Acute liver failure because of chronic lymphocytic leukemia: case report and review of the literature

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ABSTRACT

Infiltration of the liver by hematologic malignancies is an uncommon cause of liver failure. B-Cell chronic lymphocytic leukemia (CLL) is a usually indolent disease that may infiltrate the liver, but based on a review of the literature, has never been reported to induce acute liver failure. Here, we describe the case of a 78-year-old woman with acute liver failure secondary to infiltration with CLL being unresponsive to chemotherapy and causing death. This case is notable because of its atypical presentation and ultimate poor prognosis.

KEY WORDS

Chronic lymphocytic leukemia, small lymphocytic lymphoma, acute liver failure, fulminant hepatic failure

1. CASE DESCRIPTION

A 78-year-old woman presented to the Montreal General Hospital in April 2010 with a 1-week history of fever, productive cough, worsening fatigue, bilateral leg swelling, and jaundice. Three years prior to admission (PTA), she had been diagnosed with stage 0 B-cell chronic lymphocytic leukemia (CLL). Initial lymphocyte count was 10.2×10^9/L, and flow cytometry demonstrated a population of cells that were positive for CD5, CD19, CD23, and CD38. One year PTA, she developed cervical and axillary lymphadenopathy indicative of progression to stage 1 CLL. She continued to be followed without treatment. Three months PTA, she was diagnosed with deep-vein thrombosis complicated by pulmonary embolism, for which she received low molecular weight heparin. The patient was a non-smoker and non-drinker, and had no family history of cancer or gastrointestinal diseases.

Physical examination on final admission revealed dullness on percussion and fine crackles on auscultation in the lower lung fields, and also cervical, axillary, and inguinal lymphadenopathy, scleral and sublingual jaundice, and bilateral pitting leg edema. Abdominal examination revealed no masses, no hepatosplenomegaly, and no evidence of ascites.

Admission laboratory tests showed white blood cells 18.10×10^9/L (normal: $4.80–10.80\times10^9$/L), hemoglobin 100 g/L (normal: 120–160 g/L), platelets 325×10^9/L (normal: $140–440\times10^9$/L), sodium 135 mmol/L (normal: 136–147 mmol/L), and potassium 3.4 mmol/L (normal: 3.5–5.0 mmol/L). Liver function tests revealed total bilirubin 103.7 µmol/L (normal: 1.7–18.9 µmol/L), direct bilirubin 69 µmol/L (normal: 1.7–8.6 µmol/L), aspartate aminotransferase 225 U/L (normal: 10–31 U/L), alanine aminotransferase 217 U/L (normal: 10–31 U/L), alkaline phosphatase 615 U/L (normal: 53–141 U/L), gamma glutamyl transferase 478 U/L (normal: 7–50 U/L), and lactate dehydrogenase 434 U/L (normal: 110–210 U/L). Serology was negative for Epstein–Barr virus, cytomegalovirus, and hepatitis A, B, and C viruses. Screening for alcohol and acetaminophen in the blood was negative. Testing for Wilson disease, hemochromatosis, and α1-antitrypsin deficiency was unrevealing.

Imaging of the abdomen by computed tomography (CT) and ultrasonography revealed massive retroperitoneal lymphadenopathy, a normal liver and spleen, and no evidence of hepatic vascular obstruction. There was also no evidence of gallstones nor of biliary obstruction, the latter confirmed by magnetic resonance cholangiopancreatography. Doppler ultrasound of the legs showed no deep-vein thrombosis. Imaging of the chest by CT revealed areas of consolidation consistent with pneumonia, and a course of broad-spectrum antibiotics was started, with resolution of the patient's respiratory symptoms.

Liver biopsy revealed cholestasis, moderate steatosis, and in the portal spaces, prominent small lymphocytic infiltrates that co-expressed CD20, Bcl2, CD5, CD43, and faintly CD23, consistent with a diagnosis of CLL (Figure 1). There was no evidence of progression to a large B-cell lymphoma, thus ruling out a Richter transformation. A diagnosis of liver failure because of leukemic infiltration was made, and the patient was started on fludarabine, cyclophosphamide, and rituximab on hospital day 13.

