

Case report 2

Lymphomas with massive splenomegaly – a case series

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Abstract

Hairy cell leukaemia (HCL) is an uncommon chronic B-cell lymphoma. Classical HCL and its variant are separate entities. Splenic marginal zone lymphoma (SMZL) is rare accounting for <2% of lymphoid neoplasms². A 62-year-old woman presented with constitutional symptoms and mild splenomegaly was having pancytopenia, monocytopenia and hairy cells in the peripheral blood. Bone marrow aspiration was a dry tap while trephine biopsy revealed diffuse lymphoid cell infiltration with characteristic fried egg appearance and fibrosis. Morphological and immunophenotypic diagnosis was HCL. She was successfully treated with IV-cladribine and G-CSF for chemotherapy induced severe neutropenia. She achieved complete remission in 6 months. A 56-year-old woman presented with abdominal distension and lower limb swelling was having marked splenomegaly, absolute lymphocytosis, mild neutropenia and anaemia. Blood film revealed lymphocytes showing moderate

cytoplasm and cytoplasmic projections. With bone marrow biopsy and flow cytometry, splenic B-cell lymphoma/leukaemia with prominent nucleoli was diagnosed and was treated with rituximab monotherapy. A 76-year-old woman presented with progressive abdominal fullness, unintentional weight loss and early satiety was having splenomegaly, bicytopenia and absolute lymphocytosis consisting predominantly of small mature lymphocytes and occasional lymphocytes with polar villi. Morphological and immunophenotypic results confirmed SMZL. She was treated with rituximab monotherapy.

Introduction

Malignant lymphomas account for a relevant, yet probably underestimated number of cases among the causes of isolated splenomegaly. As a secondary lymphoid organ, spleen may be involved by lymphoid neoplasms during their dissemination process. However it rarely represents the exclusive site of lymphomatous burden. Lymphomas commonly presenting as splenic lymphomas are splenic marginal zone lymphoma (SMZL), splenic diffuse red pulp B-cell lymphoma, hairy cell leukaemia, hairy cell leukaemia-variant, B-prolymphocytic lymphoma, T-large granulocytic lymphoma and hepatosplenic T-cell lymphoma⁴. Cells with cytoplasmic expansions in peripheral blood have been described in a variety of small B-cell lymphomas including splenic lymphoma with villous lymphocytes (SLVL), hairy cell leukaemia (HCL) and hairy cell leukaemia variant (HCL-V).

Here we discuss three case reports of HCL, splenic B cell lymphoma/leukaemia with prominent

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nucleoli formerly known as HCL-V and SMZL which were successfully managed at Colombo South Teaching Hospital, Sri Lanka in 2023.

Case 1

A 62-year-old woman, with diabetes, hypertension and hypothyroidism presented with generalised body weakness, malaise, loss of appetite and loss of weight for 1 month. She had no shortness of breath, bleeding manifestations or recurrent infections. On examination she was afebrile and pale and had mild splenomegaly with no hepatomegaly or lymphadenopathy.

On investigation, FBC revealed WBC $2.6 \times 10^9/L$ with moderate neutropenia ($0.79 \times 10^9/L$), monocytopenia ($0.02 \times 10^9/L$), severe anaemia (Hb-45g/L) and marked thrombocytopenia ($PLT-47 \times 10^9/L$). Her ESR 142mm/1st hr, CRP <5, serum LDH 210U/L and DAT was negative. Liver and renal function tests were normal. Abdominal ultrasound scan revealed mild splenomegaly (14cm) with no hepatomegaly or lymphadenopathy. In the blood picture there were normochromic normocytic red cells, teardrop cells, polychromatic cells and occasional nucleated red blood cells. There were lymphocytes with circumferential villi.

The bone marrow aspirate which was a dry tap showed small to medium sized atypical lymphoid cells with clumped chromatin. Some cells showed nuclei with ground glass chromatin appearance and circumferential villi. In flow cytometry CD45/SSC plot, 17% cells were gated in the region expected for lymphocytes. Out of these, 44.3% were CD19 positive clonal B-cells with surface Ig-kappa restriction (bright). These B-cells were positive for CD20, CD79a, CD123, CD103, CD11c (moderate) and negative for CD5 and CD10. In trephine biopsy, 80% of bone marrow cellularity was a diffuse infiltrate of atypical lymphoid cells with abundant cytoplasm with characteristic 'fried egg appearance' and mild to moderate fibrosis with suppressed trilineage haemopoiesis. Given the classic morphological and immunophenotypic features, she was diagnosed as HCL.

