We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Splenic B-Cell Lymphoma/Leukemia, Unclassifiable

Parastou Tizro, Rami Abdulbaki, Anita Aggarwal, Aaron Auerbach and Victor E. Nava

Abstract

Splenic B-cell lymphoma/leukemia, which is unclassifiable, includes low-grade B-cell lymphoproliferative disorders that do not fit into any other splenic lymphoid neoplasm based on current WHO classification. Presently, two provisional entities, splenic diffuse red pulp small B-cell lymphoma (SDRPL) and hairy-cell leukemia variant (HCL-v), are the most recognizable members of this group. SDRPL is an uncommon malignancy representing less than 1% of all non-Hodgkin lymphomas. Frequent clinical manifestations include splenomegaly and lymphocytosis. SDRPL is currently considered a diagnosis of exclusion and requires clinical and paraclinical correlation, including blood smear, bone marrow and spleen morphology, and the correct immunophenotype (typically positive for CD20, DBA.44, and IgG; and negative for CD5, CD10, CD23, CD43, annexin A1, CD11c, CD25, CD103, and CD123), and cytogenetic findings. Cyclin D3 is expressed in the majority of SDRPL in contrast to other types of small B-cell lymphomas. HCL-v is a less common disease accounting for 0.4% of all chronic lymphoproliferative disorders. It resembles classical HCL and SDRPL by diffusely infiltrating the splenic red pulp but is considered biologically unrelated. Splenomegaly and atypical lymphocytosis without monocytopenia are common. Distinguishing features of HCL-v include morphology, immunophenotype (the absence of CD25, CD200, CD123, annexin A1, and TRAP), genotype (wild-type *BRAF*), and prognosis.

Keywords: spleen, lymphoma, splenic B-cell lymphoma/leukemia unclassifiable, splenic diffuse red pulp small B-cell lymphoma, hairy cell leukemia-variant

1. Introduction

Splenic B-cell lymphoma/leukemia, unclassifiable, is a rare category of spleen neoplasm with unknown etiology that lacks established, precise diagnostic criteria and remains a diagnosis of exclusion. This category includes the two relatively rare entities of splenic diffuse red pulp small B-cell lymphoma (SDRPL) and hairy cell leukemia variant (HCL-v), which are provisionally recognized in the current World Health Organization (WHO) classification. Other splenic small B-cell lymphomas that do not fit into the current diagnostic scheme can also be part of this category [1].

2. Splenic diffuse red pulp small B-cell lymphoma

SDRPL is an indolent but incurable non-Hodgkin lymphoma (NHL) composed of small mature B-lymphocytes that involve the red pulp of the spleen, as well as bone marrow and peripheral blood. Therefore, it is usually diagnosed at stage IV [1]. The cell of origin is believed to be an unidentified B-cell precursor. SDRPL was first classified as a provisional entity in the 2008 WHO classification of lymphoid neoplasms [2] and was later grouped under splenic B-cell lymphoma/leukemia, unclassifiable in the 2016 revision [1]. In the older literature, this entity may overlap with splenic marginal zone lymphoma (SMZL)-diffuse variant, SMZL with diffuse red pulp involvement, and splenic red pulp lymphoma with numerous basophilic villous lymphocytes, which are terms largely abandoned.

2.1 Epidemiology

The true incidence of SDRPL is unknown, as it is a new part of the spleen lymphoma classification. In general, it has been reported to represent 1–2% of all lymphoid malignancies [3] and may account for up to 10% of the B-cell lymphomas diagnosed in splenectomy specimens [4, 5]. In a single-center case series of 37 patients, SDRPL reportedly represented 0.5% of all chronic lymphoid malignancies diagnosed by peripheral blood examination [6]. SDRPL has a slight male predominance with a male/female ratio of 1.5–2.5:1. The patients are usually older than 40 years of age with a median age of 65–77 years [6, 7].

2.2 Clinical presentation

Patients with SDRPL usually present with mild lymphocytosis and abdominal pain due to massive splenomegaly. Leukopenia and thrombocytopenia due to hypersplenism and bone marrow infiltration are frequent [1]. Almost all cases are diagnosed at clinical stage IV with involvement of peripheral blood and bone marrow, as mentioned above. Splenic hilar lymphadenopathy is frequently reported. However, peripheral lymph node involvement is very uncommon. B symptoms are reported only in one-third of cases. In a retrospective study of 17 cases with SDRPL, liver involvement was reported in 18% of cases while erythematous and pruritic skin papules were seen in 10% of patients [7]. Concurrent chronic hepatitis B infection has also been described in two cases of SDRPL [8].

