

Received: 2021.05.21
Accepted: 2021.07.03
Available online: 2021.07.13
Published: 2021.08.23

Hepatic AL Amyloidosis without Significant Light Chain Elevation in a Patient Treated with CyBorD Plus Daratumumab

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 60-year-old
Final Diagnosis: Amyloid light-chain amyloidosis • hepatic amyloidosis
Symptoms: Abdominal pain • anemia • emesis
Medication: —
Clinical Procedure: Bone marrow biopsy • exploratory laparotomy • hepatectomy • stem cell transplant
Specialty: Hematology • Oncology

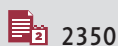
Objective: Unusual clinical course
Background: Immunoglobulin light chain (AL) amyloidosis is a plasma cell disorder in which excess light chain deposits in tissues, resulting in organ dysfunction and damage. Typically, AL amyloidosis presents as a systemic disease affecting multiple organs, and most patients have elevated serum free light chains. However, the presentation of AL amyloidosis is highly variable. The purpose of this case report is to raise awareness of the atypical presentations of AL amyloidosis in order to facilitate more rapid diagnosis, which has the potential to prevent additional organ damage when appropriate therapy is provided.

Case Report: We describe a case of AL amyloidosis with amyloid deposition confined to the liver and bone marrow and lack of significant serum light chain elevation. The patient initially presented with a spontaneous hepatic hematoma, and was ultimately found to have hepatic AL amyloidosis, with monoclonal plasma cells in the bone marrow and monoclonal protein on serum protein electrophoresis. Our patient responded to treatment with cyclophosphamide-bortezomib-dexamethasone, the anti-CD38 antibody daratumumab, and autologous stem cell transplant, resulting in hematological and organ response.

Conclusions: AL amyloidosis can present with end-organ damage confined to isolated organs, and it can present without the expected elevation in serum light chains. Such patients can benefit from appropriate treatment, including traditional chemotherapy, daratumumab, and stem cell transplant. As effective treatments for AL amyloidosis are now available, prompt diagnosis has the potential to limit end-organ damage and potentially improve patient outcomes.

Keywords: Daratumumab • Immunoglobulin Light-chain Amyloidosis • Paraproteinemias

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/933241>



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Background

Immunoglobulin light chain (AL) amyloidosis is a hematological disorder in which a clonal population of plasma cells produces excess monoclonal light chain [1]. The excess light chain, which may be of lambda (λ) or kappa (κ) type, misforms into a β -pleated sheet and deposits into tissues, resulting in organ dysfunction [1]. Consequently, diagnostic criteria for AL amyloidosis require the presence of organ dysfunction secondary to amyloid deposition as identified by Congo Red staining, which detects the β -pleated sheet conformation, as well as demonstration by mass spectrometry or immunoelectromicroscopy that the amyloid is derived from light chains [2]. A monoclonal plasma cell proliferative disorder must also be present as evidenced by serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow [2].

AL amyloidosis is a systemic disease that typically affects multiple organ systems, and typical presentations include renal impairment with nephrotic range proteinuria, diastolic heart failure with septal wall thickening, hepatomegaly with elevated alkaline phosphatase, and neuropathy [1,3]. Herein, we present an unusual case of AL amyloidosis in which end-organ damage was limited to the liver and bone marrow. The patient also lacked significant light chain elevation and responded to treatment with the anti-CD38 antibody daratumumab.

Case Report

A 60-year-old woman presented with spontaneous hepatic hematoma complicated by hemoperitoneum. The patient described waking up in the morning with acute onset, severe epigastric abdominal pain and non-bloody, non-bilious emesis. A few months prior, she had presented with a hepatic hematoma that failed initial conservative management and was treated by embolization. Neither hepatic hematoma was preceded

