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Fatal Acute Liver Failure due to Reactivation of Hepatitis B Following Treatment with Fludarabine/Cyclophosphamide/Rituximab for Low Grade Non-hodgkin's Lymphoma

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Abstract
Background: Reactivation of chronic hepatitis B in HBsAg carriers is a well known complication of chemotherapy. The clinical spectrum ranges from asymptomatic hepatitis to fatal hepatic failure. Although it impairs the prognosis of cancer treatment, it may be overlooked due to other possible causes of liver damage.
Case report: The patient presented with acute liver failure after 6 cycles of rituximab, fludarabine, and cyclophosphamide for low grade non-hodgkin's lymphoma. Differential diagnoses were chemotherapy-induced liver failure, autoimmune hepatitis, phenprocoumon-induced liver failure and infiltration of the liver by lymphoma. Finally, reactivation of hepatitis B with a fibrosing cholestatic pattern was identified.
Conclusion: This case reminds clinicians that patients receiving high-intensive chemotherapy or immunosuppressive therapy should be screened for HBsAg. HbsAg positive patients should obtain prophylactic antiviral therapy with lamivudine or another substance active against HBV.

Key words: chemotherapy, reactivation, hepatitis B, liver failure

Presentation of Case

Past Medical History

A 55 year-old man was transferred to our tertiary care university hospital with acute liver failure. Four weeks before he had been admitted to another hospital with jaundice, nausea and vomiting. A treatment with prednisolone (1 mg/kg body weight) had been administered for suspected autoimmune hepatitis with positive smooth muscle antibodies. Because of progressive deterioration and development of severe hepatic encephalopathy (grade III) the patient was transferred to our hospital.

The information on medical history available upon transfer to our hospital was as follows: the patient had indolent Non-Hodgkin-Lymphoma diagnosed in 1992. It was managed by watchful waiting and eventually with 4 courses of cyclophosphamide, vincristine and prednisone. From December 2003 to April the following year a disease relapse was treated with 6 cycles of rituximab (375 mg/m^2; day 0), fludarabine (30 mg/m^2; day 1-3), and cyclophosphamide (250 mg/m^2; day 1-3). In addition, the patient had been treated with phenprocoumon for thrombosis of the calf and the popliteal veins diagnosed in March; the treatment had been stopped when liver function worsened in the beginning of June. Finally, the patient had a past history of hepatitis B virus (HBV) infection.

According to the available information we considered the following differential diagnoses:

- Autoimmune hepatitis
- Chemotherapy-induced liver failure (veno-occlusive disease)
- Phenprocoumon-induced liver failure
- Infiltration of the liver by lymphoma
- HBV reactivation

Diagnostic Workup

Laboratory testing showed a pattern of acute liver failure, and HBs Ag (Table 1); further workup including ultrasonography and CT scan as well as bone marrow biopsy showed no signs of persistent or recurrent lymphoma. A transjugular liver biopsy showed signs of highly replicative hepatitis B virus infection with a fibrosing cholestatic pattern as assessed by immunohistochemistry (Fig. 1).

Final Clinical Diagnosis

Reactivation of a chronic hepatitis B following chemotherapy

Further Course

Despite treatment with lamivudine the patient´s clinical condition deteriorated to full-blown liver failure with multiorgan failure requiring mechanical ventilation and continuous venovenous hemofiltration. The patient died from refractory septic shock six days after admission to our hospital. Liver transplantation was declined by the interdisciplinary transplantation team, since the patient had underlying lymphoma.

Table 1. Course of laboratory values.