Imaging studies often show diffuse splenic enlargement without discrete splenic lesions, and increased FDG-avidity may be seen on PET/CT [4]. Rarely, normal splenic size/appearance and FDG uptake are present [3].

2.3 Diagnosis

Diagnosis of SDRPL rests mainly on the exclusion of other lymphomas by correlating histopathology of spleen and bone marrow/peripheral blood, if available, with ancillary studies assessing immunophenotypic and genetic characteristics, which are not always constant in the literature. Although unequivocal diagnostic criteria for SDRPL are still being developed, generally, the combination of morphology and immunohistochemistry in the correct clinical setting allows definitive categorization. Bone marrow examination showing a purely intrasinusoidal pattern in combination with villous lymphocytosis in peripheral blood smears, together with appropriate immunophenotypic/molecular findings excluding other low-grade B-cell lymphomas, may be sufficient for diagnosis. However, splenic biopsy or

splenectomy identifying a diffuse infiltration of the red pulp by neoplastic B cells with a characteristic immunophenotype may also be necessary for unequivocal classification [7]. Genetic studies are increasingly being performed and may facilitate the subclassification of difficult cases or those with limited tissue.

2.3.1 Laboratory findings

The most common laboratory finding in SDRPL is low-grade lymphocytosis (median lymphocyte count of $5.4 \times 10^9/L$), which can be a useful diagnostic hint to differentiate it from HCL-v that classically shows higher lymphocytosis. Although not present uniformly among all studies, thrombocytopenia (median platelet count $<100 \times 10^9/L$) and leukopenia have been frequently reported in SDRPL. However, anemia is a rare finding [7]. Other laboratory results are usually unremarkable except for hepatitis B virus tests [8].

2.3.2 Morphologic findings

Splenectomy specimens show diffusely enlarged spleen with a homogenous red-brown cut surface (described as “beefy”) and occasional wedge-shaped subcapsular infarcts. Spleen nodularity has not been reported in SDRPL cases, and its presence should warn against this diagnosis. However residual lymphoid nodules composed of T-cells may be found [7].

Splenic histology reveals a purely diffuse pattern of infiltration of the red pulp cords and sinusoids by monomorphous small to medium-size mature B cells with regular ovoid nuclei, clumped chromatin, and pale cytoplasm, which spares the white pulp [9]. Focal plasmacytic differentiation can be present as in other low-grade B-cell lymphomas. Reactive T-cell lymphoid nodules or residual B-cell lymphoid follicles are occasionally present in early disease [9]. Sinusoidal disruption results in erythrocyte collections surrounded by tumor cells, which form the characteristic blood lakes seen in some cases. These so-called true blood lakes tend to be smaller (**Figure 1**) than those seen in HCL. In contrast, pseudo-blood lakes formed by sinusoidal dilation, which can also be present in other splenic lymphomas, are lined by littoral cells (CD8-positive/CD34-negative) and vascular endothelial cells (CD8-negative/CD34-positive) [7, 10]. The absence of white pulp involvement by follicular or nodular proliferation is a supportive finding to allow correct categorization [10].

The peripheral blood smear shows villous lymphocytes (**Figure 2**) in variable degrees, which may be indistinguishable from those present in other small B-cell lymphomas. However, complete circumferential distribution or longer villi should not be seen, in contrast with HCL and HCL-v.

Bone marrow trephine core biopsy typically reveals a predominantly intrasinusoidal infiltration, but occasionally interstitial and nodular aggregates may also be present. This sinusoidal pattern is considered more specific for the diagnosis but is not pathognomonic, and can also be seen in SMZL and HCL-v [10]. Neoplastic lymphoid follicles have not been reported in bone marrow specimens with SDRPL unlike in other low-grade B-cell neoplasms, such as SMZL and follicular lymphoma.

Skin involvement may be seen in advanced cases showing an unspecific patchy peri adnexal/perivascular pattern of infiltration [7].

