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Hepatitis B virus reactivation in a patient with follicular lymphoma treated with fludarabine and rituximab containing immuno-chemotherapy

Zsófia Ujj, Ádám Jóna (jona dot adam1 at gmail dot com) #, Miklós Udvardy, István Tornai, Attila Kiss, Béla Telek, Róbert Szász, Gyula Reményi, Péter Ilonczai, Árpád Illés, László Rejtő
Division of Hematology and Division of Gastroenterology, Institute for Internal Medicine; University of Debrecen, Clinical Center, Debrecen, Hungary

: corresponding author

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Abstract

Introduction: Reactivation of hepatitis is one of the most serious complications of cytotoxic and immunosuppressive therapy in hepatitis B virus (HBV) carrier lymphoma patients. Prophylactic use of lamivudine can reduce reactivation of HBV in patients with hematologic malignancies treated with immuno-chemotherapy.

Case report: We report a case of a HBV carrier patient with follicular lymphoma (FL). Patient was treated with polychemotherapy and achieved complete remission, which was followed by rituximab maintenance treatment. Later, the patient developed severe acute liver failure due to chronic hepatitis B infection reactivation. Lamivudine and supportive therapy resulted in clinical improvement with normalization of liver functions. In the following years the patient experienced three relapses of FL, which were successfully treated with rituximab, irradiation and continuous lamivudine therapy. After four years of lamivudine monotherapy, hepatitis B reactivation was observed, due to development of lamivudine resistant mutation, which was successfully controlled by the addition of adefovir dipivoxil and α-interferon. With this triple combination, the patient is in complete remission with normal liver function, for five years.

Conclusion: The high mortality rate of fulminant hepatitis highlights the need to identify and follow up all hepatitis B virus carriers and prophylactic treatment with nucleosid analog in order to prevent reactivation.

Introduction

Chemotherapy-related reactivation of hepatitis B virus (HBV) infection has been reported more often recently [1] [2] [3] [4]. Its incidence is reported to be 10.4% in HBV surface antigen (HBsAg) carrier lymphoma patients [5]. Cytotoxic therapy is often accompanied by increased viral replication, as indicated by elevated serum HBV DNA [6]. During immune recovery, the rapid immune-mediated cytolysis of HBV-infected hepatocytes is manifested as hepatitis, hepatic failure and eventually death [7] [8] [9]. Monoclonal antibodies such as rituximab, is an integral component of current lymphoma treatment regimens. These agents can produce long-time immune-suppression and increase the risk of opportunistic viral and fungal infection. Rituximab induces profound and persistent B-cell depletion, resulting in the temporary impairment of secondary humoral immunity and hence increasing the patient's susceptibility to viral infection [10] [11] [12] [13] [14]. Rituximab administered alone or in combination with cytotoxic agents particularly fludarabine, cyclophosphamide or anthracycline has been associated with HBV reactivation [15] [16]. Adding corticosteroids may additively contribute to HBV reactivation [6] [7] [17].

Lamivudine is a nucleoside analogue, with a reverse transcriptase inhibitor activity that may effectively inhibit HBV replication. Prophylactic lamivudine treatment may reduce the incidence of HBV reactivation in carriers with hematological malignancies receiving immunochemotherapy by preventing viral replication [6] [8] [12] [18] [19]. However, prolonged lamivudine treatment is associated with an increased incidence of lamivudine resistant mutants [20]. Here, we report a case of a female patient with multiple relapses and successful treatment of follicular lymphoma and HBV reactivation.

Case report

A 30-year-old female patient was revealed to be HBsAg positive in April 2000 (other hepatitis serology examinations were not done), during her routine pregnancy evaluation. She received blood transfusion after birth. She presented with cervical lymphadenomegaly in February 2001. Staging work up and biopsy proved clinical stage III/A follicular lymphoma (grade 1).

Since, rituximab was not available at this time in Hungary, two cycles of cyclophosphamide-doxorubicin-vincristine- [enlarge]

prednisone-bleomycine regimen (CHOP-Bleo) were administered. Due to the small size of the lymph nodes, no irradiation was performed. Subsequent results from a bone marrow biopsy showed bone marrow involvement, and hence stage IV, therefore therapy was changed to fludarabine-mitoxantrone-dexamethasone regimen (FND). After the first cycle of FND, transient elevation of liver enzymes was observed, which normalized after the chemotherapy. Five courses of FND resulted in complete haematological remission in September 2001.