	29.03.	25.05.	04.06.	10.06.	17.06.	Adm.*	21.06.	24.06.
Bilirubin (mg/dl)		5.9	3	5.7	23.6		29.4	29.7
g-GT (U/l)		666	737	733	336		192	88
AP (U/l)		73	189	796	214		123	
ALT (U/l)	86	271	456	1079	1374		281	
AST (U/l)	174	393	394	888	1060		467	194
Quick (%)	23	18	22	26	24		23	16
CHE (U/l)			2361	2123	1726		1406	
Creatinine (mg/dl)		0.98	0.9				1.1	4.35
LDH (U/l)		249					519	561
Microbiology								
Hepatitis A								
Anti-HAV							Positive	
Anti-HAV-IgM							Negative	
Hepatitis B								
HBs-antigen	Positive						Positive	
Anti-HBs	Negative						Negative	
Anti-HBc	Positive						Positive	
Anti-HBc-IgM	Negative						Negative	
HBeAg	Negative						Positive	
Anti-HBe	n.d.						Negative	
HBV-DNA	< 200 cop./ml						> 10^9 cop./ml	
Hepatitis C								
Anti-HCV							Negative	
Hepatitis D								
Anti-HDV							Negative	
CMV								
IgG and IgM							Negative	
HIV								
HIV-ELISA							Negative	
Immunology								
ANA							1:100 (<1:100)	
LKM							Negative (<1:100)	
SMA							1:200 (<1:100)	
AMA							Negative (<1:100)	
ANCA							Negative (<1:10)	

*Admission to our hospital

Reference values: Bilirubin 0.1-1.2, g-GT <55, AP 34-131, ALT <45, AST <35, Quick 70-130, CHE 7,000-19,000, Creatinine 0.5-1.4, LDH 104-248

Cut off values are given in brackets for immunology parameters. n.d. = not done
ANA = antinuclear antibody, LKM = liver kidney microsome, SLA = soluble liver antigen, SMA = smooth muscle antibody, AMA = antimitochondrial antibody, ANCA = antinuclear cytoplasmic antibody

Discussion

Reactivation of chronic hepatitis B in HBsAg carriers is a well known complication of chemotherapy. The clinical spectrum ranges from asymptomatic hepatitis to fatal hepatic failure. However, even in its mildest form with spontaneous recovery, a patient's prognosis from cancer may still be impaired from the interruption in chemotherapy with treatment delay, or premature termination of anticancer therapy. The incidence of reactivation in HBsAg positive patients is about 20 to 30 % [1, 2]. Several risk factors for reactivation have been identified: detectable HBV-DNA before chemotherapy, use of steroids, lymphoma or breast cancer as underlying disease [3], male sex [1]. However, results have been divergent and there is no generally accepted model for predicting reactivation. This would be of clinical relevance as it is possible to prevent reactivation by administration of the antiviral drug lamivudine. Primary prophylaxis with lamivudine has been shown