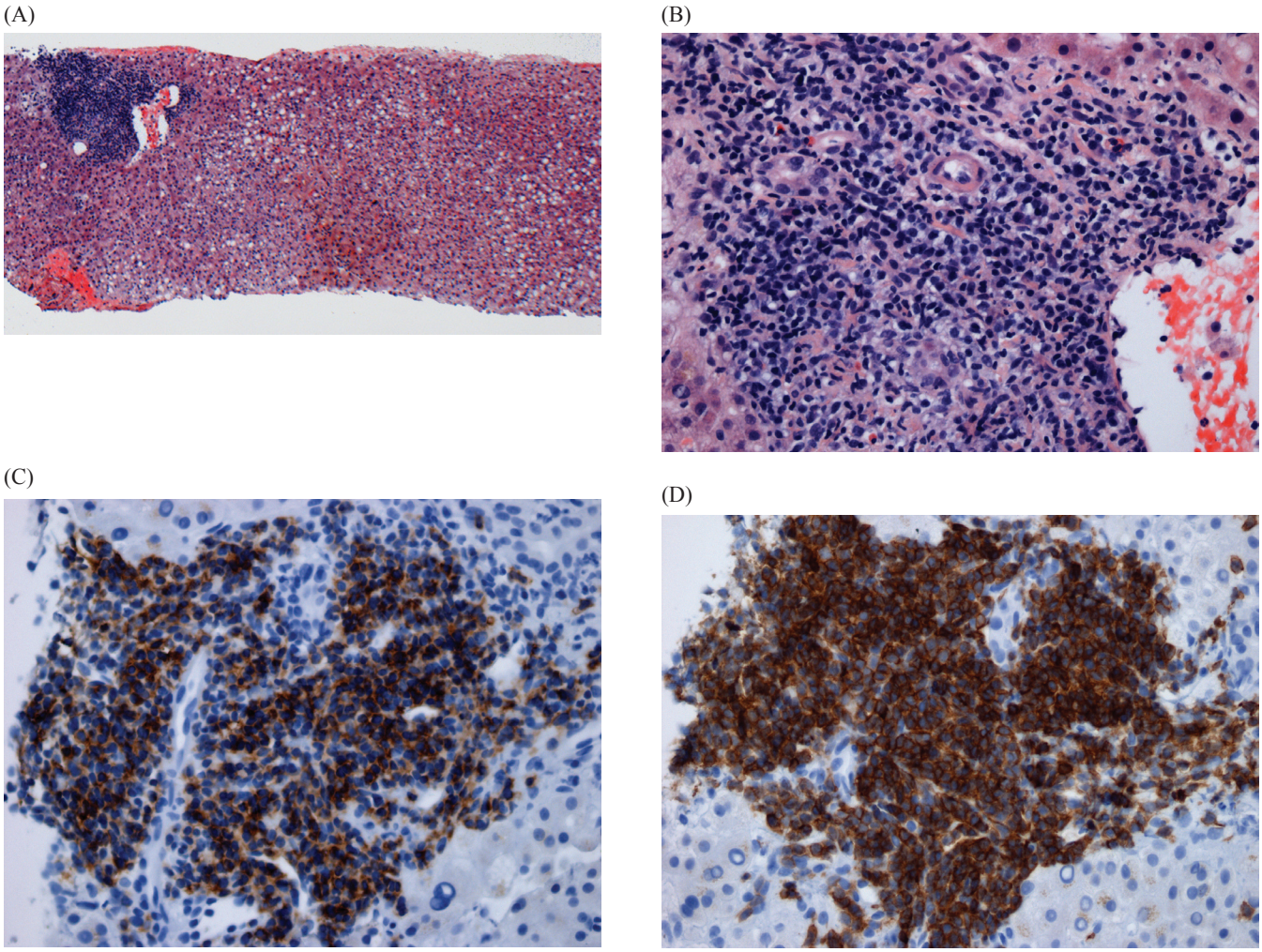

FIGURE 1 *Representative light photomicrographs of the liver biopsy, showing prominent infiltration by lymphocytes. (A) Low-power view of liver core, showing moderate steatosis and prominent portal infiltration by lymphoid cells. Hematoxylin and eosin stain, 40× magnification. (B) Higher-power view of portal tract infiltrated by small lymphoid cells. Hematoxylin and eosin stain, 200× magnification. (C) Immunohistochemical staining for CD20 confirms the B-cell phenotype of chronic lymphoid leukemia (200× magnification). (D) Immunohistochemical staining for CD5, co-expressed with CD20, is consistent with the diagnosis of chronic lymphoid leukemia (200× magnification).*

Liver function tests were closely monitored and remained unchanged during chemotherapy. Several septic episodes associated with urinary tract and upper respiratory tract infections supervened. These, combined with progressive hepatic encephalopathy, resulted in deterioration of the patient's mental status, with a decreased level of consciousness and irreversible delirium. The patient died 48 days after admission. No post-mortem examination was done.

