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CASE REPORT

Occult hepatitis B reactivation following rituksimab treatment in a patient with Waldenström's macroglobulinemia

Waldenström makroglobulinemili hastada rituksimab tedavisi sonrası gelişen gizli hepatit B reaktivasyonu

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ABSTRACT

The anti-CD20 monoclonal antibody rituximab has been used extensively in the treatment of B-cell lymphoma. Several studies reported hepatitis B virus (HBV) reactivation after rituximab. The majority of these cases have been described in chronic carriers of HBV, whereas reactivation in occult hepatitis B virus (OHBV) carriers may occur.

The presented case with the diagnosis of Waldenström's macroglobulinemia was HBsAg negative and anti HBcIgG positive before chemotherapy. The patient was started on CVP (cyclophosphamide, vincristine, prednisolone) chemotherapy. However, no clinical or laboratory response was obtained and the patient was considered unresponsive to three cycles of CVP therapy. Therefore R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone) was planned as the second therapy. Laboratory work-up after the first cycle of R-CHOP therapy revealed an aspartate aminotransferase (AST) level of 267 U/L and alanine aminotransferase (ALT) level of 318 U/L. HBsAg and anti HBcIgG were positive and HBV DNA was 56400 IU/ml. Lamivudin 100 mg/day was started. Four weeks after the initiation of lamivudin therapy, ALT and AST levels returned to normal. Currently, the patient has received the fourth cycle of R-CHOP therapy. ALT and AST levels continue to be in normal range. This condition was considered to be the reactivation of OHBV following rituximab.

The aim of this case presentation is to call attention to HBV reactivation possibility in cases taking immunosupressive medications like Rituximab. *J Clin Exp Invest 2012; 3(4): 541-544*

Key words: Waldenström's macroglobulinemia, rituximab, occult HBV infection

ÖZET

Anti CD 20 monoklonal antikor olan rituksimab B hücreli lenfomaların tedavisinde yaygın olarak kullanılmaktadır. Bir çok çalışmada rituksimab tedavisi sonrası hepatit B virüs (HBV) reaktivasyonu gösterilmiştir. Bu vakaların büyük bir kısmı kronik HBV taşıyıcılarında tanımlanmış olmakla birlikte, gizli hepatit B virüs taşıyıcılarında reaktivasyon gelişebilir.

Waldenström Makroglobulinemisi tanısı konulan olgumuzda kemoterapi öncesi bakılan HBsAg (-) ve Anti HBc IgG (+) idi. Hastaya CVP (siklofosfamid, vinkristin, prednizolon) kemoterapisi başlandı. Ancak klinik ve laboratuar olarak yanıt alınamadı ve hasta 3 kürlük CVP tedavisine yanıtsız kabul edildi. Hastaya ikinci basamak tedavi olarak R-CHOP (rituksimab, siklofosfamid, adriamisin, vinkristin ve prednizolon) verilmesi planlandı. 1. kür R-CHOP tedavisi sonrası yapılan tetkiklerde aspartat aminotransferaz (AST) değeri: 267 U/L ve alanin aminotransferaz (ALT) değeri: 318 U/L olarak bulundu. Bakılan HBs Ag (+), HBV DNA: 56400 İU/ml ve Anti HBcIgG (+) olarak saptandı. Lamuvidin 100 mg/gün başlandı. Lamuvidin tedavisinin başlanmasından 4 hafta sonra AST ve ALT değerleri normale döndü. Hasta en son olarak 4. kür R-CHOP tedavisini aldı. AST ve ALT değerleri normal aralıkta olarak takip ediliyor. Bu durum Rituksimab sonrası gelişen gizli hepatit B reaktivasyonu olarak kabul edildi.

Bu vakayı sunmamızdaki amaç; Rituksimab gibi immünsüpressif tedavi alan olgularda HBV reaktivasyonu olabileceğine dikkat çekmektir.

Anahtar kelimeler: Waldenström makroglobulinemisi, rituksimab, gizli hepatit B enfeksiyonu.

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INTRODUCTION

Hepatitis B virus (HBV) reactivation is a serious complication of cytotoxic or immunosuppressive therapies. The incidence of reactivation following chemotherapy in chronic HBV carriers varies between 21 to 53%.[1] An unknown number of subjects in the general population harbor occult HBV infection, i.e. the presence of HBV genomes in the liver in the absence of detectable amounts of HBsAg and even of any other conventional markers of HBV infection in the blood.[2] Occult HBV infection has been known to reactivate under immunosuppression and to cause episodes of acute hepatitis B.[1] In this setting, routine detection of HBsAg before chemotherapy may not be sufficient.

We have presented a case diagnosed with Waldenström's macroglobulinemia developing an occult reactivation of hepatitis B following rituximab therapy and successfully treated with lamivudin. This case was presented to draw attention to occult HBV infections and to state that there is an increased risk of occult HBV reactivation with the addition of rituximab to CHOP therapy.

