CD5-negative chronic lymphocytic leukemia/small lymphocytic lymphoma in a patient with gastrointestinal mantle cell lymphoma: an unusual case report

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Abstract: Richter's syndrome, the development of high-grade non-Hodgkin lymphoma in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), may be triggered by viral infections (eg, Epstein-Barr virus infection). Herein, we report an unusual case of CD5-negative CLL/SLL patient with gastrointestinal mantle cell lymphoma (MCL) and hepatitis B virus infection. CLL/SLL was diagnosed based on lymph node immunohistochemistry and bone marrow pathology. This patient was treated with seven cycles of multi-agent chemotherapy. During treatment, the hepatitis B viruses were activated. Then, after 20 months of antiviral treatment with entecavir, he developed abdominal discomfort and abdominal lymphadenopathy and was diagnosed with MCL based on intestinal biopsy. This work indicates that the hepatitis B virus in patients with CLL/SLL may accelerate the progress or transformation to MCL.

Keywords: Richter's syndrome, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, hepatitis B virus infection

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is common leukemia in adults and accounts for approximately 30% and 7% of lymphoid and nodal lymphomas, respectively.¹ Second malignancies are frequent complications in CLL/SLL patients, and this process is commonly referred to as Richter's syndrome (RS). About 2–8%, 0.5%, and 0.1% of CLL/SLL patients progress to diffuse large B cell lymphoma, Hodgkin's lymphoma, and multiple myeloma, respectively.² Studies show that RS is commonly associated with Epstein-Barr virus (EBV),^{2–4} karyotypic changes,⁵ and gene mutations.^{6–8} CLL/SLL usually expresses CD5 antigen, but 7–20% of CLL/SLL patients are CD5 negative.⁹ Primary gastrointestinal mantle cell lymphoma (MCL) is a rare and progressive disorder that accounts for only 1–4% of primary gastrointestinal lymphoma.¹⁰ Here, we reported an unusual case that a 61-year-old patient previously diagnosed as CD5-negative CLL/SLL developed MCL after chemotherapy and antiviral treatment.

Case report

A 61-year-old man with fever and lymph node enlargement for one month was admitted to our hospital. He had a fever (>38.5 °C) for one month, but no night sweats

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or weight loss. Physical examination showed that superficial lymphadenopathy and splenomegaly. Laboratory examination results were white blood cells $5.78 \times 10^9/L$ (45.2% lymphocytes), hemoglobin 120 g/L, and platelets $113 \times 10^9/L$. Hepatitis B virus (HBV) examination results were hepatitis B virus surface antigen (HBsAg, -), hepatitis B surface antibody (HBsAb, +), hepatitis B e antigen (HBeAg, -), hepatitis B e antibody (HBeAb, +), and hepatitis B core antibody (HBcAb, +). Hepatitis B virus-deoxyribonucleic acid (HBV-DNA) and EBV were negative. Bone marrow pathology indicated that CD20, PAX-5, CD23, Slg, and Bcl-2 were positive; SOX-11, CD3, CD5, MPO, CD34, CD10, Bcl-6, MUM-1, LEF-1 or CyclinD1 were negative, and Ki-67 staining revealed a proliferative index of 10% (Figure 1). Immunohistochemistry (IHC) of cervical lymph node showed that the lymphocytes were mature, small, and positive for CD20, PAX-5, CD21, CD23, and Bcl-2, but negative for CD3, CD5, CyclinD1, SOX-11, CD10 or Bcl-6, Ki-67 was 15% (Table 1). Flow cytometry showed that lymphocytes accounted for 68.94% nuclear cells (35.11% of B lymphocytes); CD19, CD20, and CD23 were positive, CD22 was weakly positive; CD10, CD5, FMC-7, κ , and λ were negative. Fluorescence in situ hybridization of bone marrow did not find abnormal Bcl-2 (18q21), Bcl-6(3q27), CEP8/MYC/IGH (11q13/14q32), and API2/MALT1 (11q22/18q21). IgVH, IgDH, and IgK were rearranged. Karyotype analysis showed 46, XY [20]. The above examinations supported the diagnosis of CLL/SLL (CD5 negative). He was subsequently treated with seven cycles of multi-agent chemotherapy, including cyclophosphamide, vincristine, and

Table 1 Characteristics of the patient

	CLL/SLL		MCL
Antigens	Bone marrow	Lymph node	Intestinal biopsy
CD5	-	-	+
CD3	-	-	-
CD10	-	-	-
CD20	+	+	+
CD23	+	+	-
CD21	ND	+	+
PAX-5	+	+	ND
CyclinD1	-	-	+
Bcl-2	+	+	ND
Bcl-6	-	-	-
Ki-67	10%	15%	45%
CD34	-	ND	ND
MPO	-	ND	ND
CK	ND	ND	-
SOX-11	-	-	+
LEF-1	-	ND	-
IRF-4	-	ND	-
(MUM1)			
Slg	+	ND	ND