2. DISCUSSION

Liver failure caused by infiltration of lymphoma or leukemia is uncommon and usually associated with a poor prognosis [1–3]. Hodgkin and non-Hodgkin lymphomas, acute leukemias, and transformation of chronic leukemias to acute stages have all been associated with sporadic cases of acute liver failure [4–22]. The important step in the diagnosis of such pathologies is a liver biopsy once other obstructive, toxic, and infective causes of liver failure have been ruled out by laboratory tests and imaging studies.

Based on a review of the current literature, only three cases of liver failure have so far been associated with CLL. Greer *et al.* [4] described a case of acute liver failure attributable to organ infiltration by a T-cell CLL. The patient's liver failure was unresponsive to chemotherapy, and he died of gastrointestinal bleeding and hepatorenal failure on hospital day 8. Shehab *et al.* [5] reported a case of acute liver failure caused by infiltration of a B-cell CLL which had undergone a Richter transformation to a diffuse large B-cell lymphoma. Finally, Costa *et al.* [6] described a

case of chronic liver failure that occurred over the span of 3 months because of hepatic venous outflow obstruction secondary to B-cell CLL infiltration of the liver. In the latter two cases, a course of chemotherapy resulted in reversal of liver failure and prompt resolution of symptoms.

Unlike the abovementioned cases, our patient had a CLL of B-cell origin without any evidence of Richter transformation on biopsy. Our case also differs from the Costa case because the liver failure was acute, not chronic, and not secondary to hepatic venous obstruction. Furthermore, unlike the cases presented by Shehab and Costa, our patient's symptoms were unresponsive to chemotherapy.

Usually, CLL tends to be an indolent disease with chronic infiltration of the liver. However, in the setting of a sudden and rapid clinical deterioration, histologic transformation of the CLL to a large B-cell lymphoma should be suspected. This transformation is heralded by sudden clinical deterioration, characterized by increasing lymphadenopathy, worsening of systemic symptoms, extranodal involvement, and elevated serum lactate dehydrogenase [23]. Although the patient presented here had the symptoms of a Richter transformation, liver biopsy failed to support such a diagnosis.

One marker that could explain this patient's atypical disease presentation and ultimate poor prognosis is her CD38 status, with 85% of lymphocytes being positive for this marker. Patients with CLL tend to have lower overall survival and progression-free survival if more than 30% of their lymphocytes are positive for CD38 [24,25]. However, this marker alone is unlikely to completely explain the rapid progression of our patient's disease from an asymptomatic stage to massive infiltration of the liver causing fulminant hepatic failure. Cytogenic studies, which could have revealed further chromosomal abnormalities associated with our patient's CLL, were unfortunately not performed.

3. CONCLUSIONS

In summary, this case is the first to be reported of a patient with CLL experiencing acute liver failure apparently resulting from lymphocytic infiltration of the liver. The diagnosis was based on liver biopsy when all other clinical causes of liver failure were ruled out by laboratory tests and medical imaging. The treatment regimen had no effect on progression of the patient's disease, and she died 48 days after admission.

4. ACKNOWLEDGMENTS

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5. CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