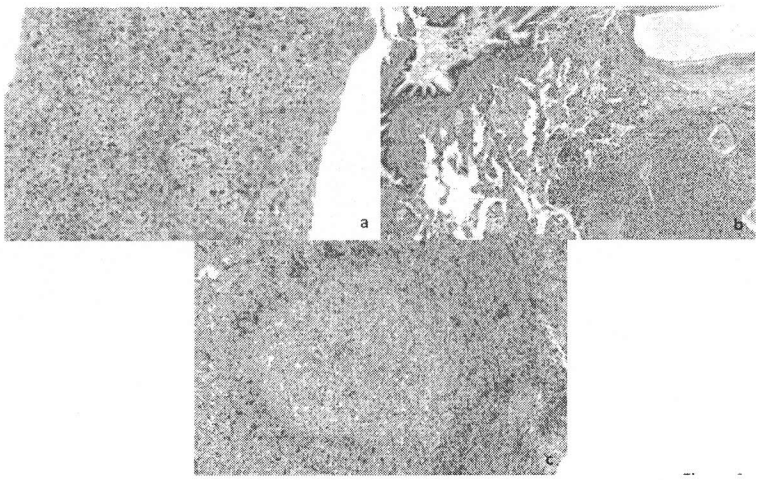

Figure 1. (A): Histology section of the patient's liver cirrhosis caused by chronic hepatits B virus infection (hematoxylin and eosin stain, 20x magnitude). (B): Histology section of relapse of FL in the lung (hematoxylin and eosin stain, 20x magnitude). (C): Histology section of relapse of follicular lymphoma (FL) in the gingiva (hematoxylin and eosin stain, 20x magnitude).

In May 2002, rituximab maintenance therapy was administered (375 mg/m2 intravenously weekly for four weeks). In November 2002, patient presented with malaise, loss of appetite, fatigue, weight loss, jaundice, and right upper quadrant discomfort. Laboratory findings revealed fulminant liver failure. Serology tests revealed HBsAg positivity and HBeAg negativity, anti-HBe and anti-HBc IgG were positve, anti-HBc IgM was negative. HBV DNA level was 9,840,000 copies/ml. Reactivation of HBV infection was diagnosed. Liver biopsy revealed cirrhosis with chronic active B virus hepatitis (Fig. 1a). Based on these findings, lamivudine at a dose of 100 mg/day along with supportive therapy was initiated in January 2003. Lamivudine treatment resulted in rapid normalisation of liver enzymes. By April 2003, serum HBV DNA had decreased to 146 copies/ml.

Histologically confirmed local relapse of NHL in the cubital region was diagnosed in May 2003. Radiotherapy and rituximab (375 mg/m2 intravenously weekly for four weeks, repeated every 3 months) were started with the continuous administration of lamivudine. In May 2004, pulmonary relapse of FL was detected by chest computed tomography (CT). The patient underwent resection of the involved pulmonary segment, intraoperative histology confirmed the relapse of FL (Fig. 1b). Hence, rituximab treatment was also administered (375 mg/m2 intravenously weekly for four weeks, repeated every 3 months). In June 2005, Coombs positive warm type autoimmune hemolytic anemia (AIHA) was confirmed (relapse of FL was excluded by positron emission tomography/ computed tomography (PET/CT)). Administration of corticosteroids and rituximab (375 mg/m2 intravenously weekly for four weeks) only temporarily reduced the intensity of hemolysis, therefore azathioprine (50 mg/day) was added to the therapeutic regimen. In November 2005, the patient experienced an excessive increase in hemolysis. Simultaneous treatment with rituximab (375 mg/m2 intravenously weekly for four weeks), corticosteroids and azathioprine reduced again the hemolysis. In January 2006, spleen irradiation (10 Gy), reduced dose corticosteroids and temporary mycophenolate mofetil (250 mg) were administered to avoid exacerbation of hemolysis. The azathioprine was omitted. Since then, rituximab has been administered every sixth month (375 mg/m2 intravenously weekly for four weeks). The patient achieved complete remission of the AIHA. Between January 2003 and May 2007 with continuous lamivudine therapy, liver enzymes (AST, ALT) were within normal ranges and HBV DNA level remained below the detection limit despite repeated rituximab and corticosteroid treatment.