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; ND, no detection.

prednisone (COP * 1), and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP * 6). After that his superficial lymphadenopathy disappeared, but was found with HBsAg (+), HBsAb (-), HBeAg (-), HBeAb (+) and HBcAb (+), and HBV-DNA rose to 2.656×10^5 copy/mL, and EBV was still negative (Figure 2). Then,

Figure 1 Immunohistochemistry of the patient's bone marrow: mature, and small lymphocytic (hematoxylin-eosin staining, H&E). CD20, CD23, Slg, Bcl-2, and PAX-5 were positive; CD5, LEF-1, Bcl-6, CD10, SOX-11, and CyclinD1 were negative, Ki-67 staining revealed a proliferative index of 10% (Scan 10×40).

Figure 2 HBV-DNA and EBV-DNA were detected by the patient. In October 2016, HBV-DNA of the patient was raised to 2.656×10^5 copy/mL, so far, EBV-DNA was still negative.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; EBV-DNA, Epstein-Barr virus-deoxyribonucleic acid.

after 20 months of the antiviral treatment without chemotherapy, he was found HBV-DNA negative. After the treatment, the patient had diarrhea. Computed tomography scan showed that abdominal lymphadenopathy and thickening of the intestinal wall. Electrocolonoscopy found total colonic lesions. IHC of intestinal biopsy showed positive CD5, CyclinD1, CD20, SOX-11, and CD21, and negative cytokeratin (CK), LEF-1, CD23, Bcl-6, MUM1, CD10, and CD3, Ki-67 staining revealed a proliferative index of 45% (Figure 3), t(11;14) of intestinal biopsy was detected by fluorescence in situ hybridization. This patient was diagnosed as MCL based on these results. At present, the patient is receiving further treatment.

Discussion

It is important to distinguish CLL/SLL from other small B-cell lymphoma, such as MCL, which is an aggressive and incurable non-Hodgkin lymphoma (NHL). The complete remission rate of MCL treated by chemotherapy is low, and the median overall survival of MCL is 4–5 years.¹¹ Our patient was diagnosed as gastrointestinal MCL after chemotherapy and antiviral treatment with entecavir. Although the presence of negative EBV during the treatment period was different from previous studies,^{2–4} our patient was found positive HBV-DNA after chemotherapy, and then he accepted 20 months of antiviral treatment. A recent study also shows that

Figure 3 Immunohistochemistry of the patient's intestinal biopsy (The arrow point to intestinal tumor tissue): CD5, CyclinD1, CD20, and SOX-11 were positive; CD10, CD23, and Bcl-6 were negative, Ki-67 staining revealed a proliferative index of 45% (Scan 10×40).

antiviral treatment can lead to a complete remission of hepatitis C virus (HCV)-associated low-grade NHL, suggesting a causative role of HCV in these tumors.¹² Meta-analyses further show HBV-infected patients have two- to three- fold higher risk of developing B-NHL.^{13–15} HBV is a hepatotropic virus, but can also infect lymphocytes and the lymphoid system that has been shown as an important reservoir of HBV.¹⁶ Like the scenario of EBV-driven lymphoma, HBV also directly infects B-cells, leading to the genetic alterations that contribute to tumor development.¹⁷ One possible mechanism is that like in HBV-induced hepatocellular carcinomas,¹⁸ HBV DNA can integrate into the B-cell genome, directly activate oncogenes or repress tumor suppressors, leading to tumor development and progression.

Gene mutation is another important cause for RS.^{6–8} As reported, the HBV-associated gene expression signature is contributed by the enrichment of genes regulated by BCL6, FOXO1, and ZFP36L1, which contributed to HBV-related lymphomagenesis.¹⁷ In this study, we detected IgVH, IgDH, and IgK rearrangement in our patient. The underlying molecular mechanisms of RS are largely unknown, and no reliable markers are available that may predict which CLL/SLL patients are prone to RS. Thus, more clinical data need to be further analyzed.

Conclusion

Viral or other infectious complications mimicking RS in the context of CLL/SLL with HBV infection are an essential differential diagnosis to RS. Experiences from this patient suggest we also should pay attention to other viral infections, such as HBV, especially for EBV negative patients.

Ethical approval and consent

Ethical approval for the publication of this case was obtained from the ethical committee of Anqing Municipal Hospital. The patient provided written informed consent to publish the case report and accompanying images.

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Disclosure

The authors report no conflicts of interest in this work.

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