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Case Series

Oncology Section

Splenic Lymphoma: A Series of Seven Cases

AVRITI BAVEJA[1], ANKIT BATRA[2], MANSI KALA[3], RESHMA KAUSHIK[4], SMITA CHANDRA[5], SANJEEV KUMAR VERMA[6]

ABSTRACT

Splenic Lymphoma (SL) is a lymphoproliferative disorder characterised by involvement of the spleen, with or without bone marrow involvement. However, advancements in imaging modalities have led to more frequent diagnosis of isolated splenic lesions. There is always a dilemma in diagnosis as to whether the pathology truly originates from the spleen or if it is part of systemic involvement in Non-Hodgkin Lymphoma (NHL). Clinical manifestations vary widely, and treatment outcomes for SL depend on accurate diagnosis. However, prognosis still remains poor in these cases compared to systemic NHL. The present case series provide a comprehensive overview of patients diagnosed with SL, focusing on their clinicopathological characteristics, therapeutic details, prognosis and outcomes. Previously isolated case reports have been published, and there is still a lack of consensus on the management of this entity. The present case series included seven cases over a two-year period, from January 2022 to December 2023. In the current case series, authors have highlighted the heterogeneity and variability in the presentation of SL and how the clinical behaviour ranges from indolent to highly aggressive. Nevertheless, the presenting clinical, laboratory and pathological features of these diseases often display significant overlaps and pose confusion in arriving at an exact diagnosis. The authors emphasise how flow cytometry helps facilitate the diagnosis and systemic therapy is the modality of choice for treatment decided based on the histology type; however, outcomes still remain dismal, highlighting the unmet need to improve accurate diagnosis and explore newer treatment options. The novelty in this series lies in the detailed analysis and comparison of different subtypes of SL, a rare group of lymphomas primarily originating in the spleen. The present case series discusses the latest World Health Organisation (WHO) classification, which redefines the Hairy Cell Leukaemia (HCL) variant as Splenic B-cell Leukaemia/Lymphoma with Prominent Nucleoli (SBLPN). Detailed molecular and genetic characteristics of various SLs are highlighted, such as the presence of the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) p.V600E mutation in HCL, Mitogen-activated Protein Kinase 1 (MAP2K1) and Immunoglobulin Heavy Variable 4-34 (IGHV4-34) mutations in the HCL-variant, and 7q distortion in Splenic Marginal Zone Lymphoma (SMZL). Emphasis is placed on the individualised treatment approach based on specific patient profiles, genetic markers and disease characteristics. The study underscores the need for further research and clinical trials to validate emerging therapies, such as the use of Rituximab plus Doxorubicin, Bleomycin, Vinblastine and Dacarbazine (R-ABVD) in Hodgkin lymphoma and combinations of novel agents in aggressive SLs like HCL-variant and CD20-negative B-cell NHL.

Keywords: Hairy cell leukaemia, Hepato-splenic lymphoma, Splenomegaly, Splenic B-cell lymphoma/leukaemia with prominent nucleoli

INTRODUCTION

Exploring the aetiology of splenomegaly poses a challenge due to its association with various hepatic or systemic diseases, particularly when splenomegaly is incidentally discovered as the sole indicator of an underlying disorder. It can manifest as either a localised or disseminated process of a haematolymphoid malignancy. Within this spectrum, SLs are a group of lymphomas where the spleen serves as the exclusive site of origin for the lymphoid malignancy. The clinical presentation of SLs is highly diverse, with numerous differentials based on the cell of origin and morphology [1-3]. These may encompass SMZL, HCL, SBLPN, lymphoplasmacytic lymphoma, Hepatosplenic Lymphoma (HSL), and T-cell Large Granular Lymphocyte (T-LGL) Leukaemia, among others. Recent advancements have contributed to a deeper understanding of the biological underpinnings of SLs. The latest WHO lymphoma classification has reflected this progress. Notably, the classification now redefines B-cell Prolymphocytic Leukaemia (B-PLL) and HCL variant as SBLPN, highlighting the evolving diagnostic landscape in this domain [4,5].