by trauma. Additional past medical history was noncontributory, and the patient had no history of cirrhosis, alcohol use disorder, or family history of bleeding or thrombosis. Imaging showed a large perihepatic hematoma of the lateral left hepatic lobe measuring 11.9×9 cm, with mass effect to the underlying hepatic parenchyma. The patient decompensated and developed severe abdominal distension with an acute drop in hemoglobin that did not respond to transfusion. The patient was taken to surgery for open left hepatectomy and exploratory laparotomy. Surgery encountered massive hemoperitoneum and extensive clot burden when entering the abdomen, and bleeding from the left hepatic vein was noted. Removal of hepatic segments 2 and 3 (corresponding to approximately half of the left lobe), the caudate lobe, and the gallbladder was required to control the bleeding, and bleeding from the hepatic vein itself was controlled surgically by oversewing. The liver was biopsied and stained positive with Congo Red (Figure 1A, 1B), consistent with a diagnosis of hepatic amyloidosis. The remainder of the hospital course was uncomplicated, and the patient's hepatic function improved gradually during the hospitalization, rendering transplantation unnecessary and permitting safe discharge.

Workup for systemic amyloidosis was initiated. Liquid chromatography tandem mass spectrometry of the hepatic biopsy demonstrated a peptide profile consistent with AL (lambda)-type amyloid deposition. Intriguingly, the patient lacked significant light chain elevation at diagnosis. Serum free light chains showed kappa light chains of 12.11 (3.30-19.40 mg/L) and lambda light chains of 15.81 (5.70-26.30 mg/L), with a normal kappa/lambda ratio of 0.77 (0.26-1.65) (Table 1). Serum protein electrophoresis demonstrated a monoclonal protein of 0.63 g/dL, which was characterized as IgG lambda by immunofixation. Bone marrow biopsy showed a hypocellular marrow (5%) with tri-lineage hypoplasia and diffuse staining for Congo Red within the interstitium and vascular walls, indicating amyloid deposition in the marrow. In addition, bone marrow biopsy was significant for lambda-restricted plasma cells

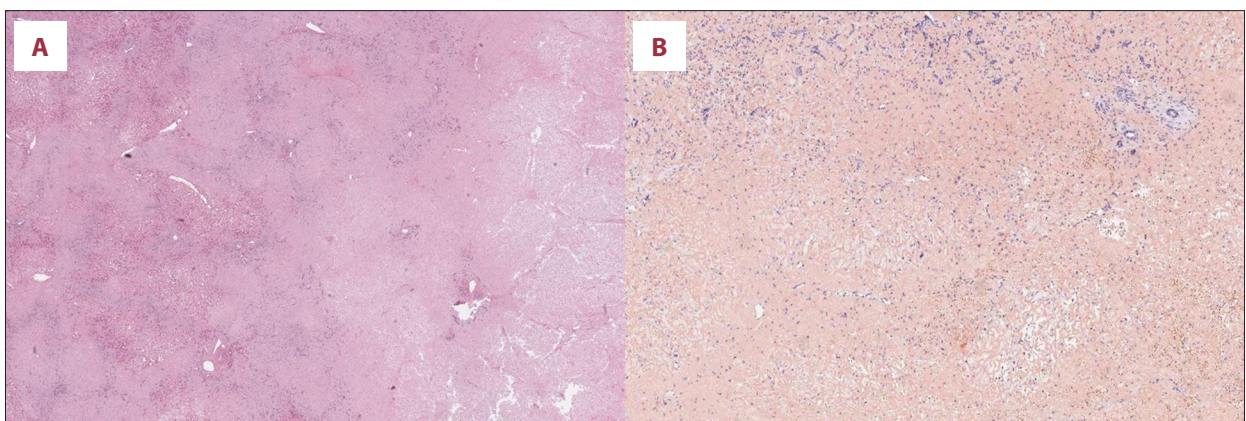


Figure 1. Liver biopsy stained positive for Congo Red, consistent with hepatic amyloidosis. (A) H&E stain (B) Congo Red stain.

Table 1. Results obtained during admission confirming diagnosis of AL amyloidosis with amyloid deposition in the liver and bone marrow. All results were obtained prior to the initiation of treatment. Normal values, when applicable, are provided in the left-hand column.