CASE REPORT

Forty-seven-year-old male patient presented with nose bleeding, fatigue and headache. Physical examination revealed hepatosplenomegaly and peripheral lymphadenopathy. Laboratory work-up revealed hemoglobin level of 12.8 g/dl, platelets 123.000/μL, c-reactive protein 20.1 mg/L (0-5), β2 microglobulin level of 5.69 g/L (1.09-2.53) and immunoglobulin M (IgM) level of 37.8 g/L (0.4-2.30). Monoclonal gammapathy in protein electrophoresis and IgM kappa monoclonal gammapathy in serum-urine immune fixation was detected. Bone marrow biopsy was carried out and diffuse infiltration with lymphoplasmocytes was reported (Figure 1 and 2). The patient was diagnosed as Waldenström's Macroglobulinemia. Viral markers were studied before induction of chemotherapy. HbsAg, anti HCV, anti HIV were negative and anti HBc IgG was found to be positive. CVP chemotherapy (cyclophosphamide, vincristine and prednisolone) was started. Cyclophosphamide 750 mg/m^2 (1 day), vincristine 2 mg/day (1 day) and prednisolone 100 mg/day (5 days) were given. A total of three cycles were administered in every three weeks. However, a clinical or laboratory response was not obtained. IgM level was still high and monoclonal gammapathy persisted in protein electrophoresis. The patient was considered unresponsive to CVP therapy and R-CHOP treatment was planned with rituximab 375 mg/m^2 (1 day), cyclophosphamide 750 mg/m^2 (1 day), vincristine 1.4 mg/m^2 (1 day), adriamycin 50 mg/m^2 (1 day) and prednisolone 100 mg/day (5 days) in every 21 days. Five days after the first cycle of R-CHOP treatment the patient presented with fatigue. Laboratory work-up revealed an aspartate aminotransferase (AST) level of 267 U/L and alanine aminotransferase (ALT) level of 318 U/L. Abdominal ultrasonography was normal. HBsAg and anti HBcIgG were found positive and HBV DNA was 56400 IU/ml. The patient was considered as having reactivation of occult hepatitis B and lamivudin 100 mg/day was started. The ALT and AST levels of the patient returned to normal after four weeks of lamivudin treatment and the HBV DNA level was 41 IU/ml. Chemotherapy was continued and the patient had received the fourth cycle of R-CHOP therapy with normal liver enzymes. This rare condition was considered to be reactivation of occult hepatitis B following the administration of chemotherapy.

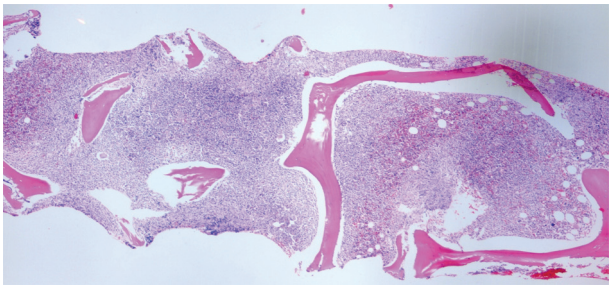

Figure 1. Bone marrow biopsy section from a patient with waldenström macroglobulinemi shows an extensive diffuse infiltrate (H&E, X100)

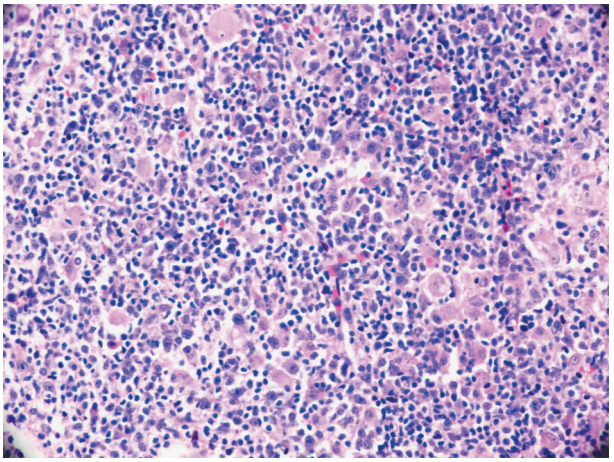

Figure 2. This clonal bone marrow disorder is morphologically characterized by a neoplastic proliferation of small lymphocytes, plasma cells, and plasmacytoid lymphocytes (H&E, X400)

DISCUSSION

Rituximab is a chimeric monoclonal antibody against the protein CD20, which is commonly used in the treatment of B cell lymphomas.[3,4] Rituximab is also an effective immunosuppressive agent which may lead to HBV replication.[5] Antracyclin based chemotherapy regimens (such as cyclophosphamide, doxorubicin, vincristine and prednisone) with the addition of rituximab (R-CHOP), forms the standard front line therapy in the treatment of CD 20 (+) B cell lymphomas.[6]

Rituximab has been found to induce profound and durable B-cell depletion. Although lysis of HBV-infected hepatocytes is mainly mediated by CD8+ cytotoxic T-cell immunity, B cells may also act as antigen-presenting cells and prime cytotoxic T-cell–specific responses in HBV infection. The B cell depletion due to rituximab may result in defective T cell response to the HBV which may lead to the viral replication.[3] This is supported by the observation of rituximab-induced severe or fatal cytomegalovirus reactivation, parvovirus B19 infection, adenovirus infection, and Pneumocystis carini pneumonia.[4]