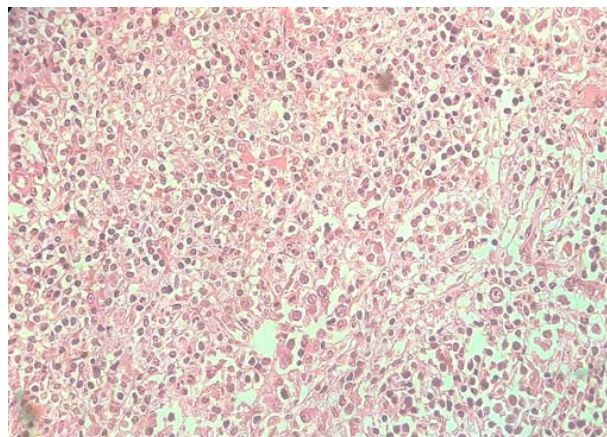


Figure 1. Bone marrow trephine (H&E stain x 40) high power view of the diffuse infiltration of atypical lymphoid cells with characteristic 'fried egg appearance'.

As she was having pancytopenia (Hb<100g/L, $PLT < 100 \times 10^9/L$ and $N < 1 \times 10^9/L$) treatment was indicated. In pre-treatment evaluation, the coagulation profile was normal, virology screening (hepatitis-B surface antibody, hepatitis-C antibody, EBV serology and HIV antibodies) was negative, TSH, serum calcium, chest X-ray, ECG, 2D-echo and dental assessment were normal while her ECOG status was 1. Only splenomegaly of 18.3cm which has increased in size compared to USS-abdomen was revealed in CT neck/chest/abdomen/pelvis.

She was treated with IV-cladribine with slight dose modifications and supportive treatment was given with fluconazole, allopurinol acyclovir and omeprazole. On day-7 of treatment, she developed severe neutropenia without a focus of infection, which was successfully treated with S/C-G-CSF 300 microgram daily for 3 days initially and alternate days for 3 days.

Case 2

A 56-year-old previously healthy woman presented to Base Hospital, Balapitiya with abdominal distension and discomfort of 2 months and B/L lower limb swelling of 1 week. She also complained of sleepiness, increased tiredness, loss of weight >10% from baseline, loss of appetite and early satiety. She denied evening pyrexia, drenching night sweats, recurrent infections or

bleeding manifestations. She was not on any medication and had no known allergies. Her baseline investigations revealed severe anaemia which needed 2 units of red cell concentrate transfusion.

On examination, she was pale, afebrile, anicteric and there was no peripheral lymphadenopathy. There was splenomegaly 20cm below left costal margin.

Her FBC showed WBC $5.96 \times 10^9/L$, absolute neutrophil count $1.12 \times 10^9/L$ and lymphocyte count $4.84 \times 10^9/L$. Haemoglobin was 64g/L with MCV 103fL and platelet count was $59 \times 10^9/L$. Her ESR was 70mm/1sthr which was high for her age and sex with CRP <5. Liver transaminases and bilirubin were normal with total protein 58.1g/L and albumin 34g/L. Renal functions were normal. Her LDH was elevated; 666U/L. Moderate to gross splenomegaly (25cm) with normal liver was seen in USS-abdomen. Blood picture revealed normochromic normocytic red cells, macrocytes and an absolute lymphocytosis with occasional lymphocytes showing moderate cytoplasm and cytoplasmic projections, variably clumped chromatin and nucleoli. Platelets were moderately low.

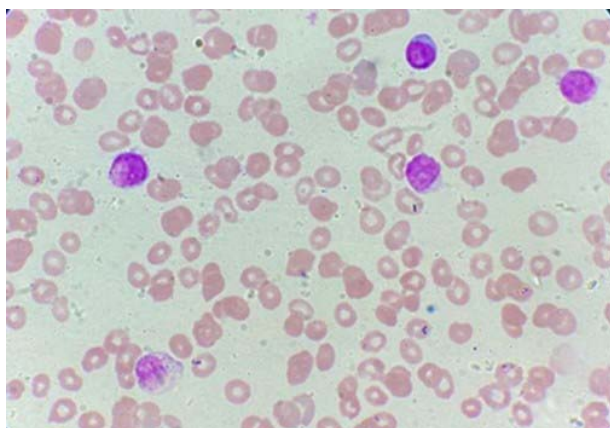


Figure 2. Blood film (Leishman stain x 40) with lymphocytes showing moderate cytoplasm and cytoplasmic projections.

