

# A Rare Presentation of Multiple Myeloma: A Case Report of Hepatic Amyloidosis

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Received: 29 July 2018  
Revised: 11 September 2018  
Accepted: 07 October 2018

## What's Known

- Primary amyloidosis can occur in patients with plasma cell dyscrasias, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), and also in lymphoplasmacytic cells disorder, such as Waldenström's macroglobulinemia.

## What's New

- We described a rare presentation of multiple myeloma (MM) patients with primal presentation of fulminant hepatic failure and biliary system involvement due to primary amyloidosis. Liver involvement due to light chain amyloidosis can be the first drastic presentation of MM. More attention must be paid to the diagnosis of these patients.

## Abstract

The clinically reported case of liver involvement with multiple myeloma (MM) is rare. Amyloidosis, defined as a tissue deposition of clonal light-chain fibrils, has been reported in 10-15% of the MM patients. We described a rare MM patient with the primal presentation of fulminant hepatic failure and biliary system involvement due to amyloidosis. Our patient had the primal symptoms of hyperbilirubinemia, ascites, hepatosplenomegaly, and anemia. Chemotherapy with a standard regimen containing bortezomib, thalidomide, and dexamethasone was implemented and led to a dramatic response. Liver involvement due to light chain amyloidosis can be the first drastic presentation of MM. It is important to consider infiltrative disorders, like MM and amyloidosis, when patients present non-specific symptoms and impaired liver function tests. Proper and timely diagnosis can directly affect the prognosis of patients. The optimal approach in the standard management of similar cases is still a matter of debate.

Please cite this article as: Sadeghi AR, Nejati M, Moghaddas A. A Rare Presentation of Multiple Myeloma: A Case Report of Hepatic Amyloidosis. *Iran J Med Sci.* 2019;44(4):342-346. doi: 10.30476/IJMS.2019.44953.

**Keywords** • Liver failure • Multiple myeloma • Amyloidosis • Hyperbilirubinemia

## Introduction

Multiple myeloma (MM) is described as a malignant proliferation of plasma cells which produce monoclonal immunoglobulin.<sup>1, 2</sup> Pathologic liver involvement has been reported in up to 45% of patients with MM.<sup>3, 4</sup> However, massive plasma cell infiltration of liver and concomitant liver failure is rare.<sup>5</sup> Amyloidosis is defined as a tissue deposition of clonal light-chain fibrils and has been diagnosed in up to 10-15% of MM patients.<sup>5-7</sup> Rarely have some reports of MM patients with main clinical presentation of liver amyloidosis infiltration been released.<sup>8-10</sup>

Relatively, most of the reported unusual manifestation of MM has been in autopsied series; since far, the data around diagnosis, clinical feature, treatment, and prognosis of patients are still unknown.<sup>11</sup> Herein, we described a rare case of MM patient, with a primal presentation of liver and biliary system involvement due to amyloidosis, who responded dramatically to standard chemotherapy.

## Case Presentation

In August 2016, a 52-year-old man with unremarkable medical history admitted to the emergency department of Omid

Hospital, a tertiary hospital in Isfahan, Iran, complaining of a 3-week malaise and weakness. Physical examination revealed a sign of bruising in posterior of left flank and thigh with unrecognizable asymmetric edema in the left leg. He denied any history of trauma or especial medication consumption.

For further evaluation, venous-arterial color Doppler sonography of distal extremity was ordered and the result ruled out deep vein thrombosis. Kidneys, bladder, and ureters were normal in ultrasonography exploration but there was a mild hepatosplenomegaly (liver diameter: 20 cm, spleen diameter: 175×55 mm).

Moreover, soft tissue ultrasonography confirmed the evidence of subcutaneous-intramuscular hematoma in posterior of proximal left thigh with 80×30×40 mm size and 3 cm depth. The MRI of pelvis without contrast also revealed a large sub-acute hematoma in the left gluteal and adductor muscles.

At the first evaluation, there were abnormal laboratory findings with regard to the liver function parameters and hematologic indices as shown in table 1. Other data could be ignored.

After obtaining an exact history, there were no identified potential risk factors for liver disease in the patient. The changes in the laboratory tests were in favor of hepatic cholestasis. For further investigation, the gastroenterologist asked for magnetic resonance cholangiopancreatography (MRCP) in order to rule out any obstruction, stricture or malignancy. MRCP results excluded any special abnormality in biliary drainage.

Consequently, tests such as antimitochondrial antibody (AMA), antinuclear antibody (ANA), acute viral hepatitis (hepatitis A,B,C), Human Immunodeficiency Virus (HIV) antibody, 2-mercaptoethanol (ME), Wright, direct and indirect Coombs, anti-leishmania antibody, anti-cytomegalovirus (CMV) antibody, and Epstein-Bar virus (EBV) were carried out and the results of all were negative. In endoscopy results,

there were multiple clean base ulcers in the duodenum, one healed ulcer in antrum, and no esophageal varices.

