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Amyloidosis and Spontaneous Liver Bleeding: A Case Report and Literature Review

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Abstract: Liver rupture with severe liver bleeding in patients with amyloidosis is an unusual but generally difficult to deal with and potentially fatal complication in these patients. Even patients with known manifestations to the lever can present with acute lever bleeding. Here we present a case report of a 62-year-old male with systemic immunoglobulin light chain (AL) amyloidosis, known manifestations to the lever and spontaneous liver bleeding which was treated conservatively without the need of surgical intervention. The etiology, panorama of clinical manifestations of hepatic amyloidosis and the management of liver bleeding in association with this unusual disease are reviewed. 18 cases of hepatic rupture and haemorrhage in association with amyloidosis in previously published cases are summarized. The choice of management should be individualized and the patient´s hemodynamic status and extent of liver bleeding are important factors to be taken into consideration. In all patients it is crucial to exclude underlying malignancy as the reason of bleeding. The patient´s hemodynamic status and the extent of liver bleeding are the most important factors to be taken into consideration in order to establish individualized management plan. Increased awareness of severe liver bleeding from amyloidosis may achieve reduced mortality of this potentially fatal complication.

Keywords: Amyloidosis, Spontaneous Liver Bleeding, Case, Review

1. Introduction

Amyloidosis is a group of haematological disorders caused by misfolding of extracellular proteins. In the extracellular matrix these proteins are organized as insoluble fibrils which can be found in most organs in the body [1]. The most common and serious form of amyloidosis is systemic immunoglobulin light chain (AL) amyloidosis, which is characterized by monoclonal immunoglobulin light chains associated with plasma cell dyscrasia [2-3]. Systemic AL amyloidosis may manifest with cardiac, kidney, neurological, soft tissue as well as gastrointestinal and hepatic involvement [1, 4]. Structural changes in the liver and hepatic vessels in combination with a variety of coagulopathies may contribute to spontaneous liver rupture and bleeding in amyloidosis [1, 5-7]. Although hepatic involvement in amyloidosis is common, liver rupture or bleeding is a rare entity. Here we present a patient who suffers from systemic AL amyloidosis with cardiac, kidney, gastrointestinal and hepatic manifestations.

2. Case Report

A 62-year-old male with advanced AL-amyloidosis and known manifestations to the heart, liver and kidneys, presented to the emergency department (Karolinska University Hospital, Stockholm) due to onset of pain and discomfort in the right upper abdominal quadrant. During the clinical examination no signs of abdominal tenderness or distension were noticed and after the administration of NSAID the patient was evaluated as pain free. The biochemical samples revealed no signs of anemia, infection or liver disorder (WBC $9X10^6$, CRP 2, g-glutamyl transferase 3.2 µkat/L, aspartate aminotransferase 0.53 µkat/L, alkaline phosphatase 1.3 µkat/L and albumin 42 g/L). PT, APTT and total bilirubin were normal. He was sent home with a referral to the radiology department for an outpatient ultrasound (US) examination because of high

suspicion of gallbladder lithiasis. The US examination revealed a large subcapsular hematoma of about 12 cm in the lateral aspect of the right hemiliver, low echogenic intrahepatic structures suspicious for coagulating and abnormal liver parenchyma around the hematoma.

Because of these findings and the suspicion of an acute liver bleeding the patient was admitted to the surgical clinic for observation. The same evening a computed tomography of the liver was performed and revealed a big subscapular liver hematoma without active extravasation and no obvious bleeding site. The liver parenchyma was infiltrated by amyloidosis and the radiologist recommended investigation with an extra radiological modality with magnetic resonance imaging (MRI) of the liver (Figure 1). No obvious signs of bleeding were noticed clinically and after one day's observation the patient was discharged home in stable condition, with a planned MRI. The subsequent MRI was performed after a week and revealed a 4, 5 cm subcapsular hematoma without changes from the previous CT. No signs of focal liver anomalies, hepatocellular carcinoma (HCC) or other malignancies, was seen (Figure 2).

The case was discussed in a multidisciplinary conference which decided that no surgical intervention was needed, and active surveillance was recommended. The patient was informed about the plan and recommended to visit the emergency department if any signs of abdominal pain or discomfort from the abdomen occurred. After three months a follow-up liver US revealed a partial regress of the hematoma and after six months the clinical examination and biochemical samples of the patient showed no worrisome features.