2.3.3 Immunophenotypic findings

Based on immunophenotyping, SDRPL belongs to the group of CD5/CD10 double negative B-cell lymphomas, but phenotypic variability has been reported [11]. The

Figure 1.
(A) SDRPL in the red pulp of the spleen showing blood lakes (H&E, 40X). (B) Higher magnification of infiltrating monomorphic small B-lymphocytes with regular nuclei, clumped chromatin, and pale cytoplasm (H&E, 400X). The lymphoma cells are strongly positive for CD20 (C) and negative for CD5 (D) by immunohistochemistry (200X).

Figure 2.
Peripheral blood smear shows villous lymphocytes in SDRPL (Wright-Giemsa, 1000X).

classic immunophenotype of the neoplastic cells usually includes positivity for CD19, CD20, IgG, and BCL2; and negativity for CD5, CD23, CD43, cyclin D1, CD10, BCL6, MUM1, CD11c, CD25, CD103, CD123, and annexin A1. DBA.44 is positive in 20–90% of cases [7, 9, 10, 12]. IgD, IgM, CD103, CD11c, CD5, CD123, and CD43 positivity has been described infrequently, although expression of IgD is more commonly associated with marginal zone B-cell lymphoma. A recent study showed cyclin D3 expression in 24 out of 33 (72%) patients with SDRPL [13]. However, this marker is not readily available in most laboratories, limiting its clinical utility. Cases with plasmacytic differentiation commonly show positivity for CD38 and/or CD138, as expected.

Flow cytometry demonstrates restricted B lymphocytes based on the expression of surface light chain immunoglobulins (kappa or lambda), which could be biclonal (IgM and IgG or IgM and IgD) or monoclonal (IgG or IgM alone) based on heavy chain type. In addition, CD103 expression can be detected in up to a third of cases [14].

2.3.4 Genetic findings

Immunoglobulin heavy chain (*IGHV*) somatic hypermutation analysis shows alterations in up to 70% of the cases with selective usage of VH3 and VH4 gene families [6, 15], as is commonly also seen in HCL. VH1 usage is uncommon, in contrast with SMZL. Complex cytogenetic alterations including t(9,14) (p13;q32), involving *PAX5* and *IGH* genes have been reported. Chromosome 7q deletion, trisomy 18, and partial trisomy 3q have been rarely published. *TP53* alterations are seen only in 5–15% of cases [8, 12, 13].

A recent whole-exome sequencing (WES) study identified mutations in the *CCND3* PEST domain in a high proportion of SDRPL cases, whereas no mutations in *NOTCH2* or *BRAF* V600E were reported [12, 13]. A distinct mutational landscape has been observed in 42 SDRPL samples as compared with eight and 46 samples from HCL and SMZL patients, respectively [15]. WES identified recurrent *BCOR* (*BCL6* corepressor) mutations or losses in 10 of 42 SDRPL cases (24%). In contrast, *BCOR* alterations were rare in SMZL (one of 46) and absent in HCL (0 of eight). *CCND3* mutations were also detected in 21% of SDRPL and 13% of SMZL cases. *BRAF* V600E mutation was present in all HCL samples (eight of eight) but only in one of 42 SDRPL and one of 46 SMZL specimens. In contrast, mutations in the NOTCH (*NOTCH2*, *NOTCH1*, and *SPEN*) and NF- κ B pathways (*KLF2*, *TNFAIP3*, and *MYD88*) were rare (0–2%) in SDRPL as opposed to SMZL. These molecular findings could aid in the differential diagnosis of primary splenic lymphomas with ambiguous morphology.

2.4 Treatment

Since SDRPL is a very rare disease there is a paucity of clinical studies evaluating different management strategies. Therefore, treatment modalities for SDRPL are evolving and usually rely on the experience with other primary splenic lymphomas, such as SMZL. The most utilized therapeutic approaches for SDRPL include splenectomy, rituximab monotherapy, or expectant management. Although splenectomy can achieve durable remission, it is by definition non-curative since residual disease remains in the bone marrow and peripheral blood compartments [7, 12].

2.5 Prognosis

Patients with SDRPL as a rule have a chronic clinical course with a median survival compared to those of individuals with SMZL (8–10 years), but significantly

superior to those with HCL-v. Although standard treatment is still unavailable, splenectomy is an excellent alternative to producing durable remission in most cases. However, around 25% of patients follow a more progressive course, which may be related to genetic alterations in *NOTCH1*, *MAP2K1*, and *TP53* [12].