Evidence of amyloid deposition	
Bone marrow biopsy	The marrow is mostly replaced by pink, amorphous proteinaceous material, consistent with amyloid. The Congo Red stain is positive for amyloid deposition in the interstitial areas as well as in vascular walls.
Liver biopsy	Preliminary pathology obtained intra-operatively: The liver shows marked amyloid deposition within sinusoidal spaces, highlighted on Congo Red and trichrome stains. This is associated with extensive loss of hepatic parenchyma. Mass spectrometry: Liquid chromatography tandem mass spectrometry (LC MS/MS) was performed on peptides extracted from Congo Red-positive, micro-dissected areas of the paraffin-embedded specimen. LC MS/MS detected a peptide profile consistent with AL (lambda)-type amyloid deposition.
Evidence of organ dysfunction	
Alkaline phosphatase (U/L) Normal: 38-126	309 day of admission, 357 day of discharge, maximum during admission 379
Bilirubin (total) (mg/dL) Normal: 0.3-1.2	0.9 day of admission, 11 day of discharge, maximum during admission 17.3
Bone marrow biopsy	Hypocellular marrow (5%) with tri-lineage hypoplasia
Platelets (K/mcL) Normal: 153-367	Platelets: 294 day of admission, 522 day of discharge, minimum during admission 20
PT (seconds) Normal: 12.1-15.0	PT: 15.6 day of admission, 15.6 day of discharge, maximum during admission 18.8
Transaminases (U/L) Normal AST: 14-36 Normal ALT: 0-34	AST: 75 day of admission, 131 day of discharge, maximum during admission 1441 ALT: 42 day of admission, 64 day of discharge, maximum during admission 903
Evidence of plasma cell proliferative disorder	
Bone marrow biopsy	Based on CD138 and CD38, flow cytometric studies show a population of plasma cells (2% of the leukocytes in the flow cytometry preparation) which are lambda-restricted. CD138 immunohistochemistry was difficult to interpret due to diffuse staining within the amyloid deposits. In-situ hybridization studies for Kappa and Lambda light chains reveal that the plasma cells are lambda light chain-restricted (kappa: lambda ratio of 1: 4). MUM-1 stain: Plasma cells account for approximately 5% of the cellularity.
Bone marrow biopsy cytogenetics	Three copies of 1q21 (17%), 3 copies of intact MYC (33%), and 3 copies of IGH with one copy missing the 5'-IGH (46%). A hyperdiploid subclone showing the same abnormalities was noted in a small number of cells. There was no evidence of loss of 13q or TP53, and no FGFR3-IGH or CCND1-IGH rearrangement in this specimen.
Free light chains (mg/L) Normal kappa: 3.30-19.40 Normal lambda: 5.70-26.30 Normal kappa/lambda ratio: 0.26-1.65	Kappa/lambda: 12.11/15.81, Ratio=0.77
Serum protein electrophoresis, monoclonal protein (g/dL) Normal: 0	0.63
Urine protein electrophoresis Normal: 0	+ for monoclonal free Lambda light chains

Table 2. Markers of hematological response. Light chains were never significantly elevated, and as the difference between involved (lambda) and uninvolved (kappa) light chains was never greater than 40 mg/L, hematological response could not be assessed by tracking light chains. Our patient always had a normal kappa/lambda ratio. Therefore, we assessed the hematological response by trending serum monoclonal protein, which declined with CyBorD, the addition of DARA, and then reached a nadir after stem cell transplant.

	SPEP-IgG lambda monoclonal protein (g/dL)	Serum free light chains (mg/L): kappa/lambda	Kappa/lambda ratio	Difference between involved (lambda) and uninvolved (kappa) serum free light chains (mg/L) (dFLC)
After liver biopsy showing amyloid, 10 days into admission	0.63	12.11/15.81	0.77	3.7
While receiving cycle 1 of CyBorD, 1 month post discharge	0.99	16.94/18.13	0.93	1.19
Status post CyBorD cycle 2	0.63	14.84/16.29	0.91	1.45
Status post CyBorD cycle 3	0.47	19.17/15.32	1.25	-3.85
Status post CyBorD cycle 4+DARA cycle 1	0.31	10.20/9.88	1.03	-0.32
Status post CyBorD cycle 5+DARA cycle 2	0.38	9.29/13.44	0.69	4.15
Status post CyBorD cycle 7+DARA cycle 4	0.27	7.85/11.29	0.70	3.44
Status post CyBorD cycle 8+DARA cycle 5	0.29	9.34/10.94	0.85	1.60
Induction stopped before ASCT	0.37	9.91/12.35	0.80	2.44
Status post ASCT	0.18	16.76/17.96	0.93	1.20