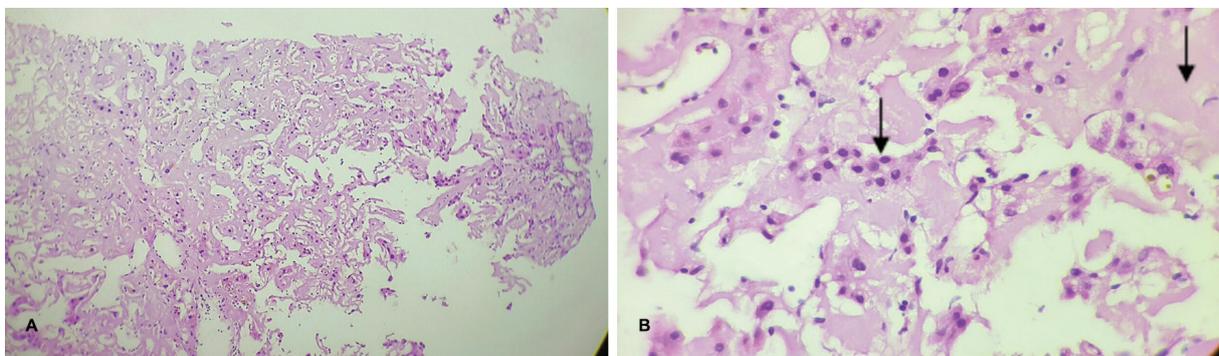
To find out the main complication, liver biopsy was performed in the patient and stained by hemotoxylin and Eosin. As it is shown in figure 1, liver biopsy revealed the deposition of amyloid protein, and amyloidosis diagnosis was confirmed.

Reverse transcription polymerase chain reaction (RT-PCR) for the detection of BCR-ABL P210-P190 fusion gene was also performed and the result was negative. Serum protein electrophoresis revealed the results as follows: Albumin 48.1 %, alpha1 globulin 7.1%, alpha 2 globulin 7.2%, beta globulin 19.3%, gamma globulin 18.3% with total 7.1 g/dL, and albumin globulin ratio of 0.93.

The clinical condition of the patients was progressive; liver enzymes showed an increasing trend. The total and direct bilirubin were 25 mg/dl and 20 mg/dl, respectively. In the last examination conducted by the gastroenterologist, the patient had encountered deteriorative clinical features due to hepatic amyloidosis and non-obstructive cholestasis. He again referred to the oncologist for the progressive symptoms of anemia, severe

**Table 1:** The primal laboratory evaluation of patients

| Laboratory indices                   | Laboratory data (Unit) |
|--------------------------------------|------------------------|
| White blood cell (WBC)               | 28000 cell/micL        |
| Hemoglobin (Hg)                      | 9.3 g/dl               |
| Platelet (Plt)                       | 385000 cell/micL       |
| Aspartate transaminase (AST)         | 50 IU/L                |
| Alanine transaminase (ALT)           | 22IU/L                 |
| Alkaline phosphatase (ALP)           | 1503 IU/L              |
| Gamma-glutamyltransferase (GGT):     | 1563 IU/L              |
| Bilirubin total                      | 5.5 mg/dL              |
| Bilirubin direct                     | 3.2 mg/dL              |
| Partial thromboplastin time (PTT)    | 32 second              |
| International normalized ratio (INR) | 1.7                    |
| Ferritin                             | 597ng/mL               |



**Figure 1:** Deposition of amyloid protein is depicted by Haemotoxylin and Eosin staining through liver biopsy. The hepatocyte plates are atrophied (left arrow), and there is massive deposition of amyloid (right arrow) along the sinusoids in the space of Disse (original magnification 100× (A) and 400× (B)).

ascites, and severe lower extremity edema.

After that, the oncologist performed two diagnosis approaches including paracentesis of ascites and bone marrow aspirate and biopsy (BMA/BMB). The result of paracentesis was transudative fluid without any malignant cells. The other finding showed more than 50% of infiltrated plasma cells and monoclonality in bone marrow biopsy. Immunophenotyping on BMB specimen revealed a population in the monocytic gate which expressed CD38, CD138, CD56, and CD45 (myeloma cells) about 6% of all nucleated cells while it was negative for CD19 marker.

Serum protein electrophoresis's results such as total protein 5.4, albumin to globulin ratio 0.69, Albumin 40.8%, Alpha 7.4%, Alpha 2 10.3%, Beta 19.2% and Gamma 22.3% was also concordant with bone marrow plasmacytoma. Kappa monoclonal light chain bands were seen in serum and urine immunofixation test. Furthermore, the diagnosis of MM was confirmed. However, the patient had no sign of bone pain or lesion, hypercalcemia or elevated creatinine.

The liver biopsy specimen was sent for immunohistochemistry evaluation and kappa light chain amyloidosis was confirmed as well. Due to the critical condition of the patient, the oncologist decided to initiate promptly standard chemotherapy regimen for treatment of high risk MM.