6. REFERENCES

1. Lee WM. Acute liver failure. *N Engl J Med* 1993;329:1862–72.
2. Myszor MF, Record CO. Primary and secondary malignant disease of the liver and fulminant hepatic failure. *J Clin Gastroenterol* 1990;12:441–6.
3. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut* 1998;42:576–80.
4. Greer J, Cousar J, Miller R, *et al.* T4+ (helper phenotype) chronic lymphocytic leukemia: case report with liver failure and literature review. *Med Pediatr Oncol* 1988;16:356–62.
5. Shehab TM, Kaminski MS, Lok AS. Acute liver failure due to hepatic involvement by hematologic malignancy. *Dig Dis Sci* 1997;42:1400–5.
6. Costa F, Choy CG, Seiter K, Hann L, Thung SN, Michaeli J. Hepatic outflow obstruction and liver failure due to leukemic cell infiltration in chronic lymphocytic leukemia. *Leuk Lymphoma* 1998;30:403–10.
7. Padilla GF, Garibay MA, Hummel HN, Avila R, Méndez A, Ramírez R. Fulminant non-Hodgkin lymphoma presenting as lactic acidosis and acute liver failure: case report and literature review [Spanish]. *Acta Gastroenterol Latinoam* 2009;39:129–34.
8. Dellon ES, Morris SR, Tang W, Dunphy CH, Russo MW. Acute liver failure due to natural killer–like T-cell leukemia/lymphoma: a case report and review of the literature. *World J Gastroenterol* 2006;12:4089–92.
9. Kojima H, Shimizu S, Yoshida C, *et al.* Rapidly progressive Lennert's lymphoma terminating in fulminant hepatic failure. *Leuk Lymphoma* 2003;44:1409–12.
10. Santos ES, Raez LE, Salvatierra J, Morgensztern D, Shanmugan N, Neff GW. Primary hepatic non-Hodgkin's lymphomas: case report and review of the literature. *Am J Gastroenterol* 2003;98:2789–93.
11. Lettieri CJ, Berg BW. Clinical features of non-Hodgkin's lymphoma presenting with acute liver failure: a report of five cases and review of published experience. *Am J Gastroenterol* 2003;98:1641–6.
12. Thompson DR, Faust TW, Stone MJ, Polter DE. Hepatic failure as the presenting manifestation of malignant lymphoma. *Clin Lymphoma* 2001;2:123–8.
13. Yeshurun M, Isnard F, Garderet L, *et al.* Acute liver failure as an initial manifestation of low-grade non-Hodgkin's lymphoma transformation into large-cell lymphoma. *Leuk Lymphoma* 2001;42:555–9.
14. Morali GA, Rozenmann E, Ashkenazi J, Munter G, Braverman DZ. Acute liver failure as the sole manifestation of relapsing non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol* 2001;13:1241–3.
15. Anderson SH, Richardson P, Wendon J, Pagliuca A, Portmann B. Acute liver failure as the initial manifestation of acute leukaemia. *Liver* 2001;21:287–92.
16. Stewart KS, Gordon MC. Non-Hodgkin lymphoma in pregnancy presenting as acute liver failure. *Obstet Gynecol* 1999;94:847.
17. Suzuki N, Tsuji H, Nakamura S, Asabe H, Sueishi K, Fujishima M. An autopsy case of Ki-1 lymphoma associated with hepatic failure. *Am J Gastroenterol* 1998;93:115–17.

18. Souto P, Romaozinho JM, Figueiredo P, *et al.* Severe acute liver failure as the initial manifestation of haematological malignancy. *Eur J Gastroenterol Hepatol* 1997;9:1113–15.
19. Yoshikawa M, Yamane Y, Yoneda S, *et al.* Acute hepatic failure due to hepatosplenic B-cell non-Hodgkin's lymphoma in a patient infected with hepatitis C virus. *J Gastroenterol* 1998;33:880–5.
20. Woolf GM, Petrovic LM, Rojter SE, *et al.* Acute liver failure due to lymphoma. A diagnostic concern when considering liver transplantation. *Dig Dis Sci* 1994;39:1351–8.
21. Zafrani ES, Gaulard P. Primary lymphoma of the liver. *Liver* 1993;13:57–61.
22. Salo J, Nomdedeu B, Bruguera M, *et al.* Acute liver failure due to non-Hodgkin's lymphoma. *Am J Gastroenterol* 1993;88:774–6.
23. Robertson LE, Pugh W, O'Brien S, *et al.* Richter's syndrome: a report on 39 patients. *J Clin Oncol* 1993;11:1985–9.
24. Van Bockstaele F, Verhasselt B, Philippe J. Prognostic markers in chronic lymphocytic leukemia: a comprehensive review. *Blood Rev* 2009;23:25–47.
25. Jelinek DF, Tschumper RC, Geyer SM, *et al.* Analysis of clonal B-cell CD38 and immunoglobulin variable region sequence status in relation to clinical outcome for B-chronic lymphocytic leukaemia. *Br J Haematol* 2001;115:854–61.

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