[enlarge]

In May 2007, the patient had significant elevation of liver enzymes and HBV DNA levels increased above 110,000,000 copies/ml with lamivudine resistant mutants, which was identified by polymerase chain reaction (PCR) based sequencing of the HBV deoxyribonucleic acid (DNA). Therefore, adefovir dipivoxil (10 mg/day) was added to lamivudin treatment and rituximab administration was interrupted. Due to permanent elevation of liver enzymes, the antiviral therapy was complemented with α-interferon (2x1.5 million units/ week). In October 2007, the patient had local gingival relapse of FL, thus, she received involved-field irradiation and rituximab maintenance therapy (375 mg/m2 intravenously weekly for four weeks, repeated every 3 months) (Fig. 1c). By February 2008, transaminase levels were normalized and serum HBV DNA levels decreased to 260 copies/ml. 18FDG PET/CT was performed in November 2008 and November 2011, showed no evidence of disease. Patient was last seen in October 2013, and she was in complete metabolic and hepatological remission (Fig. 2).

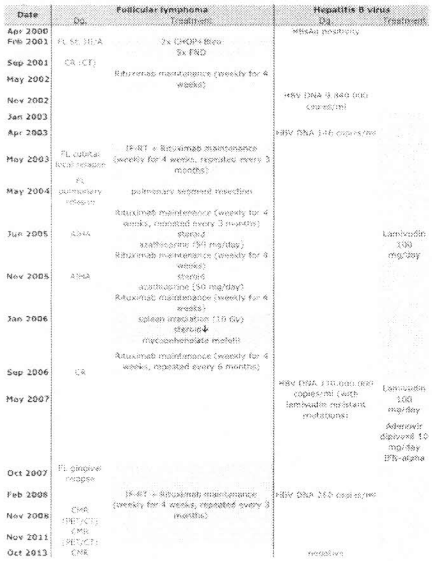

Figure 2. Parallel medical history and treatment of follicular lymphoma and hepatitis B. Dg. – Diagnosis, FL – follicular lymphoma, St. – stage, CR – complete remission, CT – computed tomography, AIHA – autoimmune hemolytic anaemia, CMR – complete metabolic response, PET/CT – positron emission tomography/ computed tomography, HBsAg – hepatits B surface antigen, HBV DNA – hepatitis B virus deoxyribonucleic acid, IFN-alpha – interferon-alpha, CHOP+Bleo - cyclophosphamide-doxorubicin-vincristine-prednisone-bleomycine regimen, FND - fludarabine-mitoxantrone-dexamethasone regimen, IF-RT – involved field radiotherapy

Conclusion

Clinical evidence in 2001 suggested, that stage III follicular lymphoma may be effectively treated with combined cyclophosphamide-doxorubicin-vincristine-prednisone-bleomycine (CHOP-bleomycin) and involved-field radiotherapy. This treatment modality was reported to result in complete hematological remission and bcl-2 negative status by polymerase chain reaction analysis (PCR). The high plateau in the survival curve suggested potential cure [21] [22]. Other studies reported better response rates in stage IV disease with fludarabine (e.g. fludarabine-mitoxantrone-dexamethasone (FND)) with better long-term failure free survival, PCR negativity and potential curability [23] [24] [25]. At the time of our case report, the FND regimen was standard of care for stage IV follicular lymphoma at M.D. Anderson Cancer Centre, however no subsequent study has confirmed the survival advantage of FND [26].

Several cases of hepatitis and hepatic failure due to HBV reactivation have been reported in the literature during or after several months after rituximab administration or rituximab containing chemotherapy [13] [27]. Corticosteroids, fludarabine, anthacyclines, vinca alkaloids, alkylating agents and anti-metabolites are also able to enhance the reactivation of HBV. The transient elevation of AST and ALT observed after the first cycle of FND was already due to the HBV reactivation. Prophylactic administration of lamivudine might have been started before chemotherapy, but its prophylactic use was not generally approved in Hungary in 2001.

Most cases of HBV reactivation occur several months following rituximab-containing therapy, suggesting the potential effects of rituximab. Our patient developed severe hepatic failure six months after rituximab treatment. Lamivudine inhibits viral replication in hepatocytes resulting in a prompt decrease in AST levels and a reduction of HBV DNA levels [1]. Since hepatitis reactivation can occur 100-200 days after the withdrawal of immunochemotherapy, lamivudine should be administered for a long period or even continuously, particularly in patients with relapsing NHL [8]. In our case continuous administration of lamivudine prevented the HBV reactivation during rituximab treatment for almost four years. The recent increase in HBV DNA levels during lamivudine treatment suggested the presence of lamivudine resistance, requiring the addition of adefovir dipivoxil and interferon-α. With this triple combination, complete biochemical and virological remission was achieved with a 7-log reduction of HBV DNA levels. Rituximab maintenance treatment can only be administered in patients with normal liver enzyme function. The combination of two nucleosid analogues and interferon-α is not approved therapy for hepatitis B. In immuncompetent patients the combination of pegylated interferon-α 2a + lamivudine could not increase the sustained virological response rate as compared to the peginterferon monotherapy.