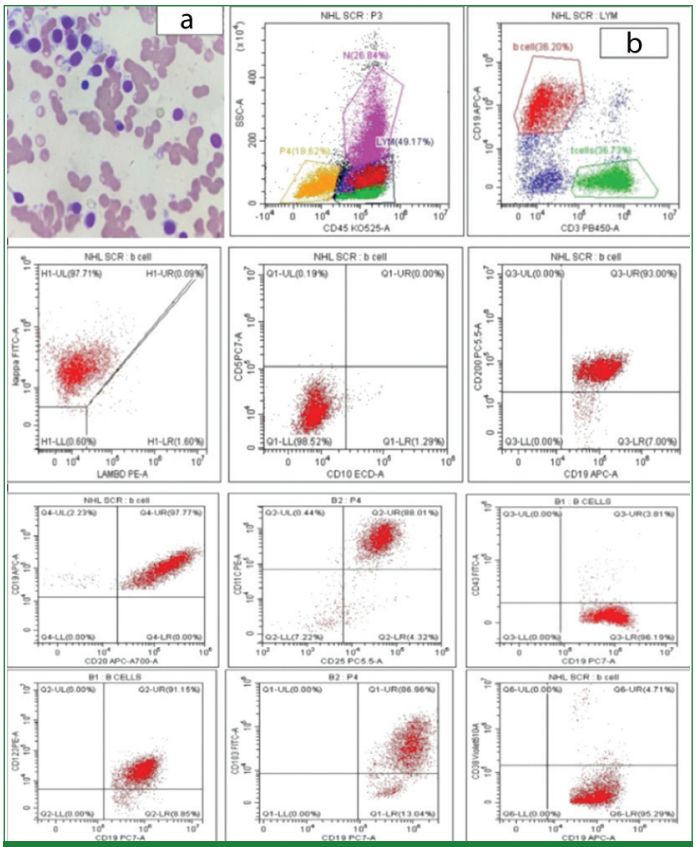
CASE SERIES

Cases were collected retrospectively from January 2022 to December 2023 in the Department of Clinical Haematology. Data retrieval was conducted utilising electronic health records. This case series included lymphoma patients, specifically those presenting with SL. Lymphomas other than SL were excluded. These cases were included using convenient sampling. Clinicopathological variables such as age, gender, hepatosplenomegaly, lymphadenopathy, B-symptoms, peripheral blood findings, immunophenotyping, treatment specifics and outcomes were expressed as percentages for comprehensive understanding. Treatment protocols were Individualised to suit each patient's diagnosis, and regular monitoring was ensured during follow-up visits. Key metrics such as median overall survival and median relapse-free survival were calculated and reported in days to provide insights into the prognosis and disease course of the patients under study. All procedures performed in studies involving human participants were according to the ethical standards of the present Institutional Ethics Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Authors present a case series comprising seven patients diagnosed with SL. The diagnosis of SL was established through imaging studies, bone marrow investigations, flow cytometry, cytogenetic and molecular studies. The age range in the current case series was 18-69 years, with 5 (71.4%) patients being males. The series delineates SL cases diagnosed as follows:

Case 1

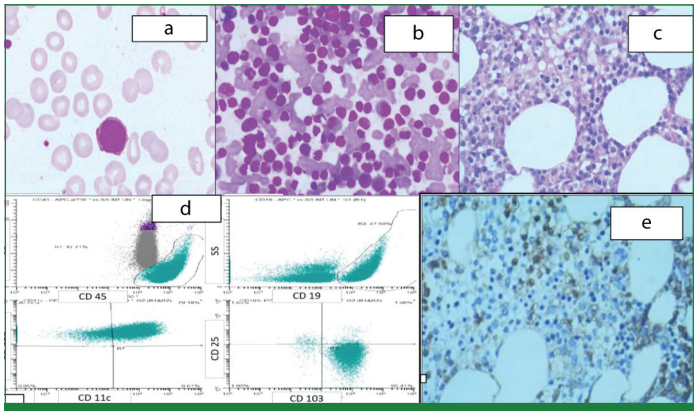
A 55-year-old female presented with a two-month history of progressively increasing generalised weakness and fatigue. She had received three units of Packed Red Blood Cells (PRBCs) in the past. On examination, pallor was present; she also had massive hepatosplenomegaly but no lymph node enlargement on general examination. Her Complete Blood Counts (CBC) showed pancytopenia with haemoglobin 8 g/dL, total leukocyte count was 1800 cells per cumm, and platelet count of 72000 cells per cumm. Peripheral blood smear showed occasional atypical lymphoid cells with hair-like projections. Bone marrow biopsy showed hypercellular marrow with an interstitial increase in atypical lymphoid cells along with focal aggregates. These cells were small to intermediate in size with round nuclei, moderate cytoplasm, clumped chromatin and inconspicuous nucleoli. Immunophenotyping using flow cytometry was positive for CD20, kappa, CD200, CD103, CD25, CD11c and CD123. Immunohistochemistry showed abnormal lymphoid cells positive for annexin A1 [Table/Fig-1]. Molecular mutation testing was positive for the BRAF mutation, confirming the diagnosis of HCL. Cladribine was administered at a dose of 0.14 mg/kg for five days, along with supportive care. The patient exhibited symptomatic improvement post-therapy, although minor infections persisted for 2-3 months, which were managed on an outpatient basis.



