, inrathelial cholestasis, or florid liver failure.

In up to 90% of patients with AL amyloidosis, a monoclonal protein is detectable in the serum and/or urine by routine protein electrophoresis or immunofixation. Examination of the bone marrow (BM) reveals monoclonal plasma cells, even though the clonal plasma cell burden is small (i.e. median infiltration of 7 to 10%), compared with that in symptomatic multiple myeloma.

We report here a patient with AL amyloidosis who presented with marked hepatomegaly. Intriguingly, the serum protein electrophoresis revealed polyclonal hypergammaglobulinemia with polyclonal increase of immunoglobulins instead of the presence of monoclonal component with decreased residual immunoglobulins, delaying the correct diagnosis.

**CASE PRESENTATION**

A 65-year-old woman, who had been treated for compression fracture of the L2 lumbar vertebra at an orthopedic clinic, was referred to the Department of Hematology of our hospital with the suspicion of a hematological malignancy due to leukocytosis and hypergammaglobulinemia. On examination, the liver was markedly enlarged at 10-finger-width below the right costal margin to reach the level of anterior iliac spine, and was firm with a dull edge and smooth surface, and was non-tender. There was no ascites or leg edema.

The hemoglobin level was 12.9 g/dL, white blood cell count $14.18 \times 10^3/\mu L$, and platelet count $257 \times 10^3/\mu L$. The white cell differential was 31.5% lymphocytes, 6.5% monocytes, 0.5% eosinophils, 1.0% basophils, 57.5% segmented neutrophils, and 3.0% banded neutrophils. Red cells exhibited rouleaux formation, and Howell-Jolly bodies were seen. Total serum protein was 8.9 g/dL, albumin 3.2 g/dL, lactate dehydrogenase 256 IU/L, aspartate aminotransferase 46 IU/L, alanine aminotransferase 13 IU/L, total bilirubin 2.3 mg/dL, γ glutamyl transpeptidase 274 IU/L, ALP 730 IU/L (reference range, 100 to 335 IU/L), choline esterase 146 IU/L, blood urea nitrogen 12.0 mg/dL, creatinine 0.7 mg/dL, uric acid 6.8 mg/dL, and C-reactive protein 0.5 mg/dL. Serum protein electrophoresis showed the polyclonal hypergammaglobulinemia pattern with 35.6% albumin, 3.4% α1 globulin, 6.4% α2 globulin, 14.5% β globulin, and 40.2% (35.8 mg/mL) γ globulin. The level of IgG was 3,150 mg/dL, IgA was 1,289 mg/dL, and IgM was 203 mg/dL. Computed tomography (CT) of the body with the administration of contrast material demonstrated marked hepatomegaly with homogeneous contrast enhancement; the cranio-caudal liver span was 24.2 cm (Figure 1A). The size of the spleen was normal.

The patient was admitted to another hospital, where she developed hematemesis due to multiple gastric ulcers; she was then transferred to the Department of Gastroenterology of our hospital. CT scan of the whole body disclosed pneumonia, pleural fluids, and ascites, in addition to the marked hepatomegaly. Evaluation of blood flow with pulsed and color Doppler ultrasonography revealed reverse flow at the portal trunk, splenic vein, and superior mesenteric vein. Prothrombin time was 17.0 sec. Serology of the hepatitis B and C virus antigens was negative.

A biopsy of the liver through percutaneous fine-needle approach revealed replacement of the liver parenchyma with amorphous eosinophilic materials (Figure 1B). The materials were stained positive with Congo red staining, and the Congo red-stained materials exhibited the apple-green birefringence of amyloid under polarizing light microscopy. An upper gastrointestinal endoscopy revealed grade 0 to 1 esophageal varices at the lower esophagus, and biopsies of the gastric mucosa revealed Congo red-stained amyloid deposits with characteristic birefringence (Figure 2).