Bone marrow aspiration showed markedly hypercellular marrow fragments and cell trails with 42% small mature lymphoid cells with some showing moderate cytoplasm and cytoplasmic

projections. All other cell lines were suppressed. Trephine biopsy confirmed the diffuse infiltrate of small mature lymphoid cells accounting for 80% of marrow cellularity and suppression of trilineage haemopoiesis. Immunophenotyping by flow cytometry revealed bone marrow infiltration by a CD20 positive, CD5 and CD10 negative mature B-cell neoplasm that was also CD11C positive and CD25, CD103, CD123, CD200 negative.

Massive splenomegaly of 27cm with dilated portal vein and mild hepatomegaly of 17cm was shown in CE-CT chest/abdomen/pelvis. There was no lymphadenopathy. Serum protein electrophoresis was normal.

With above morphological and immunophenotypical findings splenic B-cell lymphoma/leukaemia with prominent nucleoli (HCL-V) was diagnosed.

It was decided to treat her with rituximab monotherapy 6-8 cycles. Pre-treatment evaluation was done. Virology screening and mantoux test was negative. Cardiac assessment with 2D-echo revealed good biventricular function and 55% ejection fraction but had grade-III MR. Her ECOG performance score was 1. After obtaining informed written consent, she was commenced on IV-rituximab 375mg/m² weekly.

She was given 8 cycles of weekly rituximab with no treatment related complications. After the 8th cycle splenomegaly was reduced to 12 cm below the costal margin and WBC was $3.72 \times 10^9/L$ with neutrophils $1.25 \times 10^9/L$ and lymphocytes $1.89 \times 10^9/L$. Haemoglobin was 13.8g/dL and platelet count has risen to $97 \times 10^9/L$. She was considered to have obtained partial response to rituximab monotherapy. Now she is on 2 monthly follow up at haematology clinic.

Case 3

A 76-year-old woman, with a history of right sided ischemic stroke, with progressively worsening abdominal fullness and discomfort over 1 year. She also complained of unintentional weight loss and early satiety for 1-2 months but denied loss of appetite evening pyrexia or drenching night

sweats. On examination, she was ill looking, cachectic, pale and had moderate splenomegaly of 8cm below left costal margin but no hepatomegaly or lymphadenopathy.

Her investigations revealed Hb 61g/L, MCV 100.6fL, MCHC 30g/dL, WBC 13×10^9 /L, absolute lymphocyte count 10×10^9 /L, platelets 38×10^9 /L and reticulocyte count 4%. Blood picture showed leucocytosis with absolute lymphocytosis, predominantly of small mature lymphocytes and occasional lymphocytes with polar villi suggestive of a chronic lymphoproliferative disorder more in favour of SMZL.

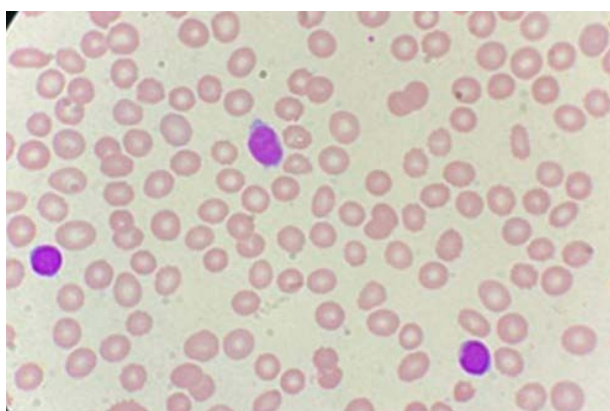


Figure 3. Blood film (Leishman stain $\times 40$) showing lymphocytes with polar villi.