[Table/Fig-1]: a) Bone marrow aspirates shows hairy cells, these cells are intermediate in size with clumped chromatin, inconspicuous nucleoli and moderate cytoplasm with hairy projections in some; b) Shows flow cytometry dot plots showing abnormal lymphoid positive for CD19, CD200, Kappa, CD25, CD103, CD11c and CD123 (MGG stain, Photomicrograph of Bone marrow at 400X).
HCL: Hairy cell leukaemia

Case 2

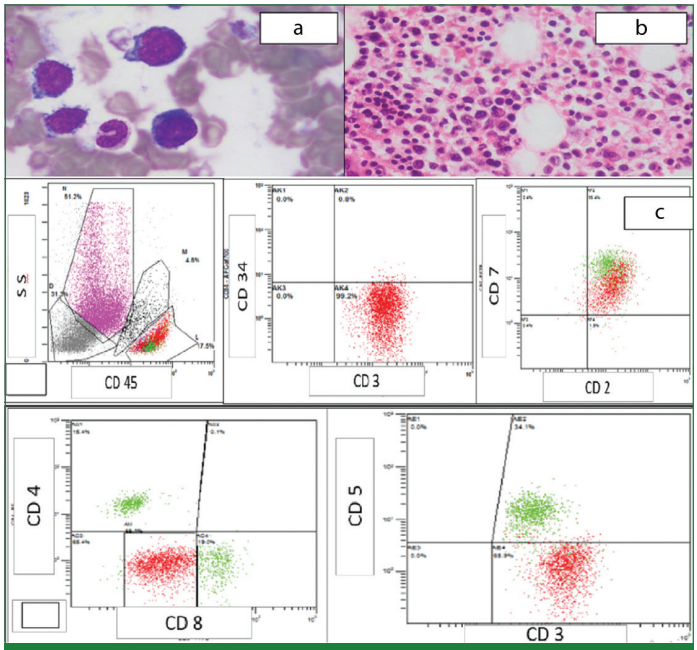
A 69-year-old female presented with easy fatigability, on-and-off fever, early satiety and a dragging sensation in the abdomen. She had no known co-morbidities or family history. On examination, she had pallor and massive splenomegaly. Peripheral smear showed abnormal lymphoid cells featuring prominent nucleoli. Immunophenotyping revealed bright positivity for CD45, CD20, CD19, CD23, CD11c, CD103 and lambda, while testing negative for CD25, CD123, CD200, annexin 1 and BRAF p.V600E mutation [Table/Fig-2]. The case was labelled as variant HCL, now labelled as SBLPN according to the latest WHO classification [4]. The patient received cladribine (0.14 mg/kg for five days) and rituximab (weekly for six weeks) therapy, resulting in disease response and subsequent remission lasting approximately 14 months.



[Table/Fig-2]: a) Peripheral smear showing lymphocytes which are intermediate in size with round nucleus, prominent nucleoli and moderate cytoplasm with cytoplasmic projections; b,c) Bone marrow aspirate and biopsy, respectively showing abnormal lymphoid replacing the normal haematopoiesis; d) Flow cytometry dot plots showing abnormal lymphoid positive for CD19, CD103, CD 11c, axes and negative for CD25; e) Immunohistochemistry for annexin A1 is negative (MGG stain, Photomicrograph of Bone marrow at 400X).

Case 3

An 18-year-old male presented with fever and night sweats for two months. On examination, there was massive splenomegaly, with approximately 20% abnormal lymphoid cells observed on bone marrow examination. Initially, clinical and morphological findings suggested acute leukaemia [Table/Fig-3]; however, further analysis revealed these abnormal lymphoid cells to be positive for CD45, CD3, CD2, CD7 (dim), CD56 and TCR Gamma Delta, while negative for CD8, CD4 and CD5. Cytogenetic analysis revealed amplification of 7q22-31, supporting the diagnosis of HSL. The patient was initiated on hyperfractionated therapy, which consisted of two combinations of drugs given in an alternating fashion like {Hyper-Cyclophosphamide, Vincristine Sulfate, Adriamycin and Dexamethasone (Hyper-CVAD)} and advised for autologous stem cell transplant. Unfortunately, the patient succumbed to the disease within six months of diagnosis.

