CASE REPORT

Marked and Rapid Regression of Hepatic Amyloid Deposition in a Patient with Systemic Light Chain (AL) Amyloidosis after High-dose Melphalan Therapy with Stem Cell Transplantation

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Abstract

A 52-year-old woman with a high serum alkaline phosphatase (ALP) level underwent a liver biopsy, which showed diffuse heavy deposition of AK amyloid, and was diagnosed as having immunoglobulin light chain (AL) amyloidosis. Although she received high-dose melphalan with stem cell transplantation and achieved a hematologic complete response (CR), her ALP level began to increase one year after treatment. Further examinations revealed that she was still in a CR state with dominant bone-type ALP, and re-biopsied liver specimens demonstrated marked regression of amyloid deposition, providing important evidence that the turnover of hepatic amyloid proteins can actually occur more rapidly than previously thought.

Key words: plasma cell dyscrasia, light chain (AL) amyloidosis, hepatic amyloidosis, histological regression of amyloid, liver biopsy

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Introduction

Amyloidosis derived from immunoglobulin light chains (AL) is a hematological disorder (1), and the systemic form of this disease causes dysfunction of multiple vital organs, including the heart, kidneys and gastrointestinal tract (2). Abnormal plasma cells in bone marrow play a central role in the pathogenesis of systemic AL amyloidosis as a source of amyloidogenic monoclonal immunoglobulin (M-protein). Many intensive chemotherapy regimens, including high-dose melphalan with autologous peripheral blood stem cell transplantation (HDM/SCT) (3, 4), have been developed to halt the synthesis of amyloid precursor proteins, resulting in a significantly improved prognosis (5). It is widely accepted that organ functions, including cardiac, renal and hepatic biomarkers, can recover following successful treatment (6, 7). However, only two reports have demonstrated statistically significant post-treatment histopathological regression of deposited AL amyloid in gastroduodenal mucosa (8) or abdominal wall fat biopsy specimens (9), and repeated renal biopsies have failed to prove this finding (10). Hepatic involvement with hepatomegaly and liver dysfunction is a common manifestation of systemic AL amyloidosis (11); however, there has been only one case report of the histological regression of hepatic AL amyloid deposition after chemotherapy (12). We herein describe a case of systemic AL amyloidosis in which regression of hepatic amyloid deposition was histologically confirmed on sequential biopsies performed before and after treatment, with a more rapid regression of hepatic AL amyloid than that observed in previous reports.

Case Report

A 52-year-old woman with no significant past or family history was found to have a high serum alkaline phosphatase (ALP) level (571 IU/L, normal <330) on an annual