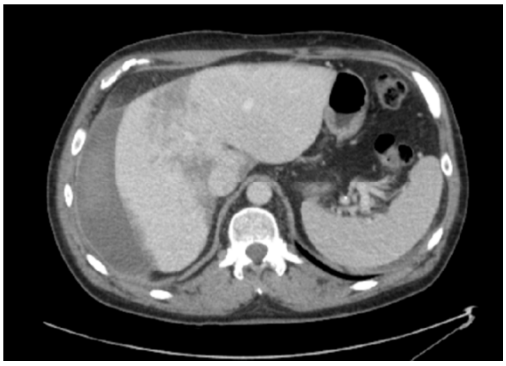

Figure 1. *Representing subcapsular hematoma in CT scan.*

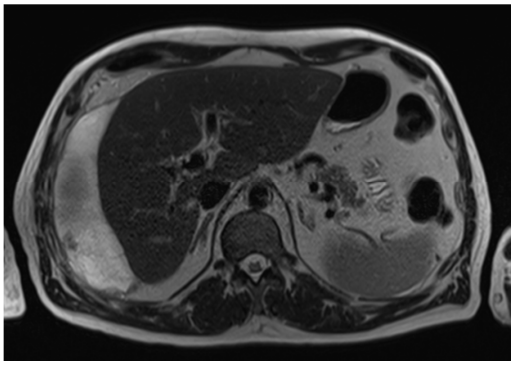

Figure 2. *Representing subcapsular hematoma in MRI.*

3. Discussion

Amyloidosis is a heterogeneous group of disorders defined by the misfolded fibril precursor protein. Amyloidosis can be divided into systemic and localized forms, with systemic forms accounting for 80-90% of all cases [8]. In systemic AL amyloidosis there is excessive production of immunoglobulin light chains as a result of plasma cell dysfunction. In approximately 15% of the cases the patient has multiple myeloma [1]. The incidence of systemic AL amyloidosis is estimated to 8 per million per year [3]. Other forms of amyloidosis include systemic AA amyloidosis which is secondary to infection, inflammation or neoplasia, β2M amyloidosis which occurs after years of dialysis, hereditary systemic amyloidosis which is caused by autosomal dominant mutation and senile systemic amyloidosis which is associated with the normal aging process [1]. Systemic AL amyloidosis is treated with chemotherapy regimens, while systemic AA amyloidosis is treated with therapies targeting the underlying inflammatory etiology. For hereditary systemic amyloidosis the definitive treatment is organ transplantation [1].

Hepatic involvement is seen in approximately 70% of patients with systemic AL amyloidosis, and is also present in other forms of amyloidosis. Hepatic amyloidosis is usually asymptomatic. When hepatic amyloidosis becomes symptomatic the patients often have involuntary weight loss, hepatomegaly, proteinuria and elevated serum alkaline phosphatase level [9]. Also C-reactive proterin and serum albumin are elevated in amyloidosis but the differences are less significant [4]. There are also some more rare complications associated with hepatic amyloidosis such as portal hypertension and cholestatic jaundice [10-12]. The differential diagnoses of hepatic amyloidosis include primary liver tumors and liver metastases [9]. Radiological tests of hepatic amyloidosis include ultrasonography, CT and MRI but are all unspecific [1, 13]. To confirm the diagnosis of amyloidosis histological analysis is required. The gold standard method is Congo red staining and amyloid deposits display green birefringence under cross-polarized light. Tissue biopsy is commonly obtained from rectum or abdominal fat due to low risk of complications [1]. Obtaining biopsies from a liver with amyloid involvement has been associated with increased risk of bleeding compared to a normal liver [4, 9].

Amyloid deposits can be found in liver parenchyma, liver stroma as well as liver vasculature [1]. The pathogenesis of liver rupture in amyloidosis is not fully understood. There are speculations that amyloid deposits make the liver capsule stiff and easier to break at the same time as the liver itself gets larger because of swelling or bleeding. In addition, amyloid deposits in the vessel walls may make the vessels fragile [6-7]. Moreover, deficiencies of coagulation factors, especially factor X, as well as well hypofibrinogenemia may contribute to bleeding [5-6]. Previous studies suggest that the prothrombin time should be monitored in patients with primary hepatic amyloidosis as around 30% of these patients may have prolonged prothrombin time resulting in increased

risk of bleeding [5, 9].

Liver rupture with severe liver bleeding in patients with amyloidosis is a rare and potentially fatal complication. Other conditions associated with spontaneous liver rupture include large hepatocellular carcinoma, preeclampsia and malaria [6]. By literature search we have found 18 cases of hepatic rupture and haemorrhage in association with amyloidosis as listed below. Only cases with available abstracts in English are presented. In about a third of the cases the diagnosis of amyloidosis is established after the patients present with acute liver rupture and hematoma. Involuntary weight loss and hepatomegaly are the two most common symptoms if the patient presents any symptoms at all. Some patients may have a previous history of hemorrhages or hematomas since coagulation defect is associated with amyloidosis. The presence of proteinuria in combination with elevated serum alkaline phosphatase level should lead to the suspicion of hepatic amyloidosis.