Immunofixation tests of the serum and urine detected no monoclonal component (Figure 3A). However, the serum free light chain (FLC) assay revealed an excess of FLC-κ (FLC-κ, 1,290 mg/L [reference range, 3.3 to 19.4
Amyloidosis with marked hepatomegaly

Figure 1. Liver involvement of AL amyloidosis. (A) Transverse (a), coronal (b), and sagittal (c) CT images at presentation, exhibiting marked hepatomegaly. The craniocaudal liver span was 24.2 cm. The sagittal plane image shows wedge compression fracture of the L2 lumbar spine. The Th12 thoracic spine may have been affected. (B) Biopsy of the liver, showing deposits of amyloid: a, loupe image of the biopsy specimen (Hematoxylin and eosin [H&E] staining); b, higher magnification picture (H&E staining); c, Congo red staining; and d, polarizing light microscopy image.

Figure 2. Amyloid deposits in the gastric mucosa. a, loupe image of a biopsy specimen; b, higher magnification of the area enclosed by the rectangle in a, focusing upon the amyloid deposits; c, Congo red staining; and d, polarizing light microscopy image.
mg/L]; FLC-λ, 86 mg/L [5.7 to 26.3 mg/L]; FLC ratio, 15.00 [0.26 to 1.65]). The BM biopsy revealed that the inter-trabecular space was filled with amyloid deposits of identical features with those of the liver (Figure 3B, a to d). Examination of the BM aspiration smear detected plasma cells comprising 10.4% of the nucleated cells (Figure 3B, e), and the cells were CD19+, CD20dim, CD28−, CD38+, CD45RA−, CD45RO−, CD56+/−, and CD138+, and showed cytoplasmic immunoglobulin κ light-chain restriction by multicolor flow cytometry (Figure 4). The plasma cells carried the CCND1-immunoglobulin heavy chain (IGH) fusion gene by fluorescence in situ hybridization (FISH) of the interphase nuclei (Figure 3B, f). β2 microglobulin was 4.13 µg/mL. Brain natriuretic peptide (BNP) was 180.0 pg/mL (reference, <18.4 pg/mL).

**TREATMENT AND COURSE**

We finally made the diagnosis of AL amyloidosis involving the liver, stomach, and BM. No cardiac abnormality was found by echocardiography. We treated the patient with bortezomib and low-dose dexamethasone in combination with or without cyclophosphamide (i.e. CBd or Bd regimen). The course was complicated by aspiration pneumonia due to prolonged bedrest, bleeding from rupture of esophageal varices, and severe pain and impaired physical activity due to additional vertebral compression fractures. Nevertheless, the values of IgG and IgA readily fell to the normal levels, and polyclonal hypergammaglobulinemia was resolved after the first cycle of CBd (Figure 5). The serum FLC κ/λ ratio also decreased, but remained higher than the reference range. Hepatomegaly was steadily resolved in response to per-

![Figure 3](image-url)

**Figure 3.** Investigation of clonal plasma cells. (A) Immunofixation tests of the serum and urine showing the absence of monoclonal component but a polyclonal gammopathy pattern of the serum. (B) Amyloid deposits in the BM and features of clonal plasma cells: a, lower magnification picture of the biopsy specimen (H&E stain); b, higher magnification picture (H&E staining); c, Congo red staining; d, polarizing light microscopy image; e, plasma cells on the BM smear slide (Wright staining, ×100 objective lens); and f, nuclear FISH using the dual-color, dual-fusion probe composed of red-labeled CCND1 and green-labeled IGH. Two fusion signals are indicated by yellow-colored arrowheads (top left).
Figure 4. Multicolor flow cytometry of plasma cells in the BM. The CD138$^+$ and CD38$^+$ cells were separated into CD19$^-$ (red color) and CD19$^+$ (blue color) fractions. The CD19$^+$ and CD138$^+$ cells were CD56$^{-/0}$, CD45RA$^-$, CD45RO$^-$, CD20$^-$, and CD28$, and expressed cytoplasmic $\kappa$ light chain, indicating clonal plasma cells.