CyBorD – cyclophosphamide-bortezomib-dexamethasone; DARA – daratumumab; ASCT – autologous stem cell transplant.

(kappa: lambda ratio of 1: 4), with plasma cells comprising 5% of cellularity (MUM-1 stain). IgG was 1418 (700-1600 mg/dL), IgM was 25 (40-230 mg/dL), and IgA was 84 (70-400 mg/dL). All supporting diagnostic results are shown in **Table 1**. PET/CT whole-body imaging showed no evidence of plasmacytomas or lytic lesions.

We next focused on amyloidosis staging. A transthoracic echocardiogram demonstrated normal septal wall thickness and ventricular function (left ventricular ejection fraction 70%), NT-proBNP was 805 pg/mL (normal for age <900 pg/ml), and Troponin I was not elevated, ruling out cardiac amyloidosis. Endoscopic biopsy and Congo Red staining showed no evidence of amyloid deposition in the GI tract. There was no decrease in GFR or evidence of nephrotic syndrome. A physical exam showed no neurological findings, macroglossia, or pseudohypertrophy. Consequently, there was no evidence of amyloidosis affecting organs other than the liver and bone marrow in our patient.

On initial presentation, before the patient decompensated, hepatic biomarkers were mildly elevated: AST was 75 (14-36 U/L), ALT was 42 (0-34 U/L), alkaline phosphatase was 309 (38-126 U/L), and total bilirubin was 0.9 (0.3-1.2 mg/dL). Transaminases and total bilirubin rose markedly during our patient's admission, reflecting the hepatic hematoma, but gradually declined once bleeding had been controlled (**Table 1**). Prothrombin time (PT) and INR were mildly elevated on admission, with a PT of 15.6 (12.1-15 seconds) and INR of 1.2. PT and INR rose when the patient decompensated (maximum 18.3 and 1.5, respectively) but subsequently returned to normal ranges by discharge. PTT was 34 (25-38 seconds) on admission and was never elevated. Factor X activity was also normal (95%, normal 81-157%).

Our patient was discharged medically stable, and treatment of AL amyloidosis was initiated. In AL amyloidosis, the efficacy of treatment is assessed by hematological response and organ response, both of which correlate with overall survival [4,5]. Hematological response is measured by trending the

difference between the involved and uninvolved free light chain (dFLC), although negative serum and urine immunofixation for monoclonal protein is also required for a complete hematological response [4]. Our patient lacked significant light chain elevation, and at diagnosis the dFLC was already less than 40 mg/L (Table 2), which is the requirement to achieve a very good partial hematological response [4]. Therefore, we trended serum monoclonal protein as a marker of hematological response, in hopes of achieving the negative immunofixation required for a complete response [4]. Organ response, which is not currently graded and is classified only as present or absent, is determined by monitoring a marker of organ dysfunction that is specific to the organ known to be affected by amyloid disease [4]. For patients with hepatic AL amyloidosis, organ response is defined as a 50% decrease in an elevated alkaline phosphatase value or a decrease in liver size, measured radiographically, by at least 2 cm [4].

