Chronic lymphocytic leukemia-associated cholangiopathy

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CASE PRESENTATION

A 41-year-old woman with untreated low-grade B-cell chronic lymphocytic leukemia (CLL), diagnosed by peripheral blood flow cytometry nine months previously (white blood cell count $14.7 \times 10^9/L$; lymphocytes $10.4 \times 10^9/L$), was referred to the University of Calgary Liver Unit (Calgary, Alberta) with abnormal serum levels of liver enzymes: alkaline phosphatase 138 U/L to 204 U/L (normal lower than 115 U/L); aspartate aminotransferase 42 U/L (normal lower than 32 U/L); alanine aminotransferase 53 U/L (normal range 1 U/L to 40 U/L); and gamma-glutamyl transferase 115 U/L to 187 U/L (normal lower than 35 U/L). She was asymptomatic and her medical history consisted only of hypothyroidism treated with thyroxine. She was taking no other regular medications or herbal supplements. She consumed one to two standard alcoholic beverages per week. The physical examination was normal (body mass index 21 kg/m²). A screen for metabolic liver diseases was negative, as were tests for viral hepatitis. Antinuclear antibody was positive at a titre of 1:5210, with a speckled homogeneous pattern (NSP1). Rheumatoid factor was also positive (85 kU/L; normal lower than 20 kU/L). Anti-smooth muscle, antineutrophil cytoplasmic antigen, immunoglobulin A antitransglutaminase and antimitochondrial antibodies were negative. Serum immunoglobulin levels were all normal. Ultrasound of the liver was normal. Percutaneous liver biopsy was performed. The biopsy core (2 cm) included 17 portal areas; seven were expanded by a monotonous infiltrate composed predominantly of small lymphocytes. There was no parenchymal infiltrate. Bile ducts within

lymphocyte-infiltrated portal spaces were pushed toward the periphery (Figure 1). Of note, four bile ducts showed distinct lymphocytic infiltration within the biliary epithelium (cholangiopathy), resulting in a significant narrowing of the bile duct lumen (Figures 2 and 3). The lymphocytic infiltrate was further characterized by immunohistochemical staining for the following: CD3, CD5, CD10, CD20, CD23, Bcl-2, cyclin-D1 and Ki67. The results of the immunological staining profile were classical for CLL (the Bcl-2 staining is shown in Figure 4).

DISCUSSION

The association of B-cell CLL and bile duct damage has not been previously reported. The patient was treated with a combination of fludarabine (40 mg/m² orally on days 1 to 3, intravenous cyclophosphamide 750 mg/m² on day 1, and intravenous rituximab 375 mg/m² on day 1). One month later, all liver biochemical tests had completely normalized except for a persistent mild increase in serum gamma-glutamyl transferase level (73 U/L).

CLL is the most common leukemia (1) and has a variable clinical course, which can range from years of asymptomatic survival to rapid progression (2). Fifteen per cent to 27% of all hematological

Figure 1 Liver core biopsy stained with cytokeratin 19 (CTK19) demonstrating a portal tract with chronic lymphocytic leukemia infiltration and bile ducts (black arrows) pushed toward the periphery of the portal tract (original magnification $\times 10$)

Figure 2 A hematoxylin and eosin-stained liver core biopsy section showing multiple small lymphocytes invading the bile duct epithelium with reactive changes in the biliary epithelium and lumen loss (original magnification $\times 40$)

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Figure 3) Bile duct stained with cytokeratin 19 (CTK19) (brown colour). The intraepithelial lymphocyte does not stain (black arrow) while the biliary epithelium stains strongly positive for CTK19 (original magnification $\times 40$)

malignancies have liver involvement, which is diagnostic of stage IV disease (3). CLL can have a wide range of hepatic presentations (3). Baumhoer et al (3) analyzed liver biopsy specimens from 13 CLL patients and found portal infiltration in 77%; however, bile duct lesions were not detected. In our patient, leukemic B-cells were clearly seen within the bile duct basement membrane and were associated with morphologically appearing apoptotic biliary epithelial cells. The biliary lesion we have described in the context of CCL could ultimately manifest as a vanishing bile duct syndrome, as was recently described for peripheral T cell lymphoma (4), and should be added to the differential diagnosis of cholangiopathy.

Figure 4) Lymphocytes within the portal spaces were strongly positive for Bcl-2. Bcl-2 positivity is illustrated by the brown stain (original magnification $\times 20$)

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-49.
2. Boelens J, Lust S, Vanhoecke B, Offner F. Chronic lymphocytic leukaemia. *Anticancer Res* 2009;29:605-15.
3. Baumhoer D, Tzankov A, Dirnhofer S, Tornillo L, Terracciano LM. Patterns of liver infiltration in lymphoproliferative disease. *Histopathology* 2008;53:81-90.
4. Gill RM, Ferrell LD. Vanishing bile duct syndrome associated with peripheral T cell lymphoma, not otherwise specified, arising in a posttransplant setting. *Hepatology* 2010;51:1856-7.

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