Traditionally emergency laparotomy with packing and sometimes hepatic artery ligation has been performed in the event of liver rupture, although transarterial embolization has become an emerging treatment option during the recent decade. In a case report Lehmann et al suggest transarterial embolization to be first choice to manage spontaneous liver rupture [7]. In six of the cases laparotomy was carried out with mixed outcomes, four cases resulting in death and two cases resulting in recovery. Transarterial embolization was performed in six cases, in four of them the patients were treated successfully and in two of them the patients deceased. Notably, in the case reported by Lehmann et al in which laparotomy was performed followed by transarterial embolization, the clinical course resulting in death was complicated by wound infection and necrosis. Emergency liver transplantation was carried out for two younger patients with hereditary lysozyme systemic amyloidosis and both of them recovered postoperatively. We only found one case in which the patient was successfully managed with conservative treatment alone and our case is the second reported case with liver hematoma treated conservatively. It is worth mentioning that the patient we present had only mild clinical symptoms from his liver hematoma without any signs of circulatory failure. The choice of management should be individualized. The patient´s hemodynamic status and extent of liver bleeding are particularly important factors to be taken into consideration. Moreover, we think that it is crucial to exclude underlying malignancy in patients with liver bleeding, even those with known diagnosis of amyloidosis. Also, the patients should be carefully informed with the risk of re-bleeding and should be aware of such symptoms.

4. Conclusions.

Liver rupture with severe liver bleeding in patients with amyloidosis is a rare and potentially fatal complication. Traditionally emergency laparotomy and hepatic artery ligation has been performed in the event of liver rupture, although transarterial embolization has become an emerging treatment option during the recent decade. Emergency liver transplantation has been performed in cases of younger patients with notable results. In rare cases conservative treatment can be the treatment option in patients with mild clinical symptoms and no signs of circulatory failure. The choice of management should be individualized and the patient´s hemodynamic status and extent of liver bleeding are important factors to be taken into consideration. In all patients it is crucial to exclude underlying malignancy as the reason of bleeding.

Table 1. *Previously published cases of liver rupture and/or bleeding in patients with amyloidosis.*

Study	Patient	Known amyloidosis	Type of amyloidosis	Clinical manifestation	Intervention	Outcome
Röllinghoff et al, 1976 (14)	37 yo female	Yes	Systemic AL	Intrahepatic haemorrhage	Unknown	Death
Hurd et al, 1980 (15)	45 yo female	Yes	Systemic AL	Bilobar subcapsular hematomas	Laparotomy with packing	Death
Levy-Lahad E et al, 1986 (16)	57 yo male	Yes	Systemic AL and small-cell lymphoma	Subcaspsular liver hematoma	Conservative treatment with blood products	Resolving hematoma
Ades et al, 1989 (17)	46 yo female	No	Systemic AL	Subcapsular and extracapsular liver hematomas	Laparotomies with ligation of hepatic artery and packing	Death
Harrison et al, 1996 (18)	15 yo male	Yes	Hereditary lysozyme systemic amyloidosis	Subcapsular and extracapsular liver hematomas	Emergency liver transplantation	Recovery
Ooi et al, 1996 (19)	41 yo male	No	Systemic AL	Liver rupture with intraperitoneal bleeding	Laparotomies with packing	Recovery
Satue et al, 1996 (20)	32 yo female	Yes	AA amyloidosis secondary to Mediterranean fever with renal failure	Liver rupture with intraperitoneal bleeding	Resuscitation	Death
Bujanda et al, 1997 (21)	59 yo male	Unknown	Unknown	Liver rupture with subcapsular hematoma	Laparotomy	Intraoperative death
Kacem et al, 1998 (22)	46 yo male	No	Systemic AL	Recurrent subcapsular liver hematomas	First time laparotomy with local coagulation, second time conservative treatment	Recovery
Mukhopadhya et al, 2004 (23)	48 yo male	Yes	Systemic AL and multiple myeloma	Intraperitoneal haemorrhage with rupture of the right lobe	Transarterial embolization	Recovery
Loss et al, 2006	34 yo female	No	Hereditary lysozyme	Liver rupture with intraperitoneal	Emergency liver	Recovery

Study	Patient	Known amyloidosis	Type of amyloidosis	Clinical manifestation	Intervention	Outcome
(6)			systemic amyloidosis	hematoma	transplantation	
Naito et al, 2009 (24)	42 yo male	Yes	Systemic AL	Subcapsular hematoma in the right lobe	Transarterial emobolization	Recovery
Tam et al, 2009 (25)	55 yo female	No	Systemic AL	Recurrent subcapsular hematomas	First time exploratory laparoscopy followed by conservative treatment, second time conservative treatment	Death
Lehmann et al, 2012 (7)	81 yo male	No	Systemic AL	Large confluent subcapsular hematoma and rupture of both liver lobes	Laparotomy followed by transarterial embolization	Death
Szturz et al, 2013 (26)	Female	No	Systemic AL	Recurrent intraperitoneal haemorrhage	Repeated surgical revision not specified	Death
Mousa et al, 2014 (27)	50 yo male	Yes	Systemic AL and multiple myeloma	Intraperitoneal haemorrhage with rupture of the left lobe	Transarterial embolization	Recovery
Suda et al, 2017 (28)	79 yo male	Yes	Systemic AL	Intraperitoneal haemorrhage	Transarterial embolization	Death
Lohana et al, 2019 (29)	44 yo female	No	Systemic AL	Intrahepatic haemorrhage	Transarterial embolization	Recovery

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