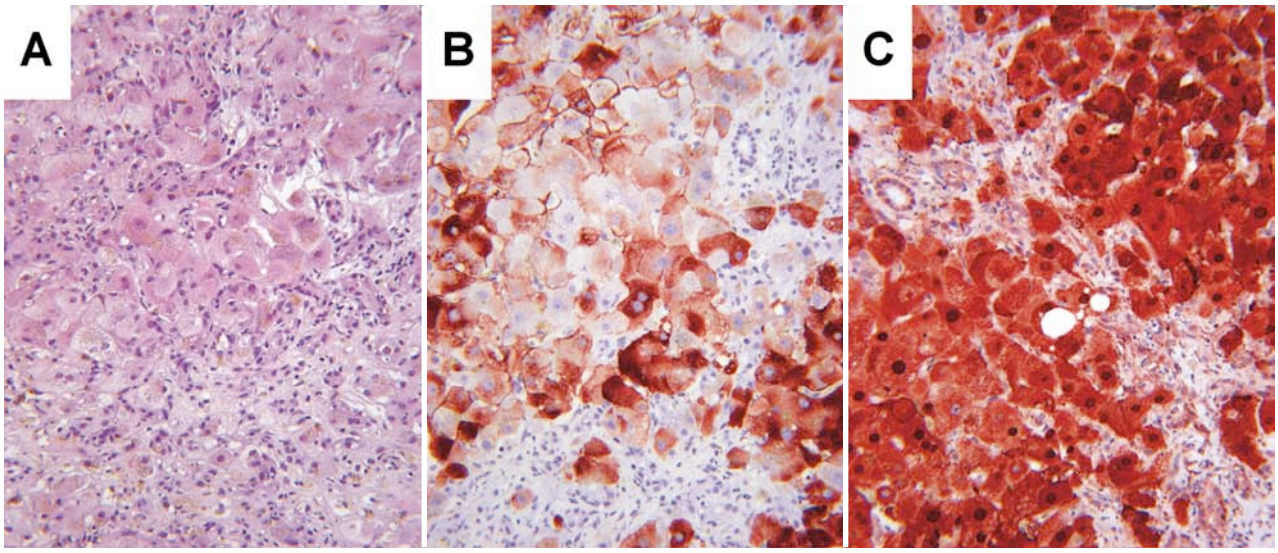

Fig. 1. Liver histology obtained by transjugular liver biopsy. The hematoxylin-eosin stain (A) shows destruction of large parts of the parenchyma, marked cholestasis, intralobular fibrosis, and moderate inflammatory infiltration. Immunohistochemistry reveals production of HBc (B) and HBs (C) in nearly all hepatocytes. The pattern is consistent with the diagnosis of fibrosing cholestatic hepatitis due to highly active hepatitis B.

to reduce the frequency and severity of hepatitis flares, and to improve survival in HbsAg positive patients [4]. The largest prospective analysis has found a reduction in reactivation from 24.4 % to 4.6 %, in incidence of hepatitis from 44.6 % to 17.5 %, in severity of hepatitis and disruption of chemotherapy, although mortality was not affected significantly in this series [5]. A similar reduction could be demonstrated by the same investigators in breast cancer patients, a group at particular risk for reactivation [6]. Therefore, the recommendation for prophylactic lamivudine treatment in HBsAg positive patients has been incorporated into the practice guidelines of the American Association for the Study of the Liver (AASLD) [7]. Accordingly, patients receiving chemotherapy or immunosuppressive therapy should undergo screening for HBsAg. Prophylactic antiviral therapy with lamivudine is recommended for HBsAg positive patients at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy, and maintained for 6 months after completion of chemotherapy or immunosuppressive therapy [7].

The optimal duration of lamivudine treatment is not clear. To our knowledge there is no consensus. The continuation of lamivudine for a variable period of one to six months after completion of chemotherapy was shown to be equally effective in reducing viral reactivation [8, 9]. Nevertheless, the AASLD guidelines recommend a course beginning with the onset of chemotherapy and lasting 6 months beyond the completion of chemotherapy [7]. After the end of lamivudine treatment a flare of hepatitis may develop. In the series reported today up to 6 % developed hepatitis after withdrawal of lamivudine, which was self-limiting in all cases described so far [5, 8].

At the moment there are no sufficient data on newer anti-HBV agents that might be beneficial in the setting of chemotherapy or immunosuppression in hepatitis B carriers. It is reasonable to assume that substances like adefovir, tenofovir or entecavir might have advantages with regard to viral potency and resistance profile. Therefore these substances might be preferred, if longer duration of treatment is anticipated.

The patient presented had at least two risk factors for reactivation of his hepatitis B virus infection (i. e. lymphoma, male sex). In addition, fludarabine is regarded as highly immunosuppressive [10], which further enhances the risk of HBV reactivation [11]. Liver function tests were elevated already in March, but the workup resulted in the misdiagnosis of autoimmune hepatitis. Retrospective analysis showed prior knowledge of HBsAg, that was taken into consideration too late though. Thus, the case should remind clinicians that patients receiving high-intensive chemotherapy or immunosuppressive therapy should be screened for HBsAg, at least if they are at risk. HbsAg positive patients should obtain prophylactic antiviral therapy with lamivudine or another drug active against HBV.

Competing interests: The authors declare that they have no competing interests.

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