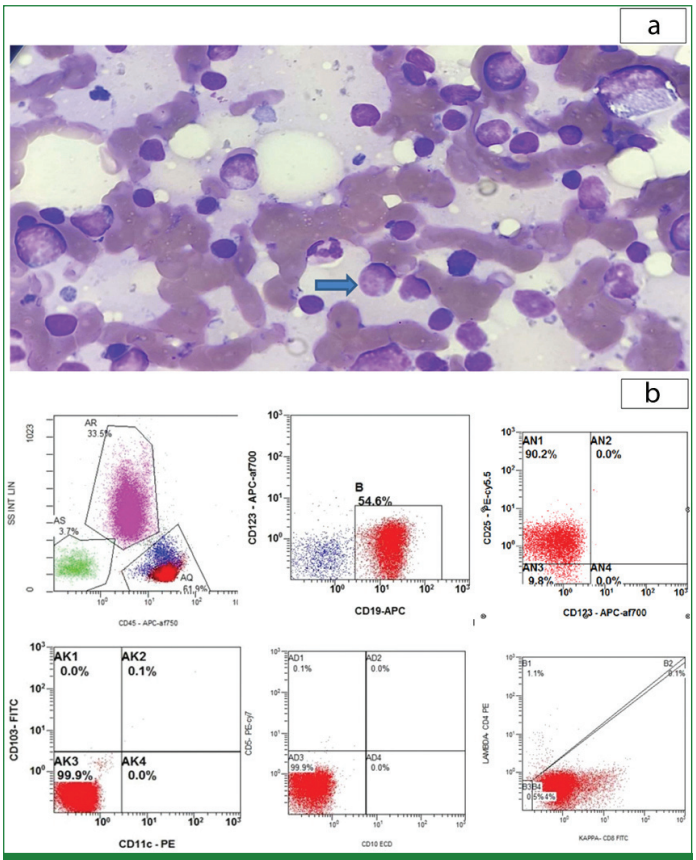


[Table/Fig-3]: a) Bone marrow aspirate shows cell which were intermediate in size with round nuclei, 0-1 nucleoli and basophilic scant to moderate cytoplasm (1000X); b) Bone marrow biopsy showing sinusoidal pattern of abnormal lymphoid; c) Flow cytometry dot plots showing abnormal lymphoid positive for CD45, CD3, CD2, CD7 and negative for CD4, CD8 and CD 5 (400X) (MGG stain).

Case 4

A 48-year-old male presented with abdominal discomfort for two years. He had no known co-morbidities and no history of smoking

or alcohol consumption. On examination, massive splenomegaly up to the umbilicus was noticed. Work-up for chronic liver disease was normal, and his peripheral smear showed no remarkable findings. However, there was subtle involvement of abnormal lymphoid cells noted in the bone marrow aspirate, confirmed by flow cytometry revealing a small population of CD20-positive B-lymphoid cells that were CD5 and CD10-negative. These abnormal B-lymphoid cells were monoclonal with kappa light chain restriction, and he was subsequently diagnosed with SMZL [Table/Fig-4]. His viral profile, which included Hepatitis B, C and Human Immunodeficiency Virus (HIV), was negative. Therefore, the patient was initiated on chemoimmunotherapy with a weekly dose of rituximab for four weeks, following which he achieved a Complete Response (CR).



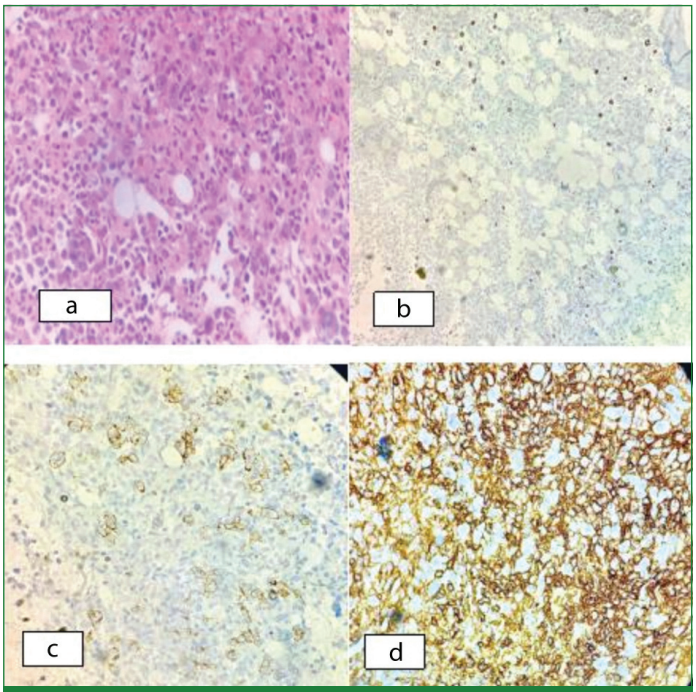
[Table/Fig-4]: a) Bone marrow imprints showing subtly increased abnormal lymphoid (1000X); b) Flow cytometry dot plots showing abnormal lymphoid positive for CD19, CD20, Kappa, CD25 and negative for CD103, CD11c, CD10, CD5, CD123 and lambda (MGG stain).