Chemotherapy regimen, including bortezomib (Velcade® Takeda Pharmaceutical Company), thalidomide (Thalomid®, Celgene Corporation), and dexamethasone, was commenced for the patient. Dosing schedule for bortezomib was intravenous administration of 1 mg/m<sup>2</sup> on day 1, 4, 8, and 11, followed by a rest period of up to 20 days. This schedule was administrated for 8 cycles. Thalidomide was ordered by a dose of 100 mg daily for 8 (21-day) cycles and dexamethasone by induction dose of 40 mg once daily on day 1 to 4, 9-12, and 17-20 in combination with bortezomib. This was then changed to 40 mg once weekly on day 1, 8, 15, and 22 every 28 days.

After two months, the patient responded to the treatment and all hepatic symptoms such as icterus (total and direct bilirubin 0.9 and 0.2 mg/dl, respectively) and ascites disappeared. The measurement of monoclonal (M) protein in serum and urine showed an acceptable range with gamma globulin 1.6 g/dL, total protein 6.2 g/dL, and albumin to globulin ratio of 0.78. The free light chain in serum and urine reduced to an undetectable range by immunofixation assay. Accordingly, BMA/BMB demonstrated complete remission by less than 5% plasma cells' feature.

To maintain the medical response, thalidomide was administrated 100 mg daily and after 30 months follow-up, the malignancy was still under control. Off note, the patient signed a *consent form* showing agreement for the release of the detailed information about the disease.

## Discussion

Liver involvement in MM mostly has subsequent histological patterns: Light chain deposition disease, amyloidosis, extramedullary plasmacytoma, sinusoidal involvement, or in the form of a diffuse infiltrative.<sup>5</sup> In our case, liver involvement probably occurred due to the diffuse sinusoidal flooding with a propensity to injure the liver parenchyma.

Multiple myeloma and primary amyloidosis can be typically diagnosed at the same time. However, less commonly, myeloma develops more than six months after the diagnosis of amyloidosis (delayed progression). In a series of 4319 patients visited at the Mayo Clinic between 1990 and 2008 with a diagnosis of myeloma, there were 47 patients (1.1%) in whom the diagnosis of primary amyloidosis followed by the diagnosis of myeloma by at least six months.<sup>12</sup> Although the primal symptom of our patient was liver failure, the diagnosis criteria for MM was completed by BMA/BMB assessment and the detection of plasmacytoma in bone marrow was followed by elevated gamma globulins in serum electrophoresis at the time of amyloidosis detection.

Multiple myeloma with primary amyloidosis has been shown to have a worse prognosis in comparison with MM alone.<sup>8, 9, 13, 14</sup> Cross et al. reported a case of a 46-year-old white woman diagnosed with amyloid deposition in liver biopsy and simultaneous MM with bone marrow involvement.<sup>14</sup> In a similar case, Yamamoto et al. reported a 79-year old Japanese woman with advanced hepatic failure due to kappa-AL amyloidosis and a concurrent diagnosis of IgG-K type multiple myeloma. Both cases rapidly progressed to death as a result of marked hepatic deterioration.<sup>9</sup> In comparison with previous similar cases, the complications of the disease in our case were successfully managed by new chemotherapy drugs.

Although our patient had the symptoms of jaundice with profoundly elevated total bilirubin and liver enzymes indicating the future poor prognosis, he exaggeratedly responded to chemotherapy regimen without any sign of relapse or liver complication after 30 months follow-up.

In our case, the first highlighted symptom

was hepatic and biliary system dysfunction due to the deposition of the amyloid precursor in the hepatic tissue. Furthermore, for MM patients with no routine symptoms such as CRAB (hypercalcemia, renal failure, anemia, or bone defect), diagnostic evaluation should be done more precisely.

Moreover, the treatment of MM patients with hepatic dysfunction can be challenging as well. Dose adjustment would be required for most chemotherapeutic agents. Dose reduction has been recommended for new anti-cancer agents such as bortezomib.<sup>5</sup> We escalated the bortezomib dose to 1 mg/m<sup>2</sup>, accordingly.

Chemotherapy with a standard regimen of bortezomib, thalidomide, and dexamethasone was implemented and, after only two months of treatment, primary signs and symptoms such as ascites and bilirubinemia were truly disappeared. The predominant response to the standard chemotherapy regimen, beside the unusual primal clinical presentation, makes the case history as a unique and vulnerability-reporting.

To the best of our knowledge, our case was the first reported patient with the primal symptoms of hyperbilirubinemia (more than 20 mg/dl for total bilirubin), ascites, hepatosplenomegaly, and anemia due to hepatic amyloidosis.

## Conclusion

Liver involvement without any classical clinical manifestation due to light chain amyloidosis can be the first drastic presentation of MM. More attention must be paid to the diagnosis of such a complicated patient. It is important to consider infiltrative disorders, like MM and amyloidosis, when patients are presented with non-specific symptoms and impaired liver function tests. Proper and timely diagnosis can directly affect the prognosis of patients. The optimal approach in standard management of similar cases is a topic for further debate.

**Conflict of Interest:** None declared.

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