Our patient received 3 cycles of Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD), resulting in a decline of serum monoclonal protein from a maximum of 0.99 g/dL to 0.47 g/L (Table 2) and a significant reduction in alkaline phosphatase from 923 to 327 (Figure 2). Although the decline in alkaline phosphatase achieved the >50% reduction needed for organ response, the patient had a persistent M spike and alkaline phosphatase was still elevated. Therefore, the anti-CD38 antibody daratumumab (DARA) was added to deepen the response. Our patient ultimately received a total of 8 cycles of CyBorD, 5 of which included DARA. After these 8 cycles, alkaline phosphatase declined to a nadir of 220 (Figure 2) and serum monoclonal protein declined to 0.29 g/dL (Table 2), indicating deepening of both hematological and organ response. The patient then underwent melphalan-based consolidation therapy with stem cell rescue, resulting in a further decrease of serum monoclonal protein to 0.18 g/dL and stable alkaline phosphatase (Table 2 and Figure 2, respectively). She is currently planned to undergo re-staging on post-transplant day 100, at which time maintenance treatment with lenalidomide will be considered.

Discussion

We report a case of AL amyloidosis with amyloid deposition confined to the liver and bone marrow, without significant light chain elevation, that responded to treatment with CyBorD plus daratumumab. Isolated hepatic involvement and lack of light chain elevation are both rare in AL amyloidosis. Approximately 10-20% of AL amyloidosis patients do not have significant serum free light chain production or an abnormal kappa/lambda chain ratio [6-8]. Likewise, our patient never had significant light chain secretion, and the difference between involved and uninvolved free light chains (dFLC) in our patient

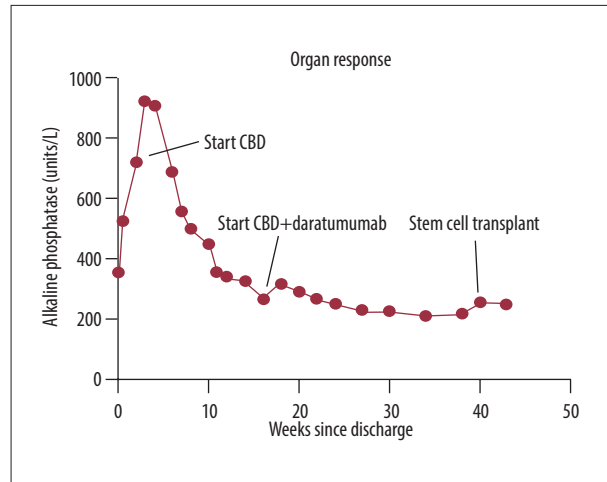


Figure 2. Alkaline phosphatase down-trended with initiation of CyBorD (cyclophosphamide-bortezomib-dexamethasone) and then decreased further after daratumumab was added, reflecting organ response. Alkaline phosphatase remained stable after autologous stem cell transplant.

was consistently less than 40 mg/L (Table 2). Intriguingly, a dFLC of less than 50 mg/L is independently associated with improved survival, as well as a higher rate of complete hematological response [9]. The ideal method to monitor hematological response in patients with AL amyloidosis who have low light chain levels remains unclear. A “low dFLC partial response” has been defined as a decrease of dFLC to less than 10 in patients who present with a dFLC of 20-50 [9], and a low dFLC partial response correlates with overall survival [9]. However, as our patient consistently had a dFLC of less than 10, she could not be assessed for a low dFLC partial response. In the absence of guidelines, we opted to monitor hematological response by serum monoclonal protein.

In a large case series of 98 patients with hepatic AL amyloidosis, 33% of patients also presented with nephrotic syndrome, 12% also presented with congestive heart failure, and 11% also presented with peripheral neuropathy or carpal tunnel syndrome [10], suggesting that most patients with hepatic AL amyloidosis present with involvement of additional organ systems.

The diagnosis of hepatic AL amyloidosis, particularly hepatic amyloidosis without additional systemic findings, is challenging, with one study reporting that clinicians only considered the diagnosis of amyloid, before liver biopsy, in 26% of cases [10]. Among patients with hepatic amyloidosis, hepatomegaly and elevated alkaline phosphatase are the most common findings [10], but these are nonspecific, illustrating the difficulty of differentiating hepatic amyloidosis from more common etiologies of liver disease. Furthermore, a large retrospective study of 673 AL amyloidosis patients who were ultimately

diagnosed by tissue biopsy showed that serum and urine immunofixation each only identified 78% of patients with disease [11]. Serum free light chains were also only abnormal in 77% of patients [11]. This suggests that when amyloidosis is suspected, a thorough laboratory investigation is required to rule out disease, and clinicians should not hesitate to perform bone marrow and tissue biopsy if clinical suspicion is high. Given that effective therapy for AL amyloidosis is available, delays in diagnosis represent a missed therapeutic opportunity to minimize end-organ damage and improve outcomes.

