CASE REPORT

Richter's transformation presenting as splenic rupture after 6 years of complete remission of chronic lymphocytic leukaemia

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SUMMARY

Richter's transformation is a rare clinical condition occurring in about 5–10% of patients with chronic lymphocytic leukaemia (CLL). Patients usually present with lymphadenopathy, hepatosplenomegaly and elevated serum lactate dehydrogenase levels. These patients have a very poor prognosis with a median survival of about 10 months. We present a patient, with a history of CLL in complete remission, who presented with splenic rupture requiring splenectomy. She was eventually diagnosed with diffuse large B-cell lymphoma with Richter's transformation.

BACKGROUND

Richter's transformation is an uncommon clinical phenomenon, which occurs due to the development of lymphoma in patients with known diagnosis of CLL. There are multiple immune and genetic factors responsible for this, and no clear risk factors have been identified. Hepatosplenomegaly is one of the presenting symptoms in this condition. We present a rare case of Richter's transformation which presented with splenic rupture requiring urgent medical intervention.

CASE PRESENTATION

Our patient is a 71-year-old Caucasian woman who presented to the emergency department (ED) with symptoms of nausea, early satiety and lethargy for 1 week and dyspnoea on exertion along with mild lower left quadrant abdominal discomfort for 1 day. The patient was diagnosed with CLL 6 years ago and was treated with cytoxan withfludarabine. She has been in under complete remission since then. Her past medical conditions include history of deep vein thrombosis in her lower limb and paroxysmal atrial fibrillation on anti-coagulation. The patient denied any history of smoking or alcohol abuse, and her family history was significant for lung cancer in her father.

The initial examination in the ED showed that the patient was afebrile and her vitals were within normal limits. Abdominal examination in the ED revealed mild discomfort on palpation in the lower left quadrant of the abdomen, which was non-radiating. Rest of her systemic examination was unremarkable. Her complete blood count was significant for a white cell count of 3.1K/CMM, red blood cell count of 2.66 M/CUMM, haematocrit of 24.6%, platelets of 87K/CMM, mean platelet

volume of 7.3 fL, mean corpuscular volume of 92.5 fL, mean corpuscular haemoglobin of 31.2 pg, mean corpuscular haemoglobin concentration of 32.9%, red cell distribution width of 16.6% and haemoglobin of 8.4 mg/dL, which was reduced compared to her baseline of 10–11 mg/dL. Her creatinine clearance was also decreased. Our initial impression was acute diverticulitis, acute kidney injury due to dehydration and symptomatic anaemia. Further workup revealed elevated lactate dehydrogenase level of 2275 IU/L (n=116–243 IU/L), normal liver function tests, reduced haptoglobin (<10 mg/dL), normal uric acid 7.7 mg/dL (n=2.6–8.1 mg/dL) negative coombs test, negative stool occult test, normal serum iron, serum folate, serum vitamin B₁₂ levels and peripheral smear showed absolute monocytosis and neutrophilia, nucleated RBCs and the presence of smudge cells. We attributed the anaemia to haemolysis with possible bone marrow involvement.

INVESTIGATIONS

A CT of the abdomen without contrast was done on admission which showed acute diverticulitis, massive splenomegaly of 25.3 cm along with sub-capsular haemorrhage (figure 1). The patient's haemoglobin remained stable and her renal function improved with intravenous fluids. On the fourth day, the patient's hospital course was complicated by hypovolemic shock with a blood pressure of 80/50 mm Hg and drop in haemoglobin to 6.4 mg/dL. The patient required multiple fluid and blood transfusions. A repeat CT scan of abdomen

Figure 1 CT scan of abdomen without contrast showing blood in the splenic capsule.

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Figure 2 CT scan of abdomen with contrast showing worsening haemorrhage around the spleen.

and pelvis with contrast revealed an increase in the size of the subcapsular haematoma of the spleen along with new splenic intraparenchymal haemorrhage (figure 2).

DIFFERENTIAL DIAGNOSIS

Our initial impression during the admission was that the patient had acute diverticulitis and haemolytic anaemia. The initial CT scan showed splenomegaly which was attributed to CLL. She likely had a splenic laceration due to the mechanical sheer stress.

TREATMENT

The patient was taken to operation theatre for an urgent exploratory laparotomy on the fourth day. It revealed a hemoperitoneum along with a lacerated spleen. The hemoperitoneum was evacuated and a splenectomy was performed. The spleen was sent to pathology, which revealed an enlarged spleen measuring 28×17×9 cm and weighing 1920 g. The laceration measured about 12×1.5×1 cm and the spleen revealed nodular proliferation of large transformed B-lymphocytes with positive immunohistochemistry for CD 20, CD5, (figures 3–8), thus confirming diagnosis of large B-cell lymphoma and Richter's transformation.