Figure 5. Course of the serum FLC $\kappa/\lambda$ ratio, serum levels of IgG and IgA, and calculated levels of $\gamma$ globulin during the first year of treatment. The treatments consisting of CBd (cyclophosphamide 300 mg/m$^2$ PO, bortezomib 1.3 mg/m$^2$ SC, and dexamethasone 40 mg PO on days 1, 8, 15, and 22 for a 5-week treatment cycle), Bd (bortezomib 1.3 mg/m$^2$ SC and dexamethasone 40 mg PO on days 1, 8, 15, and 22 for a 5-week treatment cycle), and Ld (lenalidomide 15 mg PO on days 1 to 21 and dexamethasone 20 mg PO on days 1, 8, 15 for a 4-week treatment cycle) regimens are indicated at the top. Ld was considered ineffective.
sistent administration of bortezomib for >2 years, and laboratory data related to liver function improved, albeit marginally (Figure 6). The difference between involved FLC-κ and uninvolved FLC-λ (dFLC) became below the threshold of very good partial response (VGPR), i.e. <40 mg/L, and the level was maintained for >2 years (Figure 6). The cumulative bortezomib dose for 2 years was 72.6 mg/m². Significant complications of bortezomib were grade 2 diarrhea that occurred on the day of administration of the drug and grade 1 peripheral sensory neuropathy. Leukocytosis persisted during the course; there was no evidence indicative of myeloproliferative neoplasm.

**DISCUSSION**

We described here a female patient who presented with marked hepatomegaly with firm consistency. As the laboratory data demonstrated the pattern of polyclonal hypergammaglobulinemia and a low level of albumin, we initially considered liver cirrhosis. However, as we subsequently found amyloid deposits in multiple organs and clonal plasma cells in the BM, we correctly recognized that a plasma cell dyscrasia was underlying her condition. This report suggests that clinicians should consider hepatic involvement of AL amyloidosis in the differential diagnosis whenever a patient presents with unexplained hepatomegaly. Other characteristic features of this patient included spontaneous vertebral compression.

**Figure 6.** Response to bortezomib-based treatment for >2 years. Top pictures, coronal plane CT images of the abdomen, showing the reduction of liver size. Bottom table, parameters indicative of organ (hepatic) response and hematological response, in addition to laboratory data related to liver function. The response criteria: hepatic response in organ response, decrease in radiographic liver size by at least 2 cm; very good partial response in hematological response, dFLC <40 mg/L.
sion fractures and the presence of Howell-Jolly bodies in the blood; the former has been described to be an initial presentation of AL amyloidosis in preferential association with hepatic and BM involvement and κ light-chain, and the latter accounts for hyposplenism resulting from splenic involvement. On the other hand, 2% of cases in the Mayo clinic series (n = 474) had a >20 × 10^3/μL white cell count; however, it is unclear whether leukocytosis is related to AL amyloidosis. Finally, quantitation of serum FLCs should be utilized as an adjunctive diagnostic modality that may demonstrate clonality in patients with AL amyloidosis who do not have monoclonal proteins by immunofixation. It should be noted, however, that the uninvolved FLC-λ was not suppressed but elevated in the present case, presumably reflecting polyclonal gammopathy.

Polyclonal hypergammaglobulinemia or polyclonal increase of immunoglobulins is most often due to an infectious, inflammatory, or reactive process. In a retrospective cohort study (n = 148) from the Mayo clinic, liver disease, including autoimmune and viral etiologies, was the most common pathology associated with this condition, followed by connective tissue disorders, chronic infection, hematologic disorders, and non-hematologic malignancies. The cause of polyclonal hypergammaglobulinemia is yet to be elucidated, but it is thought to be the result of dysregulation of the immune system and chronic stimulation; IL-6, IL-10, several cytokines, and T cell dysfunction may have been implicated. In the present case, where the liver parenchyma was heavily infiltrated by amyloid deposits, it is possible that the hypergammaglobulinemia reflected a reactive or inflammatory process against amyloid deposits in the liver, and the rapid decrease of the γ globulin and immunoglobulin levels after the first cycle of chemotherapy was attributed to the anti-inflammatory effects of dexamethasone included in the chemotherapy regimen.