Her ESR was 110mm/1st hr and reticulocyte index was 4.3%. USS-abdomen demonstrated moderate splenomegaly (15.6x7.2cm) and CE-CT neck/chest/abdomen/pelvis confirmed moderate splenomegaly (13.9x10.8x6.4cm) with no lymphadenopathy. She had elevated serum creatinine of 1.7mg/dL (creatinine clearance 24mL/min), LDH 462U/L and uric acid 408 micromol/L and normal baseline liver function tests. Bone marrow showed diffuse interstitial infiltration of monomorphic small mature lymphocytes accounting for 65-70% of marrow cellularity and flow cytometry of bone marrow revealed a CD20 positive, CD5 negative, surface membrane immunoglobulin kappa light chain restricted clonal B-lymphocyte population. Serum protein electrophoresis revealed polyclonal hyper-gammaglobulinaemia.

Given the above clinical presentation, morphological and immunophenotypical features excluding other subtypes, SMZL was diagnosed.

It was decided to give 4-6 cycles of rituximab monotherapy depending on her response to treatment. Pre-treatment assessment demonstrated negative virology screening and mantoux test with good biventricular function and 60% ejection fraction in the 2D-echocardiogram. Her ECOG performance score was 1. After informed written consent, as there was evidence of haemolysis she was started on IV-rituximab 375mg/m² weekly instead of monthly protocol.

Discussion

Hairy cell leukaemia is a cytologically and immunophenotypically distinct neoplasm of small mature lymphoid cells with oval nuclei and characteristic abundant cytoplasm with hairy projections involving peripheral blood and diffuse infiltration of bone marrow and splenic red pulp¹. It is a rare, chronic B-cell leukaemia accounting for 2% of leukaemias with a male predominance and median age at diagnosis of 58 years².

The peripheral blood film shows medium sized lymphoid cells with an oval or intended (kidney shaped) nucleus with homogenous, spongy, ground glass chromatin, slightly less clumped than that of normal lymphocytes with typically absent or inconspicuous nucleoli. The cytoplasm is abundant and pale blue with circumferential hairy projections¹.

Bone marrow aspiration often results in a dry tap due to fibrosis induced by the hairy cell infiltrate. Bone marrow trephine biopsy often shows patchy infiltration. The hairy cell infiltrate is characterised by widely spaced lymphoid cells and the pattern of marrow involvement is commonly interstitial, becoming diffuse and creating a honeycomb appearance. 'Blood lake' pseudo sinus formation may be seen. Reticulin fibrosis may be present¹.

The classic immunophenotypic profile of HCL is bright phenotypic surface immunoglobulin, bright co-expression of CD20, CD22, CD11c, expression of CD103, CD25, CD123, TBX21, annexin-A1, FMC7, CD200 and cyclin-D1. Most cases of HCL lack both CD5 and CD10. BRAF-V600E mutation present in virtually 100% of cases of classical HCL is regarded as a disease defining event¹.

Treatment indications are bulky or progressive splenomegaly, cytopenias ($Hb < 100g/L$, $PLT < 100 \times 10^9/L$, $N < 1 \times 10^9/L$), recurrent or severe infections and systemic symptoms². Our patient was having pancytopenia therefore started on treatment.

Purine nucleoside analogues, pentostatin and cladribine remain the standard front line treatment with an overall response of 90-100%. Cladribine can be administered in as a 7 day continuous IV-infusion, daily or weekly IV-infusions or subcutaneous injection². According to British Journal of Haematology, considering the availability and cost effectiveness, the drug regimen selected was cladribine 0.14mg/kg/d as an IV-infusion over 2 hours for five consecutive days which needed five cladribine 10mg vials for the course. As the daily dose requirement was only 7.56mg according to the selected regime, >2mg daily wastage was there from one vial. The cost of cladribine was very high. Considering financial constraints and wastage, the calculated total dose ($0.14mg/kg \times 5 = 37.5mg$) was given in 4 days instead of 5 days, yielding only 4 cladribine vials with minimal wastage. (D1-7.5mg, D2, D3 and D4 10mg each).

Both pentostatin and cladribine cause temporary myelosuppression and more prolonged immunosuppression. G-CSF and prophylactic anti-infective agents such as co-trimoxazole and aciclovir could be initiated during treatment and continued for up to 6 months or until adequate neutrophil and lymphocyte recovery. They needed be commenced after 5 days of cladribine as concurrent multi-drug treatment can cause rashes that may be confused as reaction to cladribine. Following purine analogues, irradiated blood products should be given in need of transfusions².