Case 5

A 58-year-old male presented with fever, loss of appetite and weight loss for six months. On examination, there was massive splenomegaly. There was no history of diabetes or hypertension. Peripheral blood examination showed occasional atypical cells on smear. Biochemical parameters showed markedly elevated Lactate Dehydrogenase (LDH). Bone marrow examination revealed abnormal lymphoid cells characterised by a large size, round nucleus with clumped chromatin, deeply basophilic cytoplasm and cytoplasmic vacuolation. Immunophenotyping indicated bright expression of CD45, CD38 and CD56, dim expression of CD19, and lambda restriction, while being negative for CD20 and CD138, CD3, CytoCD3. MPO, CD123, CD138, CD22, CD79a, Kappa, CD13, CD33, CD117, CD15, CD64, CD11c, CD4, CD8, CD2, CD5 CD16 and CD7 High- grade CD20-negative B-cell NHL was suspected. Dose-adjusted Etoposide, Prednisone, Vincristine and Cyclophosphamide (DA-EPOCH) therapy was initiated promptly, but the disease progressed rapidly, and the patient succumbed to death within four months.

Case 6

A 45-year-old male with a history of Rheumatic Heart Disease (RHD) presented with persistent high-grade fever, weight loss, and night sweats for nine months, despite prior Anti-Tuberculosis Treatment (ATT) with no improvement. Physical examination revealed massive splenomegaly, and CBC showed pancytopenia. Initial clinical, biochemical, and bone marrow aspirate findings suggested Haemophagocytic Lymphohistiocytosis (HLH). Blood cultures and investigations were done to rule out the possibility of infective etiology. However, repeat bone marrow aspiration and immunophenotyping were sent, and the initial pathology report suggested reactive cells. Subsequently, samples were re-sent for immunohistochemistry, which indicated CD20-positive Hodgkin's Lymphoma (HL) with secondary HLH [Table/Fig-5]. Therefore, the patient commenced Cycle 1 Day 1 of ABVD therapy, but persistent fever led to the addition of rituximab (R) from Cycle 1 Day 15. Subsequent cycles of R-ABVD resulted in fever resolution and improvement in other B-symptoms. Interim Positron Emission Tomography (iPET) scan after two cycles showed Complete Remission (CR), with further consolidation therapy of four cycles of R-ABVD followed by two cycles of R-AVD, which the patient tolerated well. The patient is currently on follow-up and remains in CR.

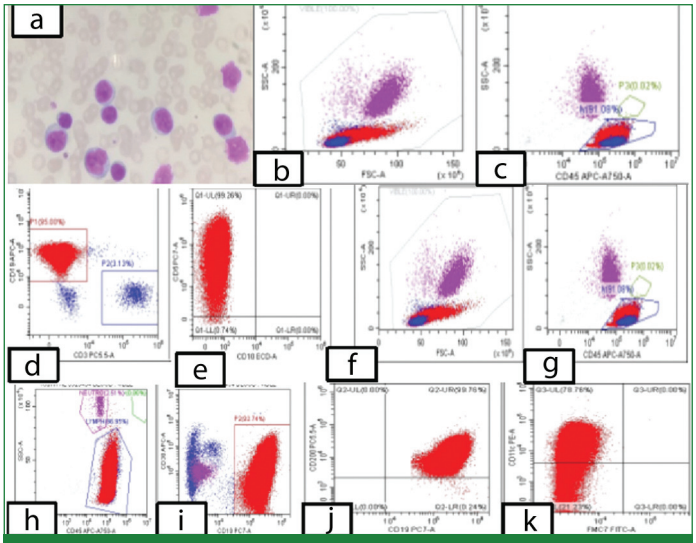


[Table/Fig-5]: a) Bone marrow biopsy shows Reed Sternberg (RS) cell in a background of reactive lymphoid cells; b) Immunohistochemistry showing RS cells negative for CD15; c) RS cells positive for CD30; d) RS cells negative for CD45 (MGG stain, Photomicrograph of Bone marrow at 400X).

Case 7

A 52-year-old male with diabetes and hypertension presented with complaints of abdominal fullness and B-symptoms. He had no peripheral lymphadenopathy but had massive splenomegaly. Physical examination suggested lymphocytosis with over 55% prolymphocytes, and flow cytometry confirmed B-PLL [Table/Fig-6]. Due to his co-morbidities and logistical issues, the patient was started on bendamustine along with rituximab. After one cycle, B-symptoms improved, and after two cycles, spleen was no longer clinically palpable. Patient received a total of six cycles of Bendamustine and Rituximab (BR) and is currently in CR, being on follow-up.