Treatment of AL amyloidosis consists of initial induction therapy with plasma cell targeting agents, after which myeloablative chemotherapy with stem cell rescue may be pursued [1]. Induction with CyBorD was selected for our patient due to the regimen's high response rate, as clinical trials have shown initial hematological response rates as high as 94% [12]. Three cycles of CyBorD alone achieved the 50% reduction in alkaline phosphatase necessary for organ response (Figure 2) but did not result in the negative immunofixation necessary for complete hematological response [4]. Although organ response has been traditionally classified as either present or absent [4], the depth of organ response is associated with survival, and new graded organ response criteria are being considered [5]. Our patient therefore had the potential to deepen both hematological and organ response with additional therapy.

Daratumumab, an anti-CD38 antibody, can induce hematological response and organ response in heavily pre-treated AL amyloidosis patients [13, 14]. Furthermore, the published "safety run-in" results from the ANDROMEDA study reported that the combination of CyBorD with daratumumab, in patients with newly diagnosed AL amyloidosis, produced a hematological response rate of 96%, a 36% complete hematological response rate, and an organ response rate of 64% [15]. Based on this evidence, we added daratumumab to CyBorD, and our patient received an additional 5 cycles of CyBorD+daratumumab (for a total of 8 treatment cycles). After induction with this regimen, alkaline phosphatase declined to a nadir of 220 U/L (Figure 2) and serum monoclonal protein declined to 0.29 g/dL (Table 2). By the graded organ response criteria, this decline in alkaline phosphatase constitutes a very good partial organ response (>60% reduction from baseline AP level to a nadir above $\times 2$ lower limit of normal, with 2 times the lower limit of normal in our laboratory being equal to 76 U/L), suggesting that our patient benefited from the addition of daratumumab [5].

The benefits of autologous stem cell transplant in AL amyloidosis patients who have been treated with CyBorD and daratumumab remain poorly described. In the published safety and preliminary efficacy results from the ANDROMEDA study, 9 patients treated with CyBorD and daratumumab went on to receive stem cell transplant [15]. Among these patients, only 4

deepened their hematological response [15]. Our patient went on to receive melphalan-based consolidation therapy with stem cell rescue, which she tolerated well. Post-transplant serum monoclonal protein declined to 0.18 g/dL (Table 2) and alkaline phosphatase remained stable (Figure 2), suggesting a transplant-deepened hematological response. A related question is whether our patient will benefit from maintenance therapy after she reaches transplant day 100. The optimal timing of AL amyloidosis treatment remains unclear, with some advocating delaying treatment until the patient experiences organ progression or symptomatic relapse [16]. Moreover, a recent retrospective study suggests that lenalidomide or bortezomib maintenance post-transplant did not significantly improve overall survival or progression-free survival [17]. Ultimately, whether our patient pursues maintenance therapy will be informed by clinical judgement and shared decision making.

Conclusions

We describe a case of AL amyloidosis confined to the liver and bone marrow. This patient also lacked the light chain elevation that is considered a traditional hallmark of disease. Our patient responded to an induction regimen containing chemotherapy and daratumumab, highlighting the effective treatment options for AL amyloidosis. Awareness that AL amyloidosis can have atypical presentations, including dysfunction in a single organ without certain expected laboratory findings, will help facilitate earlier diagnosis to optimize the efficacy of therapy.

Acknowledgements

We sincerely thank the patient, who agreed to be described in this case report. We thank the Department of Pathology at University of Maryland Medical Center, specifically Leyla Canbeldek, MD and Janina Markidan, MD for their help in obtaining the images shown in Figure 1.

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Conflicts of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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