Response assessment includes bone marrow trephine biopsy done at-least 4 to 6 months after completion of cladribine therapy. Complete remission is defined as absence of hairy cells from peripheral blood and bone marrow along with resolution of organomegaly and cytopenias. When the cytopenias are normalised and no hairy cells seen in peripheral blood, but only 50% improvement in organomegaly and bone marrow findings, it is considered a partial response which requires a second course of cladribine to achieve complete

response². In response assessment, CD20 staining in conjunction with morphological assessment is recommended, with use of DBA44 to identify subtle residual infiltration².

Compared to HCL, HCL-V exhibits variant cytological and haematological features such as leucocytosis, presence of monocytes, lymphocytes with prominent nucleoli, plastic or convoluted nuclei and/or absence of circumferential shaggy contours. Unlike in classic HCL, bone marrow is aspirable, without significant reticulin fibrosis. They also have variant immunophenotype including absent CD25, CD123, annexin-A1 and tartrate resistant acid phosphatase. Positive markers include CD72, pan-B-cell antigens, CD11c, bright phenotypic surface immunoglobulin and FMC-7. There may be expression of CD103. Have wild type BRAF and are resistant to conventional HCL therapy with lack of response to cladribine¹. It is recommended that cladribine plus rituximab be used as first line therapy, based on small published series showing improvement in outcome with the combination. Splenectomy may be considered in refractory cases to alleviate symptoms and cytopenias².

Splenic marginal zone lymphoma (SMZL) makes up <2% of all lymphoid malignancies and 20% of all marginal zone lymphomas, can transform to diffuse large B-cell lymphoma in approximately 5-10% of cases⁵. SMZL is a B-cell neoplasm composed of small lymphocytes that surround and replace the splenic white pulp germinal centres. It involves the spleen, splenic hilar lymph nodes, bone marrow and often peripheral blood. When lymphoma cells are present in the peripheral blood, they are usually characterised by short polar villi. Some may appear plasmacytoid. Tumour cells express surface IgM and usually IgD. They are positive for CD20 and CD79a and negative for CD5, CD10, CD23, CD43 and annexin-A1. CD103 is usually negative and cyclin-D1 is absent. Ki-67 staining shows distinctive targeted pattern¹.

Asymptomatic patients with SMZL can be managed with active surveillance. Criteria for treatment include presence of progressive and symptomatic splenomegaly and development of cytopenias ($Hb < 10g/dL$, $neutrophils < 1 \times 10^9/L$, $PLT < 80 \times 10^9/L$) while autoimmune manifestations

if present should be specifically treated. Front-line treatment options include splenectomy, rituximab monotherapy and chemo-immunotherapy. Although splenectomy allows rapid restoration of cytopenias and resolution of abdominal discomfort, it is not a curative procedure and may be associated with complications such as thrombosis, bleeding and infections. Therefore splenectomy has been largely replaced as a first line option by rituximab monotherapy³ given as 375mg/m² per week for 6 weeks⁵ or 4 to 8 weekly⁶ doses and at the maintenance phase every 2 months for 1-2⁵. Chemo-immunotherapy is appropriate for fit patients with disseminated disease, constitutional symptoms and/or high grade transformation⁵.

References

1. Steven H, Swerdlow EC, Harris NL, Jaffe ES, Pileri SA, In: Stein H, Thiele J, Arber DA, Hasserjian RP, Le Beau MM, Orazi A, Seibert R, eds . WHO Classification of Tumours of Haemopoietic and Lymphoid tissues. Lyon: WHO Press; 2017.
2. Parry-Jones N, Joshi A, Forcony F, Dearden C. Guideline for diagnosis and management of hairy cell leukaemia (HCL) and hairy cell variant (HCL-V). *Br. J. Haematol.* 2020; **191**: 730-7. <https://doi.org/10.1111/bjh.17055>
3. Merli M, Arcaini L. Management of marginal zone lymphoma. *The American Society of Haematology* 2022. <http://doi.org/10.1182/hematology.2022000362>
4. Lannito E, Claudio T. How I diagnose and treat splenic lymphomas. *The American Society of Haematology* 2011, blood-2010-09-271437. <http://doi.org/10.1182/blood-2010-09-271437>
5. Cheah CY, Zucca E, Rossi D, Habermann TM. Marginal zone lymphoma: present status and future perspectives. *Haematologica* 2022; **107**(1): 35-43.
6. Zucca E, Arcaini L, Buske C, Wotherspoon A, Ladetto M. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2020. <http://doi.org/10.1016/j.annonc.2019.10.010>