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health screening examination. Since the serum ALP level exhibited gradual elevation (to over 700 IU/L), she underwent a liver biopsy at 54 years of age and was diagnosed as having hepatic amyloidosis. She was then referred to our department for a further examination and treatment. She lacked any symptoms, with the exception of mild discomfort in the upper abdomen. In addition, an enlarged liver was palpable for three fingerbreadths in the right hypochondriac region. Laboratory data revealed an elevated ALP level (785 IU/L) with normal aspartate aminotransferase [(AST) (21 IU/L)] and alanine aminotransferase [(ALT) (16 IU/L)] levels. Meanwhile, the serum level of brain natriuretic peptide (BNP), a cardiac biomarker, was slightly increased (30 pg/mL, normal <20), although an echocardiogram demonstrated a well-preserved cardiac function (intraventricular septum: 0.78 cm, normal <1.2, ejection fraction: 66.79%, normal >50). Urinary protein was undetectable, and the patient’s renal function was normal (Cr: 0.52 mg/dL, normal <0.8, 24Ccr: 128.1 L/day, normal >82). Both serum and urine immunofixation were negative for M-protein; however, the level of serum κ free light chain (FLC) was significantly elevated (κFLC: 196.0 mg/L, normal <18.92, λFLC: 22.20 mg/L, normal <26.18). Liver biopsy specimens obtained at the former hospital showed diffuse heavy deposition of amyloid on Congo red staining (Fig. 1A); this amyloid was specifically immunolabeled with an anti-κ antibody (Fig. 1C). The same type of amyloid deposition was also confirmed in the biopsied gastroduodenal mucosa. Although an aspiration biopsy of the bone marrow was unremarkable, with a normal amount of plasma cells (1.0%, normal <5), a flow cytometric analysis detected a monoclonal plasma cell population, indicating that the patient had underlying plasma cell dyscrasia. An X-ray survey of the bones revealed no abnormal lesions suggestive of multiple myeloma. CT disclosed remarkable hepatomegaly, with an enlarged total liver span of 15.9 cm (Fig. 2A, B). The patient was finally diagnosed as having systemic AL amyloidosis manifesting as dominant hepatic amyloidosis and was treated with HDM/SCT (melphalan: 140 mg/m^2) according to our criteria (13), after which a hematologic complete response (CR) was achieved. Although she was then followed in the outpatient clinic with an improved ALP level (around 500 IU/L) for one year, the ALP level subsequently began to increase to over 800 IU/L. At 14 months after HDM/SCT, she was reexamined on suspicion of relapse of hepatic amyloidosis. In fact, CT showed diminished hepatomegaly with a decreased total liver span of 13.7 cm (Fig. 2C, D), while a transvenous liver biopsy revealed marked regression of amyloid deposition (Fig. 3). Both serum and urine immunofixation remained negative for M-protein, and the serum FLC level was found to be within the normal range (κFLC: 15.80 mg/L, normal <18.92, λFLC: 20.70 mg/L, normal <26.18). The patient was there-
Figure 2. CT images of the liver. A and B: CT images of the liver before treatment; marked hepatomegaly is seen on both coronal (A) and horizontal (B) sections. C and D: CT images of the liver obtained 14 months after treatment; diminished hepatomegaly is apparent on both coronal (C) and horizontal (D) sections. B and D are slices obtained at exactly the same level depending on the same vertebral body; however, the left kidney is detectable only after treatment (D). The left kidney was undetectable before treatment (B) due to the enlarged liver pushing the kidney downward.

Discussion

The liver is an organ commonly targeted by AL amyloid deposition, and liver failure is an important cause of death in patients with this disease (14). Additionally, marked hepatomegaly with severe AL amyloid deposition occasionally induces rupture (15), resulting in a fatal outcome (16). Therefore, hepatic involvement appears to be critical in estimating the prognosis of patients with systemic AL amyloidosis. In our patient, a significant decrease in liver size was observed on CT one year after radical treatment, which was histopathologically confirmed to be ascribable to the marked and rapid regression of hepatic AL amyloid deposition.

Conducting an exact assessment of hematological and organ responses is crucial to evaluate the treatment response, as any evidence suggestive of disease progression requires the administration of additional chemotherapy (17) to prevent subsequent fatal organ failure. These assessments are usually obtained from blood and urine tests (such as immunofixation tests and measurements of the BNP, FLC and ALP levels, etc.) (18) and imaging examinations, including echography and CT (6). It is possible to more easily estimate the presence of a hematologic CR if monoclonal protein is detectable before treatment (6), although the im-
that dynamic turnover of constituent proteins does occur in these lesions and that amyloid deposits can regress if the supply of amyloid precursor is halted by treatment (22). In patients with familial amyloid polyneuropathy and AA amyloidosis, clear regression of tissue amyloid deposition after treatment is seen in the abdominal fat pad (23) or gastroduodenal mucosa (24, 25), and similar findings have been reported in AL amyloidosis patients (8, 9). With regard to hepatic amyloidosis, however, regression has only been demonstrated radiographically (26, 27), not histopathologically, except for one case in which histological regression was observed 5.5 years after treatment (12). In previous reports, it also took two to four years to confirm the apparent histological regression of AL amyloid in other organs (8, 9).

In conclusion, our case is the second case to provide important evidence that hepatic amyloid deposition can actually regress histologically, as observed in other organs, and shows that this phenomenon can occur more rapidly and dynamically than previously thought, in only one year. The molecular mechanism underlying the post-treatment regression of AL amyloid in the liver remains unclear, and further studies are required.

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

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References