Patients were managed according to Institutional protocols and received ongoing monitoring and supportive care based on clinical requirements. Following completion of therapy, patients were placed on regular follow-up schedules. A summary of clinical findings, along with pathological work-up, diagnosis, treatment and follow-up, is provided in [Table/Fig-7,8]. A summary of the immunophenotypic characteristics of patients in all cases is detailed in [Table/Fig-8].



[Table/Fig-6]: Prolymphocytic Leukaemia (Splenic B cell Lymphoma with prominent nucleoli). a) Peripheral smear shows lymphocytes which are intermediate in size with round nucleus, prominent nucleoli and moderate cytoplasm; b) Flow cytometry dot plots showing abnormal lymphoid positive for CD45, CD19, CD 38, Kappa, CD 11c and CD 200 and negative for CD3, CD10 and CD5 (MGG stain, 400X).

DISCUSSION

Splenomegaly Lymphomas (SLs) are rare lymphomas where the spleen serves as the exclusive site of origin. A detailed medical history is imperative in diagnosing a case of SL. Differentials include SMZL, HCL, splenic diffuse red pulp lymphoma, Splenic B-cell Lymphoma with Prominent Nucleoli (SBLPN) Differentiation, lymphoplasmacytic lymphoma, HSL and T-cell Large Granular Lymphocytic Leukaemia (T-LGL), among others. Recently, greater understanding of the biology of the spectrum of SLs has been reported, and the latest WHO lymphoma classification has redefined the HCL variant as a SBLPN [4-8]. In this series, the authors encountered seven interesting cases: HCL, SBLPN, SMZL, HSL, a high-grade CD20-negative B NHL (a rare entity), CD20 positive classical hodgkin lymphoma and B-PLL.

Hairy cell leukaemia a subtype of mature B-cell neoplasm, has distinctive clinicopathological features with a BRAF p.V600E mutation, as seen in most cases. The first case was symptomatic, and the patient was planned for therapy. Literature review has shown that cladribine and pentostatin, two purine analogs, have equal efficacy and are used for first-line treatment for HCL, with cladribine having a better toxicity profile [4,9,10]. In cases of severe active

Case	Age (years)	Gender	B-S	HM	SM	LN	Lymphoid cells on PBF	IPT	Diagnosis	Treatment	Outcome
Case 1	55	Female	+	+	+	-	+	FC and IHC	HCL	Cladrabine	CR
Case 2	69	Female	+	-	+	-	+	FC	HCL-v/SBLPN	Cladrabine with Rituximab	CR with an OS of 14 months
Case 3	18	Male	+	+	+	-	+	FC	HSL	Hyper-CVAD	Partial response with an OS of 6 months
Case 4	48	Male	-	-	+	-	+	FC	SMZL	Rituximab	CR
Case 5	58	Male	+	+	+	-	+	FC	CD20 negative B-NHL	DA-EPOCH	Partial response in 1 month, lost to follow-up and then progressed in 1 month with an OS of 4 mnths
Case 6	45	Male	+	+	+	-	-	IHC	CD20 positive Hodgkin's Lymphoma (HL)	R-ABVD	CR after 2 cycle of R-ABVD
Case 7	52	Male	+	-	+	-	+	FC	B-PLL/SBLPN	R-Bendamustine	CHR and splenic response in 2 months

[Table/Fig-7]: Summary of case of Splenic Lymphomas (SL).
B-S: B-symptoms; HM: Hepatomegaly; SM: Splenomegaly; LN: Lymph node; PBF (ABL): Peripheral blood findings (Abnormal lymphoid); BMA(I): Bone marrow aspirate (Involved); BMA (I): Bone marrow biopsy (Involved); IPT: Immunophenotyping; CR: Complete response

Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Diagnosis	HCL	HCL-v (SBLPN)	HSL	SMZL	CD20 negative B-NHL	CD20 positive HL	B-PLL (SBLPN)
CD45	Positive	Positive	Positive	Positive	Positive	Negative	Positive
CD3	Negative	Negative	Positive	Negative	Negative	Negative	Negative
CD19	Positive	Positive	Negative	Positive	Positive	Negative	Positive
CD5	Negative	Negative	Negative	Negative	Negative	Negative	Negative
CD10	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Kappa	Positive	Positive	Negative	Positive	Negative	Negative	Positive
Lambda	Negative	Negative	Negative	Negative	Positive	Negative	Negative
CD20	Positive	Positive	Negative	Positive	Negative	Variably positive	Positive
CD103	Positive	Positive	Negative	Positive	Negative	Negative	Negative
CD123	Positive	Positive	Negative	Negative	Negative	Negative	Negative
CD25	Positive	Negative	Negative	Positive	Negative	Negative	Negative
CD56	Negative	Negative	Negative	Negative	Positive	Negative	Negative
CD11c	Positive	Positive	Negative	Negative	Negative	Negative	Positive
CD200	Positive	Negative	Negative	Negative	Negative	Negative	Positive
CD4	Negative	Negative	Negative	Negative	Positive	Negative	Negative
CD8	Negative	Negative	Negative	Negative	Positive	Negative	Negative
CD2	Negative	Negative	Positive	Negative	Positive	Negative	Negative
CD7	Negative	Negative	Positive	Negative	Positive	Negative	Negative