Transformation to a large B-cell lymphoma with aggressive behavior has been described rarely [7, 8, 16], and unusual transformation to B-cell prolymphocytic leukemia (B-PLL) is also possible [17, 18].

Future genetic profiling is necessary to discover alterations with prognostic significance in SDRPL, and consequently, molecular testing may be particularly indicated in young patients [9].

3. Hairy cell leukemia variant

HCL-v is a provisional diagnostic entity in the WHO classification since 2001 and was later included in the broader category of splenic B-cell lymphoma/leukemia, unclassifiable [1]. HCL-v was formally first described by Cawley et al. [19] as an indolent lymphoproliferative disorder with some resemblance to HCL, but biologically divergent based on the postulated cell of origin (activated late-stage B cell for HCL-v vs. mature B cell of unknown type for HCL). This divergence is reflected in its variant histomorphologic, immunophenotypic, genotypic, and clinical features. Accordingly, HCL-v does not respond well to HCL therapeutic regimens and tends to behave more aggressively [20].

As in HCL, the spleen, bone marrow, and peripheral blood are usually involved in HCL-v, which commonly present with splenomegaly due to red pulp infiltration. However, absolute lymphocytosis without monocytopenia is the norm, as opposed to the cytopenias, especially monocytopenia, observed in HCL.

3.1 Epidemiology

HCL-v has an annual incidence of approximately 0.03 cases per 100,000 population [1]. It accounts for 10–20% of lymphoproliferative disorders initially diagnosed as HCL and 0.4% of all chronic lymphoproliferative disorders, accounting for 60–75 new HCL-v cases reported annually in the United States alone [20]. The patients are usually middle-aged to elderly with a slight (1.6:1) male predominance [21]. Although a geographical predilection has not been reported so far, the disease may be more prevalent in Asian populations [21, 22].

3.2 Clinical presentation

The typical initial manifestations, including abdominal discomfort, anemia, bleeding, or infection, are usually related to splenomegaly and/or the presence of cytopenias. In earlier stages of the disease, cytopenias are mainly related to hypersplenism rather than some form of bone marrow failure. A small proportion of cases are identified incidentally by routine hematology (cell blood counts and/or peripheral blood smear reviews) [21], since leukocytosis (on average $30 \times 10^9/L$) with an absolute lymphocytosis and atypical lymphocytes may be detected before the onset of symptoms. However, the absolute number and proportion of monocytes are not decreased in contrast with the usual type of HCL [22]. While thrombocytopenia can be seen in almost half of the patients, anemia is reported in 25% of them [23]. A single institute case series study of 52 patients showed splenomegaly in most (85%) and hepatomegaly in less than a third of the patients. However, lymphadenopathy

was rare [22]. Autoimmune hemolytic anemia and extra-splenic involvement (including skin, brain, and terminal ileum) have been reported rarely [23].

3.3 Morphologic findings

The HCL-v cells display morphologic heterogeneity in the peripheral blood. In most cases, identification of villous lymphocytes is possible, however, the cytoplasmic projections tend to be more polarized, less frequent (**Figure 3**), and more robust than the typical hair-like long circumferential “pseudopods” of classical HCL. In fact, these projections may be missing completely and when present may be indistinguishable from those seen in SDRPL, SMZL, and HCL. Nuclear features may also be inconsistent and include prominent central prolymphocytoid nucleolus, convolution (instead of round to oval nuclei), and condensed or blastic chromatin, which justifies the published terminology of “hybrid form of HCL” for this entity [1, 24]. Large cells with convoluted nuclei are prominent when HCL-v transforms to high-grade B-cell lymphoma, which is uncommon [25]. In contrast with HCL, insignificant bone marrow fibrosis is detected on reticulin stains, which allows successful aspiration. The lymphomatous burden is usually minimal, vague, and interstitial (**Figure 4**). However, sometimes an intrasinusoidal growth pattern is present in common with SMZL and SDRPL [26, 27]. Similar to SDRPL and HCL, the splenic infiltrate by neoplastic B cells diffusely expand the red pulp and spares the white pulp, which appears atretic [26].