OUTCOME AND FOLLOW-UP

The patient's hospital course was complicated due to multiple factors. This included infection, poor cardiovascular and respiratory status requiring prolonged hospital stay. The patient was

Figure 3 Gross image of the spleen showing an enlarged spleen measuring 28×17×9 cm and weighing 1920 g. The laceration measures 12×1.5×1 cm. The capsule surface is pink-white, smooth and glistening.

Figure 4 Microscopic image of spleen (H&E, ×10) showing large lymphoid cells in a nodular growth separated by small lymphoid cells.

started on rituximab and she received only one dose. The patient failed to show any meaningful recovery and her cardio-respiratory status continued to decline. She was thus eventually transferred to hospice care where she passed away.

DISCUSSION

The most common leukaemia in the western world is CLL with a median age of diagnosis of 72 years.¹ Richter's transformation is a pathological term used for the description of rapid development of an aggressive lymphoma proved histologically.² The most common type seen is diffuse large B-cell lymphoma. In USA, the incidence of Richter's transformation ranges from 2% to 10%.³ The survival time period was reported to range between a few weeks to up to 15 years. The percentage of Richter's transformation in a CLL patient is reported to be 9%⁴ and 10.7%⁵ as per two studies. The median time for the transformation is about 23 months from the date of diagnosis of CLL.⁴ Our patient had a diagnosis of CLL when she was 65 years old and developed Richter's transformation 6 years later after the initial diagnosis of CLL.

The development of Richter's transformation is influenced by multiple immune and genetic factors which is poorly understood. The diffuse large B-cell lymphoma is the most common type and it is different from de novo diffuse large B-cell lymphoma. Non-del13q14 abnormalities in CLL cells are considered a

Figure 5 Higher magnification (H&E, ×40) of splenic lesion showing large lymphocytes with pleomorphism, conspicuous nucleoli and mitosis.

Figure 6 CD20 immunostain of splenic lesion showing strong membranous positivity (x40).

Figure 8 CD10 immunostain of splenic lesion is negative in large lymphoid cells (x10).

risk factor for Richter's transformation.⁶ Molecular profiling of 84 patients with Richter's transformation showed that *TP53* disruption (47.1%) and *c-MYC* abnormalities (26.2%) were the most common genetic lesions.⁷ Few studies have reported that the presence of Epstein-Barr virus is a risk factor for the development of Richter's transformation, but it is more commonly associated with the Hodgkin's variant.⁸ In 2008, Rossi and Gaidano⁹ conducted a pilot study and reported the following as predisposing factors for Richter's transformation: *CD38* expression ($CD38 \geq 30\%$), stereotyped B-cell receptor, *IGHV4-39* gene usage, telomere length < 5000 bp, lymph node size > 3 cm, and absence of *del13q14*. It was unclear whether our patient had any of the above-mentioned risk factors and there was no genetic testing done during her stay in the hospital.

Patient with Richter's transformation usually present with sudden clinical deterioration, characterised by a marked lymphadenopathy, splenomegaly, worsening 'B' symptoms (ie, fever, night sweats, weight loss). Serum lactate dehydrogenase is elevated in about 50–80% of the patients, anaemia with haemoglobin < 11 g/dL is seen in 50% of the patients and thrombocytopenia with a count of $< 100\,000/\mu\text{L}$ seen in 43% of the patients.¹⁰ Our patient had symptoms of fever, fatigue, elevated lactate dehydrogenase and anaemia on admission. For initial evaluation, radiological imaging with ^{18}F -FDG PET/CT

(^{18}F -2-deoxy-2-fluoro-d-glucose-labelled positron emission tomography) has a high sensitivity and a high negative predictive value in detecting Richter's transformation.¹¹ One study shows that bone marrow biopsy showing a combination of large cells and $\beta(2)$ -M can be used for the diagnosis of Richter's transformation.¹² Biopsy with pathological differentiation remains the gold standard for the diagnosis of Richter's transformation. Imaging can be used to guide in identifying the potential lymph nodes for biopsy.⁶ Since our patient had abdominal pain with worsening anaemia, the CT scan was done. It revealed splenic rupture and she had an emergent laparotomy along with splenectomy. Histologically, specimens show large lymphoma cells which are typical and distinct from the CLL cells and they are moderately irregular or round, with vesicular nuclei and prominent nucleoli.¹ CD20 expression is generally bright, while CD5 and CD23 expression may be dim to negative.⁶ Rarely, Richter's transformation of the Hodgkin's variety can present with Reed Sternberg cells, with expression of CD15 and CD30 by the R-S cells.¹³ In our patient, the histology of spleen revealed nodular proliferation of large transformed B-lymphocytes and positive immunohistochemistry for CD20 and CD5 (figures 4–8).