All NHL patients should be tested for hepatitis B [8] [20], by measuring HBsAg and anti-HBc before initiating treatment with rituximab. Reactivation can occur both in HBsAg positive and HBsAg negative but anti-Hbc (and anti-HBs) positive patients [28]. Prophylactic lamivudine treatment can reduce the risk of HBV reactivation in immuncompromised patients. Therefore, all HBsAg-positive patients should receive prophylactic lamivudine treatment before (immuno-) chemotherapy [27]. Initiation of lamivudine treatment is recommended one week before and to continue for at least six weeks (up to six months or more) after the end of the chemotherapy in HBsAg-positive patients [20]. Follow-up of AST, ALT and HBV DNA levels is critical for monitoring liver status [6] [7] [20] [29]. Further research is needed to establish the optimal duration of nucleoside analogue treatment [8].

Our case report indicates that rituximab treatment is effective both in relapsed FL and AIHA even after longer intervals of therapy. Addition of nucleoside analogue treatment to the use of rituximab maintenance may prevent hepatitis in HBsAg carrier FL patients. Nowadays, the more effective entecavir or tenofovir could be initiated, however in our case the triple combination of lamivudine, adefovir and interferon-α is maintained until HBV DNA level is undetectable. Interestingly, HCV does not show a high incidence of virus reactivation and severe hepatic failure in contrast to HBV, therefore, viral prophylaxis is not required [30] [31].

Our case report highlights the importance of identification and follow-up of HBV carrier lymphoma patients, and provides a possible strategy for the management of lymphoma while maintaining liver function.