3.4 Immunophenotypic findings

A cardinal difference between HCL-v and classic HCL is the absence of expression of CD25, CD200, CD123, and annexin A1 [28–30]. Immunohistochemical stains (**Figure 5**), show positivity for CD103, DBA.44 (CD72), and CD11c in most cases, which overlaps with HCL. However, the

Figure 3.
Peripheral blood smear shows villous lymphocytes in HCL-v (Wright-Giemsa, 400X).

Figure 4.
(A) Bone marrow biopsy of HCL-v shows subtle interstitial lymphomatous involvement (H&E, 200X).
(B) Higher magnification of the bone marrow demonstrating involvement by atypical lymphocytes with convoluted nuclei (H&E, 400X).

Figure 5.
Immunohistochemistry of bone marrow biopsy from HCL-v showing neoplastic cells positive for CD20 (A) and DBA44 (B). Annexin a is negative on the atypical lymphocytes and highlights myeloid cells (C). CD123 is also negative on neoplastic cells (D) (400X).

expression of CD11c and CD103 can separate HCL-v from SMZL and SDRPL. As with any mature B-cell neoplasm, the immunophenotypic profile of HCL-v also demonstrates positivity for pan-B-cell markers (CD19, CD20, and CD22) and is usually strongly positive for surface immunoglobulins expression, most commonly IgG and lambda light chain. In addition, the majority of cases express FMC7 and HLA-DR, one-third expresses CD24 and CD79a, and only a minority express CD10 and CD138. Lastly, CD5 and CD23 have been reported negative in almost every case [19, 21, 28].

3.5 Genetic findings

Although HCL-v shares classic pathologic features with other splenic lymphomas, the signaling pathways involved are different at the molecular level. For instance, alterations in TP53 are more frequent in HCL-v when compared with classical HCL. Likewise, *IGHV* somatic hypermutation is more common in HCL-v (33%) than in HCL (15%), and preferentially affects the VH4–34 gene segment (40% in HCL-v and 10% in HCL). Of interest, 44% of TP53-mutated HCL-v cases had unmutated *IGHV* [23]. Furthermore, a British DNA copy number analysis study demonstrated more abnormalities in HCL-v predominantly representing gains of chromosome 5 and losses of chromosomes 7p and 17p. [31]. However, emerging data from a Chinese cohort suggests a more complex picture with a higher ratio of large chromosomal alteration and a lower copy number variation in HCL versus HCL-v [32]. Regarding the prototypical *BRAF* V600E mutation present in HCL, multiple studies demonstrate its absence in HCL-v [33–35]. In contrast, *MAP2K1* alterations have been documented in the majority of HCL-v, and only in rare classical HCL with *IGHV*4–34 usage and wild-type *BRAF*, which suggests a common pathogenic MAPK activation in a subset of cases [36].

Additional studies are necessary to clarify the genomic landscape of HCL-v, including further analysis of the reported mutations in *U2AF1*, *ARID1A*, and *TTN* [37], and to identify meaningful biological features possibly leading to novel therapy. To that effect, it may also be beneficial to further investigate the role of cytokines (Fibroblast growth factor and transforming growth factor beta) and adhesion molecules preferentially expressed in HCL but not in HCL-v, which promote bone marrow fibrosis in the former [38].

3.6 Treatment

The treatment of HCL-v is challenging due to the rarity of the disease, which has hampered the development of definitive guidelines. Although expectant management (active observation) is an option, most patients will eventually require therapy, ranging from splenectomy to chemoimmunotherapy [23]. Indications for treatment include the development of progressive splenomegaly, rapid increase in lymphocyte count, or symptoms related to cytopenias [22]. Splenectomy alone can lead to long-lasting partial remission in about two-thirds of patients [28] and maybe the best option because it not only removes the bulk of the disease but also corrects hypersplenism alleviating cytopenias. Moreover, splenectomy followed by Rituximab may be an additional treatment option [39]. HCL-v is resistant to agents effective against HCL, such as cladribine and pentostatin [24]. However, adding rituximab to cladribine as a combination therapy has shown promising results, achieving a complete response in nine of 10 patients, of whom only two showed minimal residual disease (MRD) [40]. Anti-CD22 recombinant immunotoxin, an agent used in refractory HCL, has also been utilized successfully [22, 41].