Richter's transformation has a rapidly progressive clinical course with limited treatment options due to the extensive tumour burden and poor performance of patients. Historically, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) has been the standard of treatment for these patients.¹⁴ A retrospective study at MD Anderson Cancer Center in 12 patients showed an overall response rate of 50% and a median survival was 15 months.¹⁵ Another accepted regimen is hyper CVXD regimen (fractionated cyclophosphamide, vincristine, liposomal daunorubicin and dexamethasone) with an overall response rate of 41%.¹⁶ Multiple trials and different combination of chemotherapy regimens have been studied for the treatment of Richter's transformation, but the discussion regarding all the trials is beyond the scope of this article. Irrespective of this, the patients have a very poor prognosis with a median survival of ~ 62 months with clonally unrelated Richter's transformation compared to that of 8–14 months in patients with clonally related Richter's transformation. Our patient had a complicated course in the hospital with very poor prognosis. Even though she was initially started on rituximab, further chemotherapy was not possible as her clinical condition continued to deteriorate and she was eventually transferred to hospice care.

Figure 7 CD5 immunostain of splenic lesion showing membranous positivity in some of the large cells and small lymphocytes (x10).

Learning points

- ▶ Patients with CLL have the risk of Richter's transformation during their lifetime which is influenced by multiple genetic and immunological factors.
- ▶ Though hepatosplenomegaly, elevated LDH and enlarged lymph nodes are some of the presenting symptoms in this condition, the possibility of life-threatening splenomegaly along with laceration should also be kept in mind during evaluation for the same.
- ▶ Patients with history of CLL must be educated about these symptoms and signs and to approach medical care when in doubt.
- ▶ They should also be screened periodically with blood tests and imaging for earlier diagnosis and treatment.

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Competing interests None declared.

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REFERENCES

- 1 Hallek M, Cheson BD, Catovsky D, *et al.* Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;111:5446–56.
- 2 Lortholary P, Boiron M, Ripault P, *et al.* [chronic lymphocytic leukemia secondarily associated with a malignant reticulopathy: Richter's syndrome]. *Nouv Rev Fr Hematol* 1964;4:621–44.
- 3 Molica S. A systematic review on Richter syndrome: what is the published evidence? *Leuk Lymphoma* 2010;51:415–21.
- 4 Rossi D, Cerri M, Capello D, *et al.* Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter syndrome. *Br J Haematol* 2008;142:202–15.
- 5 Fan L, Wang L, Zhang R, *et al.* Richter transformation in 16 of 149 Chinese patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 2012;53:1749–56.
- 6 Jain P, O'Brien S. Richter's transformation in chronic lymphocytic leukemia. *Oncology (Williston Park, NY)* 2012;26:1146–52.
- 7 Rossi D, Spina V, Deambrogi C, *et al.* The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood* 2011;117:3391–401.
- 8 Tzankov A, Fong D. Hodgkin's disease variant of Richter's syndrome clonally related to chronic lymphocytic leukemia arises in ZAP-70 negative mutated CLL. *Med Hypotheses* 2006;66:577–9.
- 9 Rossi D, Gaidano G. Richter syndrome: molecular insights and clinical perspectives. *Hematol Oncol* 2009;27:1–10.
- 10 Robertson LE, Pugh W, O'Brien S, *et al.* Richter's syndrome: a report on 39 patients. *J Clin Oncol* 1993;11:1985–9.
- 11 Bruzzi JF, Macapinlac H, Tsimberidou AM, *et al.* Detection of Richter's transformation of chronic lymphocytic leukemia by PET/CT. *J Nucl Med* 2006;47:1267–73.
- 12 Ma Y, Mansour A, Bekele BN, *et al.* The clinical significance of large cells in bone marrow in patients with chronic lymphocytic leukemia. *Cancer* 2004;100:2167–75.
- 13 Mao Z, Quintanilla-Martinez L, Raffeld M, *et al.* IgVH mutational status and clonality analysis of Richter's transformation: diffuse large B-cell lymphoma and Hodgkin lymphoma in association with B-cell chronic lymphocytic leukemia (B-CLL) represent 2 different pathways of disease evolution. *Am J Surg Pathol* 2007;31:1605–14.
- 14 Coiffier B, Lepage E, Briere J, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235–42.
- 15 Tsimberidou AM, Wierda WG, Wen S, *et al.* Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. *Clin Lymph Myel Leuk* 2013;13:568–74.
- 16 Dabaja BS, O'Brien SM, Kantarjian HM, *et al.* Fractionated cyclophosphamide, vincristine, liposomal daunorubicin (daunoXome), and dexamethasone (hyperCVXD) regimen in Richter's syndrome. *Leuk Lymphoma* 2001;42:329–37.

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