Declarations

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References

1. Picardi M, Pane F, Quintarelli C, De Renzo A, Del Giudice A, De Divitiis B, *et al.* Hepatitis B virus reactivation after fludarabine-based regimens for indolent non-Hodgkin's lymphomas: high prevalence of acquired viral genomic mutations. Haematologica. 2003;88:1296-303 pubmed
2. Power J, El Chaar M, Temple J, Thomas M, Spillane D, Candotti D, *et al.* HBV reactivation after fludarabine chemotherapy identified on investigation of suspected transfusion-transmitted Hepatitis B virus. J Hepatol. 2010;53:780-7 pubmed publisher
3. Sanchez M, Buti M, Homs M, Palacios A, Rodriguez-Frias F, Esteban R. Successful use of entecavir for a severe case of reactivation of hepatitis B virus following polychemotherapy containing rituximab. J Hepatol. 2009;51:1091-6 pubmed publisher
4. Tsutsumi Y, Yamamoto Y, Shimono J, Ohhigashi H, Teshima T. Hepatitis B virus reactivation with rituximab-containing regimen. World J Hepatol. 2013;5:612-620 pubmed
5. Hsu C, Tsou H, Lin S, Wang M, Yao M, Hwang W, *et al.* Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: A prospective study. Hepatology. 2013;: pubmed publisher
6. Li Y, He Y, Jiang W, Wang F, Lin X, Zhang L, *et al.* Lamivudine prophylaxis reduces the incidence and severity of hepatitis in hepatitis B virus carriers who receive chemotherapy for lymphoma. Cancer. 2006;106:1320-5 pubmed
7. Saif M, Little R, Hamilton J, Allegra C, Wilson W. Reactivation of chronic hepatitis B infection following intensive chemotherapy and successful treatment with lamivudine: a case report and review of the literature. Ann Oncol. 2001;12:123-9 pubmed
8. Vassiliadis T, Garipidou V, Tziomalos K, Perifanis V, Giouleme O, Vakalopoulou S. Prevention of hepatitis B reactivation with lamivudine in hepatitis B virus carriers with hematologic malignancies treated with chemotherapy--a prospective case series. Am J Hematol. 2005;80:197-203 pubmed
9. Muñoz Bertrán E, Perez Ceballos E, Gómez Espín R, Ortega González I. [Hepatitis B reactivation in an HbsAg-negative/anti-HBc-positive patient with B-cell non-Hodgkin lymphoma receiving chemotherapy with rituximab]. Gastroenterol Hepatol. 2010;33:377-81 pubmed publisher
10. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis. 2011;15:e2-16 pubmed publisher
11. Cortelezzi A, Vigano M, Zilioli V, Fantini N, Pasquini M, Deliliers G, *et al.* Adefovir added to lamivudine for hepatitis B recurrent infection in refractory B-cell chronic lymphocytic leukemia on prolonged therapy with Campath-1H. J Clin Virol. 2006;35:467-9 pubmed
12. Hamaki T, Kami M, Kusumi E, Ueyama J, Miyakoshi S, Morinaga S, *et al.* Prophylaxis of hepatitis B reactivation using lamivudine in a patient receiving rituximab. Am J Hematol. 2001;68:292-4 pubmed
13. Iannitto E, Minardi V, Calvaruso G, Mule A, Ammatuna E, Di Trapani R, *et al.* Hepatitis B virus reactivation and alemtuzumab therapy. Eur J Haematol. 2005;74:254-8 pubmed
14. Moses S, Lim Z, Sudhanva M, Devereux S, Ho A, Pagliuca A, *et al.* Lamivudine prophylaxis and treatment of hepatitis B Virus-exposed recipients receiving reduced intensity conditioning hematopoietic stem cell transplants with alemtuzumab. J Med Virol. 2006;78:1560-3 pubmed
15. Sera T, Hiasa Y, Michitaka K, Konishi I, Matsuura K, Tokumoto Y, *et al.* Anti-HBs-positive liver failure due to hepatitis B virus reactivation induced by rituximab. Intern Med. 2006;45:721-4 pubmed
16. Yeo W, Johnson P. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology. 2006;43:209-20 pubmed
17. Leaw S, Yen C, Huang W, Chen T, Su W, Tsao C. Preemptive use of interferon or lamivudine for hepatitis B reactivation in patients with aggressive lymphoma receiving chemotherapy. Ann Hematol. 2004;83:270-5 pubmed
18. Dai M, Chao T, Kao W, Shyu R, Liu T. Delayed hepatitis B virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. Ann Hematol. 2004;83:769-74 pubmed
19. Tsutsumi Y, Tanaka J, Kawamura T, Miura T, Kanamori H, Obara S, *et al.* Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. Ann Hematol. 2004;83:58-60 pubmed
20. Hui C, Cheung W, Au W, Lie A, Zhang H, Yueng Y, *et al.* Hepatitis B reactivation after withdrawal of pre-emptive lamivudine in patients with haematological malignancy on completion of cytotoxic chemotherapy. Gut. 2005;54:1597-603 pubmed
21. Lopez-Guillermo A, Cabanillas F, McLaughlin P, Smith T, Hagemeister F, Rodriguez M, *et al.* The clinical significance of molecular response in indolent follicular lymphomas. Blood. 1998;91:2955-60 pubmed
22. McLaughlin P, Fuller L, Velasquez W, Butler J, Hagemeister F, Sullivan-Halley J, *et al.* Stage III follicular lymphoma: durable remissions with a combined chemotherapy-radiotherapy regimen. J Clin Oncol. 1987;5:867-74 pubmed
23. Crawley C, Foran J, Gupta R, Rohatiner A, Summers K, Matthews J, *et al.* A phase II study to evaluate the combination of fludarabine, mitoxantrone and dexamethasone (FMD) in patients with follicular lymphoma. Ann Oncol. 2000;11:861-5 pubmed
24. McLaughlin P, Hagemeister F, Romaguera J, Sarris A, Pate O, Younes A, *et al.* Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol. 1996;14:1262-8 pubmed
25. McLaughlin P, Cabanillas F, Younes A (1996) Stage IV low-grade lymphoma: randomized trial of two innovative regimens with molecular cloning of bcl-2 by PCR. Ann Oncol 7 (3):34.
26. Bowles K, Hodson D, Marcus R (2007) Follicular lymphoma in pathology diagnosis and treatment. Cambridge: Cambridge University Press:111-125.
27. Zell J, Yoon E, Ignatius Ou S, Hoefs J, Chang J. Precore mutant hepatitis B reactivation after treatment with CHOP-rituximab. Anticancer Drugs. 2005;16:83-5 pubmed
28. Important RITUXAN® (Rituximab) Safety Information - RITUXAN® (Rituximab. Available from: www.rituxan.com/hem/hcp/safety/
29. Yamagata M, Murohisa T, Tsuchida K, Okamoto Y, Tsunoda S, Nakamura M, *et al.* Fulminant B hepatitis in a surface antigen and hepatitis B DNA-negative patient with diffuse large B-cell lymphoma after CHOP chemotherapy plus rituximab. Leuk Lymphoma. 2007;48:431-3 pubmed
30. Coiffier B. Hepatitis B virus reactivation in patients receiving chemotherapy for cancer treatment: role of Lamivudine prophylaxis.

Cancer Invest. 2006;24:548-52 pubmed

31. Firpi R, Nelson D. Management of viral hepatitis in hematologic malignancies. Blood Rev. 2008;22:117-26 pubmed publisher

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