Alemtuzumab, a monoclonal antibody effective for chronic lymphocytic leukemia with mutated *TP53*, achieved morphologic remission after 8 weeks of treatment in one patient with HCL-v. However, flow cytometry detected MRD with 1.5% malignant cells [42]. The B-cell receptor inhibitor, Ibrutinib, failed to induce complete remission in 28 patients (1 treatment-naïve HCL-v, 10 relapsed HCL-v, and 17 relapsed HCL) and showed a better overall response rate in subjects with HCL [43].

3.7 Prognosis

HCL-v is a treatable but still incurable chronic disease. The median survival is 9 years, and 42% of patients die of unrelated causes. Transformation to large-cell lymphoma is seen in 6% of patients [21]. A study of 35 cases of HCL-v showed a significantly shorter five-year survival in HCL-v compared with SMZL (57% vs. 84%). In contrast, classical HCL has a good response to purine analogs with a five-year and 10-year survival reaching 90%. Poor prognostic indicators in HCL-v include *TP53* mutation, older age, and severe anemia. For example, the five-year survival was 11% in patients with *TP53* mutation compared with 73% in patients without it [23].

4. Differential diagnosis

SDRPL and HCL-v must be differentiated from each other and other low-grade B-cell lymphomas/leukemias in the spleen, in particular SMZL, HCL, and lymphoplasmacytic lymphoma (LPL). This task can be a challenge even for experienced hematopathologists since these entities may present clinical and pathologic overlap. Splenomegaly may be the principal clinical finding, and the neoplastic B cells in these four malignancies are generally double negative for CD5 and CD10. In addition, HCL-v displaying prominent nucleoli could be confused with B-PLL. However, clinicopathological correlation, including immunohistochemistry, should allow a categorical differentiation from B-PLL. Salient differential features are highlighted below focusing on distinctions among SMZL, HCL, and LPL (**Table 1**). Finally, a brief differential between HCL-v and B-PLL are presented.

4.1 Splenic marginal zone lymphoma

The key differentiating trait of classic SMZL from other diseases is nodular involvement of the white pulp frequently showing a microscopic targetoid appearance composed of a darker central zone with small lymphocytes surrounded by a peripheral zone of larger paler marginal zone cells. This pattern is better appreciated on Ki-67 immunohistochemistry. Blood lakes are absent, unlike in SDRPL, HCL, and HCL-v, which all grossly show a characteristic “beefy” red cut splenic surface (correlated with red pulp infiltration and atrophic white pulp). The bone marrow involvement may also be nodular, but interstitial and intrasinusoidal patterns are also common. Notably, well-formed reactive follicles can be seen, which are typically absent in the other entities.

Immunohistochemistry may be of limited value to diagnose CD5/CD10-negative lymphomas due to variable expression of possible differentiating markers. Ideally, both CD25 and CD103 are positive in SMZL and HCL, while CD25 and CD103 are absent in HCL-v and LPL, respectively. In contrast, SDRPL should be double negative for CD25 and CD103. However, this routine clinicopathologic information may

	Peripheral Blood	Spleen	Bone marrow	Immunophenotype	Chromosomal Aberrations	Altered Genes
SDRLP	Polar broad base small villous projections, condensed chromatin	Red pulp, blood lakes (possible)	Intrasinusoidal, interstitial ±, nodular ± (no follicles)	CD25-, CD103±, CD123-, DBA44±, Annexin A1-, Cyclin D3+, IgG+	Uncommon: Trisomy 3q, Trisomy 18, del 7q	<i>CCND3</i> , <i>IGHV3-4</i> , <i>BCOR</i> , <i>MAP2K1</i>
HCL-v	Circumferential shorter villous projections, prominent nucleoli (subset)	Red pulp, white pulp effacement, blood lakes (uncommon)	Interstitial, Intrasinusoidal, no increased fibrosis	CD25-, CD103+, CD123-, DBA44+, Annexin A1-, TRAP±	del 17p, del 7q, Gain of 5	<i>MAP2K1</i> , <i>IGHV4-34</i> , <i>U2AF1</i> , <i>ARID1A</i> , <i>TP53</i>
HCL	Circumferential long (hairy) projections, oval nucleus, inconspicuous nucleolus	Red pulp, blood lakes (common)	Interstitial, diffuse, prominent fibrosis (dry tap)	CD25+, CD103+, CD123+, DBA44+, Annexin A1+, CD200+, CyclinD1±	Chromosomes 5 and 7 abnormalities	<i>BRAF</i> V600E
SMZL	Polar shorter villi (or similar to SDRPL), condensed chromatin.	White pulp with marginal zone expansion	Nodular±, intrasinusoidal ±, interstitial± (residual follicles)	CD25±, CD103±, CD123-, DBA44±, Annexin A1-, IgD+	Gain of 3q, del 7q	<i>NOTCH2</i> , <i>IGHV1-2</i> , <i>KLF2</i>