[Table/Fig-8]: Immunophenotypic characterisation of Splenic Lymphomas (SL).
CD: Cluster differentiation; HCL-v: Hairy cell leukaemia variant; SBLPN: Splenic B-cell eukaemia/lymphoma with prominent nucleoli; HSL: Hepatosplenic lymphoma; SMZL: Splenic marginal zone lymphoma; B-NHL: B-cell Non-Hodgkin lymphoma; B-PLL: B-cell Prolymphocytic leukaemia

infections or pregnancy, one may use interferon alpha. Interestingly, it is seen that patients with CD5 expression have a poor response to interferon alpha. Authors did not assess Minimal Residual Disease (MRD) in this patient, as the literature does not clearly define the use of MRD. It has been observed that many patients with MRD-positive status remained in prolonged complete haematologic remissions.

Variant HCL remains a close differential to HCL, with a few differences. It differs from HCL in terms of presentation, with lymphocytosis instead of pancytopenia, monocytopenia, prolymphocytic morphology with prominent nucleoli and rarely hairy cell projections. Typically, HCL-v does not have variant BRAF p.V600E mutations. Instead, patients may harbour mutations in MAP2K1 and express IGHV4-34, both of which are commonly associated with inferior outcomes. The latest WHO classification categorises variant HCL and CD5-negative B-PLL as SBLPN [10,11]. Such patients may have abnormal lymphoid cells with prominent nucleoli on peripheral smear, as seen in the second case, along with a classical Immunophenotypic picture as described in the case. Overall, HCL variant is an aggressive disease with a very short median overall survival, as in the present case.

Initial chemoimmunotherapy is recommended upfront for fit patients due to a high objective response rate. Splenectomy for symptomatic massive splenomegaly has significant clinical benefits. Splenic irradiation is a valid alternative to splenectomy in elderly HCL variant (HCL-v) patients. In highly selected patients, monotherapy in the form of inhibitors for B-cell Antigen Receptor (BCR) signaling, Mitogen-activated Extracellular signal-regulated Kinase (MEK) inhibition in patients with MAP2K1 mutations, and anti-CD20 agents like Rituximab can also be considered [11].

The cell origin of SMZL is not clear; however, it is believed to originate from memory B lymphocytes. 7q distortion is believed to be involved in the pathogenesis. About 10% of patients transform to DLBCL. The prognosis of SMZL is better than other lymphomas if the patient shows no evidence of B-symptoms or disease progression. General treatment options include surgery, radiotherapy and systemic chemoimmunotherapy. Unlike other lymphomas, surgery may be an effective way for both diagnosing and treating SMZL, and the addition of postoperative adjuvant chemoimmunotherapy may prolong the survival rate. The usual age for SMZL is 65-70 years, whereas in the present case, it was seen at a much earlier age. Studies have shown that rituximab single agent has an overall response rate of approximately 95% (70% complete) and a median time to clinical response of three weeks. Estimated five-year OS and PFS rates are 90-94% and 70-75%, respectively. Even surgical removal of the spleen resulted in an 85% overall response rate with estimated five-year OS and PFS rates of 77% and 58%, respectively. For Hepatitis C Virus (HCV)- positive patients, they should receive a trial of antiviral therapy. SMZL may also be treated by six cycles of bendamustine plus rituximab regimen as first-line systemic therapy in symptomatic SMZL patients with an overall response rate of 91% and three-year estimated PFS and OS of 90% and 96%, respectively [12,13]. It is interesting to see that flow cytometry could not only pick up this subtle involvement of lymphoma in the bone marrow but also helped expedite the diagnosis in the present case, and the patients responded well to single-agent rituximab as in the literature.

Hepatosplenic T-cell Lymphoma (HSTCL), an aggressive and rare T-cell lymphoma, is usually seen in adolescents and young adults. It may present with B-symptoms and cytopenias, and sometimes mimics acute leukaemia, so utmost attention should be given to prevent misdiagnosis. Studies have shown that massive splenomegaly and lymphocytes devoid of azurophilic granules, along with lymphoma cells in bone marrow sinusoidal expansion, are commonly seen in patients with HSTCL compared to γδ T-LGL. These features support the diagnosis of HSTCL [14-16]. Cytogenetic analysis revealed 7q 22-31 amplification, leading to a diagnosis of HSL being suggested. Literature reviews have shown poor outcomes with systemic chemoimmunotherapy using Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone like regimens, without haematopoietic stem cell transplant in CR1 HSTCL having poor outcomes, with 5-year survival rates of less than 10%. The Hyper-CVAD chemoimmunotherapy regimen is considered a better option in such cases. The patient was started on the Hyper-CVAD chemoimmunotherapy regimen and was advised to undergo autologous stem cell transplant [14,15]. Despite receiving an intensive regimen like Hyper-CVAD, the patient died within six months of the diagnosis.