HBV reactivation is a common complication in HBsAg positive patients undergoing immunosuppressive anticancer therapy. On the other hand, HBV reactivation has previously been reported to be much less common in patients who had resolved HBV infection. However, with the recent increase in the use of rituximab, HBV reactivation has been increasingly reported.[4]

Different rates of HBV reactivation were reported following rituximab containing regimens. The causes for this can be intensive therapy, patient characteristics, genotypic variations in HBV and geographic variations.[3]

A study has evaluated HBV reactivation following rituximab containing chemotherapy in 261 cases with CD 20 (+) B cell lymphoma and occult HBV infection was found in 56 cases. Among these occult HBV carriers, reactivation was reported in five patients (8.9%).[3] Similarly in the study by Fukushima et al., HBV reactivation after rituximab treatment was reported in only 2 (6.3%) out of 32 patients with occult HBV infection.[7] Yeo et al. reported that there was an increased risk of HBV reactivation with the addition of rituximab to CHOP chemotherapy.[4]

Prophylactic use of antiviral agents before chemotherapy is the standard approach in HBV carriers. However, there is no consensus about the prophylactic use of antiviral agents in cases with occult HBV infections. Nevertheless, mortality rate increases in these patients when HBV reactivation occurs.[8]

The present data suggest that, for patients who are planned to receive anti B cell therapy, and are HBsAg negative should further be screened for anti HBc and anti HBs. To prevent HBV reactivation and its associated morbidity and mortality, patients those found to be positive for anti HBc, particularly patients who are negative for anti HBs, should be closely monitored with HBV DNA and serum biochemistry during and for at least 6 months after the completion of rituximab therapy, with an antiviral administered promptly on the detection of reactivation.[9] However, reports using this approach have not been found to be universally successful, with HBV associated mortality still being observed, possibly because of a delay in the antiviral administration.[10]

Yeo et al. recommended prophylactic use of lamivudin up to six months after the completion of chemotherapy containing rituximab.[4] Lamivudin is a safe and cost-effective antiviral agent, but it can induce mutations when used for a long term.[11] Currently entecavir is one of the most potent antiviral agent for chronic hepatitis B. But compared with Lamuvidin it is much more expensive.[12]

With the increasing use of rituximab and other novel antilymphocytic therapies for the treatment of lymphoma, HBV reactivation in patients who have resolved HBV infection will pose an increasing clinical challenge, especially in endemic areas. Further studies with close monitoring would provide a better understanding of the mechanism of this condition.

In our opinion in patients that considered to have immunosuppresive therapy like Rituximab, it is necessary to evaluate anti HBc IgG levels with HBS Ag before treatment. Prophylactic Lamuvidin therapy should be considered in patients with Anti HBc IgG (+) and HBs Ag (-) and treatment must be continued at least 6 months from the end of specific chemotherapy.

In conclusion, rituximab containing regimens for the treatment of B cell lymphoma may increase the likelihood of HBV reactivation in patients with isolated anti HBc positivity. Further studies aimed at preventing HBV reactivation are needed. Close monitoring of HBV serology during therapy and prophylactic or preemptive use of antiviral agents are recommended in high risk patients receiving rituximab containing chemotherapies.

REFERENCES

1. Iannitto E, Minardi V, Calvaruso G, et al. Hepatitis B virus reactivation and alemtuzumab therapy. Eur J Haematol 2005;74 (3): 254-8.
2. Viganò M, Vener C, Lampertico P, et al. Risk of hepatitis B surface antigen seroreversion after allogeneic hematopoietic SCT. Bone Marrow Transplant 2011; 46 (1):125-31.
3. Matsue K, Kimura S, Takanashi Y, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. Cancer 2010; 116 (20):4769-76.
4. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009; 27(4): 605-11.
5. Zhang B, Wang J, Xu W, Wang L, Ni W. Fatal reactivation of occult hepatitis B virus infection after rituximab and chemotherapy in lymphoma: necessity of antiviral prophylaxis. Onkologie 2010; 33 (10):537-9.
6. Armitage JO. How I treat patients with diffuse large B-cell lymphoma. Blood 2007; 110 (1):29-36.
7. Fukushima N, Mizuta T, Tanaka M, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. Ann Oncol 2009; 20 (12):2013-7.
8. European Association for The Study of The Liver: EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009; 50 (2): 227-42.
9. Yeo W, Chan PK, Chan HL, Mo FK, Johnson PJ. Hepatitis B virus reactivation during cytotoxic chemotherapy-enhanced viral replication precedes overt hepatitis. J Med Virol 2001; 65(3): 473-7.
10. Khaled Y, Hanbali A. Hepatitis B virus reactivation in a case of Waldenstrom's macroglobulinemia treated with chemotherapy and rituximab despite adefovir prophylaxis. Am J Hematol 2007; 82 (7):688.
11. Gutfreund KS, Williams M, George R, et al. Genotypic succession of mutations of the hepatitis B virus polymerase associated with lamivudine resistance. Hepatology 2000; 33 (3):469-75.
12. Lalazar G, Rund D, Shoouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol 2007; 136 (5): 699-712.