Table 1.
Differential diagnosis for splenic B-cell leukemia/lymphoma-unclassifiable.

be equivocal, and therefore, esoteric testing including cytogenetic and molecular analysis may be necessary. Cytogenetic abnormalities including deletion 7q, trisomy 3q, trisomy 12q, and *IGH* mutation are more common in SMZL than in the other diseases considered [36]. In addition, *NOTCH2*, the most commonly mutated gene in SMZL, has been detected in 20–25% of cases and is classified as a recurrent alteration in this disease [37]. Furthermore, *IGHV* mutation with a predilection for VH1–2 usage, present in SMZL, is so far absent in SDRPL, which may be of diagnostic value [7].

4.2 Hairy cell leukemia

Although HCL shares with SDRPL and HCL-v a diffuse pattern of red pulp involvement accompanied by atrophy of the white pulp, its clinicopathologic/molecular features are usually very distinctive. HCL frequently presents with significant pancytopenia and monocytopenia without lymphocytosis. In the contrast, HCL-v and SDRPL are often associated with lymphocytosis without monocytopenia. Bone marrow morphology may show focal or diffuse involvement with characteristic cytology demonstrating round/oval nuclei and somewhat abundant well-demarcated cytoplasm (conferring a “fried-egg” appearance). However, a sinusoidal pattern, which is possible in the other diseases, would make the diagnosis of HCL improbable. Furthermore, significantly increased reticulin fibrosis delineating every neoplastic cell is characteristic and almost always presents in HCL [1]. Immunophenotypically, triple-positivity for CD25, CD103, and CD123 (or quadruple-positivity considering CD11c), is very helpful for solidifying the diagnosis of HCL. In addition, expression of tartrate-resistant acid phosphate and annexin A1 may also be seen, which tend to be negative in the other entities in the differential diagnosis. Of interest, DBA.44 is a nonspecific marker that can also be expressed in SDRPL, HCL-v, and SMZL, limiting its diagnostic power. Finally, the vast majority of HCL cases harbor the *BRAF* V600E mutation, which can allow a definitive diagnosis in difficult cases [36]. Notably, *BRAF* can be detected by immunohistochemistry and can be present in 2% of SMZL [44, 45].

4.3 Lymphoplasmacytic lymphoma

LPL is a bone marrow disease typically recognized by the combination of an IgM gammopathy (with possible hyperviscosity/Waldenstrom macroglobulinemia) and the characteristic *MYD88* L265P mutation, which is present in more than 90% of cases [1, 22]. However, approximately 15–30% of cases can show progressive nodal and/or extranodal involvement resembling other low-grade splenic lymphomas involving red pulp (SDRLP, HCL, and HCL-v). Some of the distinguishing characteristics have been described in the preceding sections, including the nodular white pulp splenic involvement also seen in SMZL. In addition, double negativity for CD103 and CD123 should allow the exclusion of HCL and HCL-v. Therefore, the remaining diagnostic dilemma may be between rare *MYD88*-unmutated/IgM-negative LPL (exceedingly rare) and SDRPL, which is frequently positive for DBA.44, IgG (up to 66% of cases) and cyclin D3 by immunohistochemistry. In addition, molecular analysis may be contributory in equivocal situations, revealing *CCDN3* and *BCOR* mutations in SDRPL versus *del6q* in LPL [22, 46].

4.4 B-cell prolymphocytic leukemia

B-PLL is an extremely rare disease that may present de novo, mimicking HCL-v. B-PLL shows B cells with prominent nucleoli and without villous projections.