It is rare to see CD20-negative B-cell NHL, which accounts for less than 2% of all B-cell lymphomas. These types are commonly associated with extranodal presentation, atypical morphology, and high resistance to standard chemoimmunotherapy, leading to poor response due to their aggressive nature. Currently, there is no standard first-line treatment for CD20-negative B-cell lymphomas. Responses to standard therapies like CHOP are usually very suboptimal. Regimens such as DA-EPOCH or Cyclophosphamide, vincristine, Doxorubicin, Methotrexate alternating with Ifosfamide, Etoposide, cytarabine (CODOX-M/IVAC) or hyper-CVAD are among some suggested treatments that result in the upregulation of CD20 expression. The use of infusional dose-adjusted EPOCH with bortezomib has also been reported to cause CD20 expression upon exposure to epigenetic agents, resulting in the upregulation and resensitisation of B lymphoma cells to CD20 antibodies [17].

Approximately one-fourth of patients with cHL have Reed-Sternberg (RS) cells that show CD20 expression [18]. CD20 is expressed on the precursors of RS cells and also on B-lymphocytes, exerting a protumoural activity in the tumour microenvironment [18,19]. Some preclinical studies have demonstrated therapeutic efficacy in cHL with rituximab, both by directly killing RS cells and by targeting the surrounding microenvironment [20-22]. Due to persistent fever and findings of HLH in this patient, it was decided to add rituximab after the first cycle following a tumour board discussion. Previous studies have shown that the combination of Rituximab with ABVD (R-ABVD) in upfront therapy for patients with advanced cHL resulted in a 3-year event-free survival of 77%, representing a 22% absolute improvement compared to historical data with ABVD. However, a phase 2 study comparing R-ABVD to ABVD as frontline treatment for patients with advanced stage, high-risk (IPS >2) cHL showed an EFS benefit without any OS benefit [20-22]. Therefore, further validated studies are needed to establish the efficacy of regimens like R-ABVD. While favourable data exists in HL with regimens like Brentuximab, its cost remains a limiting factor, and escalated BEACOPP can be intolerable for many patients. More studies are required on the use of combinations like R-ABVD or R-Brentuximab in such scenarios.

B-PLL is a rare disease, typically accounting for less than 1% of B-cell leukaemia [23]. B-PLL cells typically express bright CD19, CD20, CD22, CD79a, and FMC7, with bright surface IgM±IgD and bright surface Ig kappa or lambda light chain. Trisomy 18 and del 13q are observed in 30% of cases, with Trisomy 12 being uncommonly associated. Currently, CLL-like treatment approaches are commonly used for managing B-PLL. While responses to these regimens have been reported, they are most frequently partial and not durable [24,25]. No studies are currently available for individual regimens, and treatment choices are typically based on factors such as drug access, patient profile, toxicity profiles, disease characteristics, and cost. Both patients with HL and B-PLL showed a good initial response to R-ABVD and R-Bendamustine, but longer follow-up is necessary to draw conclusions about long-term survival.

CONCLUSION(S)

The cases presented illustrate the diverse spectrum of SLs and leukaemia, ranging from well-characterised types like HCL and SMZL

to rare, aggressive variants such as HSTCL and CD20-negative B-cell lymphoma. Each case highlighted distinct clinical presentations, diagnostic challenges, and therapeutic considerations. An accurate diagnosis involves a comprehensive history, physical examination, and integrated laboratory data, along with imaging, peripheral blood, and bone marrow assessments, minimising the need for diagnostic splenectomy unless necessary. Common variants can be managed following standard treatment protocols, while rare variants lack established care guidelines. There is a critical need for multicentric efforts to understand SL biology, evaluate treatment efficacy, and develop evidence-based approaches.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Clinical Haematology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
2. Assistant Professor, Department of Medical Oncology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
3. Professor, Department of Pathology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
4. Professor, Department of Medicine, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
5. Professor, Department of Pathology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
6. Professor, Department of Medicine, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mansi Kala,
Professor, Department of Pathology, Himalayan Institute of Medical Sciences,
Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant,
Dehradun-248016, Uttarakhand, India.
E-mail: drmansikala@gmail.com

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