The outcome of patients with AL amyloidosis immediately depends on the spectrum and severity of organ involvement, especially on whether the heart is involved and to what extent. However, as the underlying abnormality in AL amyloidosis is clonal plasma cell proliferation, which is the source of the amyloidogenic light-chain deposition in the organs, long-term outcome depends on the plasma cell clone-related characteristics. Based on these considerations, the revised Mayo staging scheme includes two independent cardiac biomarkers (i.e. troponin T [TnT] and N-terminal pro-brain natriuretic protein [NT-ProBNP] or BNP) and a plasma cell clone-related parameter, dFLC, reproducibly stratifying the AL patients into four prognostic subgroups according to the presence or absence of these three risk factors. On the other hand, cytogenetic abnormalities have been reported to be associated with survival; in contrast to what has been observed in patients with multiple myeloma, t(11;14)(q13;q32)/CCND1-IGH is associated with adverse prognosis in patients with AL amyloidosis. Taken together, the current case, in which cardiac involvement was absent despite the modest increase of BNP, but the values of dFLC and FLC-κ were higher than each cut-off and the clonal plasma cells carried the t(11;14) (Table 1), was considered to be categorized into a high-risk group requiring rapid hematologic response.

The management of patients with AL amyloidosis, as well as the correct diagnosis of this complicated condition, requires multispecialty collaboration. The goal of treatment is to rapidly and maximally eliminate the production of the precursor protein (i.e. the clonal light chain) by targeting the underlying plasma cell clone. Bortezomib, which is the first proteasome inhibitor, in combination with dexamethasone and cyclophosphamide (designated as CyBorD) was first applied to patients with AL amyloidosis in two groups, demonstrating the hematological response rate of 94% and 81%, respectively. In a larger study, in which a total of 230 patients with newly diagnosed AL amyloidosis were enrolled, the overall hematological response rate was 60% and cardiac or renal response was observed in proportions of the patients. In the current case, we found
consistent reduction of the liver size over two years in association with persistent hematological response. Taken together with sporadic case reports, in which marked liver response was seen, it is suggested that plasma cell-targeting therapy can reduce the amyloid deposits from the involved organs, potentially reversing their dysfunction.

REFERENCES

Amyloidosis with marked hepatomegaly


27. 長町康弘，山内尚文，村松博士，他．自家末梢血幹細胞移植後にボルテゾミブとデキサメサゾンの併用療法で著明な肝腫大が改善した全身性 AL アミロイドーシスを伴った BJP 型多発性骨髄腫．臨床血液 2015;56:323-328.
顕著な肝腫大と多クローン性高γグロブリン血症で発症したALアミロイドーシスの1例

大野仁嗣1, 戸田有亮1, 鴨田吉正1, 岡部誠2, 本庄原3

1 天理よろづ相談所病院 血液内科
2 天理よろづ相談所病院 消化器内科
3 天理よろづ相談所病院 病理診断部

症例は65歳女性。顕著な肝腫大と多クローン性高γグロブリン血症のため紹介受診した。総蛋白8.9g/dL、アルブミン35.6%、グロブリン40.2%（35.8mg/mL）、アルカリフォスファターゼ730IU/L。CT上で計測した頭尾側方向の肝の長さは24.2cmであった。肝生検では、肝実質は好酸性の無構造の物質に置換され、それはコンゴールレッド染色陽性、偏光顕微鏡下でapple greenの複屈折を示し、アミロイド沈着であることが判明した。アミロイド沈着は胃粘膜と骨髄にも認められた。免疫固定法では血清・尿中にM成分を認めなかったが、血清遊離軽鎖（free light chain, FLC）はκ鎖に著しく偏倚していた（FLC-κ, 1,290mg/L; FLC-λ, 86mg/L）。骨髄ではクローン性の形質細胞を10.4%認めた。FISHでCCND1遺伝子と免疫グロブリン重鎖遺伝子の融合シグナルを認めた。ALアミロイドーシスと診断し、ボルテゾミブを含む化学療法を開始したところ速やかに血液学的効果を認め、very good partial responseの効果判定基準を満たした。肝腫大は2年以上にわたるボルテゾミブの投与によって徐々に縮小した。初診時の多クローン性高γグロブリン血症は、肝でのアミロイド沈着に対する反応性・炎症性過程を反映していたと考えられる。形質細胞を標的とした治療は臓器のアミロイド沈着を減少させ、低下した機能を回復させる可能性がある。

キーワード：ALアミロイドーシス、肝アミロイドーシス、血清遊離軽鎖、多クローン性高γグロブリン血症、ボルテゾミブを含む化学療法