However, B-PLL usually follows a more aggressive course with massive splenomegaly and accelerated lymphocytosis above $100 \times 10^9/L$. CD103 expression in HCL-v should resolve this quandary. However, due to variable immunophenotypes and genetic profiles, differentiation of B-PLL from HCL-v may be difficult, especially when a splenectomy specimen is unavailable (since B-PLL may show white pulp or red pulp involvement, while HCL-v is restricted to the red pulp) [1, 22, 28]. Specific molecular markers have not been identified yet to resolve this differential diagnosis. *TP53* alterations have been detected in both entities [1, 28], but *MYC* alterations have been described only in a subset to B-PLL [45].

5. Conclusion

In summary, a review of splenic B-cell lymphoma/leukemia, unclassifiable has been presented, focusing on the differential diagnosis of SDRPL and HCL-v, the two most recognizable members of this group.

Conflict of interest

The authors reported no potential conflicts of interest.

Author details

Parastou Tizro^{1*}, Rami Abdulbaki², Anita Aggarwal³, Aaron Auerbach⁴
and Victor E. Nava³

1 City of Hope Comprehensive Cancer Center, Los Angeles CA, USA

2 George Washington University Hospital, Washington, DC, USA

3 Veterans Affairs Medical Center, Washington DC, USA

4 The Joint Pathology Center, Silver Spring, MD, USA

*Address all correspondence to: ptizro@coh.org

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon: IARC; 2017
- [2] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC; 2008
- [3] Saboo SS, Krajewski KM, O'Regan KN, Giardino A, Brown JR, Ramaiya N, et al. Spleen in haematological malignancies: Spectrum of imaging findings. *The British Journal of Radiology*. 2012;**1009**:81-92. DOI: 10.1259/bjr/31542964
- [4] Shimizu-Kohno K, Kimura Y, Kiyasu J, Miyoshi H, Yoshida M, Ichikawa R, et al. Malignant lymphoma of the spleen in Japan: A clinicopathological analysis of 115 cases. *Pathology International*. 2012;**62**(9):577-582. DOI: 10.1111/j.1440-1827.2012.02844.x
- [5] Li M, Zhang L, Wu N, Huang W, Lv N. Imaging findings of primary splenic lymphoma: A review of 17 cases in which diagnosis was made at splenectomy. *PLoS One*. 2013;**8**(11): e80264. DOI: 10.1371/journal.pone.0080264
- [6] Traverse-Glehen A, Baseggio L, Bauchu EC, Morel D, Gazzo S, Ffrench M, et al. Splenic red pulp lymphoma with numerous basophilic villous lymphocytes: A distinct clinicopathologic and molecular entity? *Blood*. 2008;**111**:2253-2260
- [7] Kanellis G, Mollejo M, Montes-Moreno S, Rodriguez-Pinilla SM, Cigudosa JC, Algara P, et al. Splenic diffuse red pulp small B-cell lymphoma: Revision of a series of cases reveals characteristic clinico-pathological features. *Haematologica*. 2010;**95**(7):1122-1129. DOI: 10.3324/haematol.2009.013714
- [8] Kerbaux MN, Fernandes CM, Bezerra ED, Lage LA, Siqueira SA, Pereira J. Splenic diffuse red-pulp small B-cell lymphoma associated with hepatitis B virus: A report of two cases. *São Paulo Medical Journal*. 2016;**134**(4):359-365. DOI: 10.1590/1516-3180.2016.0035130416
- [9] Medeiros LJ, Miranda RN. Splenic Diffuse Red Pulp Small B-Cell Lymphoma. *Diagnostic Pathology: Lymph Nodes and Extranodal Lymphomas*. Second ed. Philadelphia, USA: Elsevier; 2018. pp. 574-581
- [10] Ponzoni M, Kanellis G, Pouliou E, Baliakas P, Scarfò L, Ferreri AJ, et al. Bone marrow histopathology in the diagnostic evaluation of splenic marginal-zone and splenic diffuse red pulp small B-cell lymphoma: A reliable substitute for spleen histopathology? *The American Journal of Surgical Pathology*. 2012;**36**(11):1609-1618. DOI: 10.1097/PAS.0b013e318271243d
- [11] Traverse-Glehen A, Baseggio L, Salles G, Coiffier B, Felman P, Berger F. Splenic diffuse red pulp small-B cell lymphoma: Toward the emergence of a new lymphoma entity. *Discovery Medicine*. 2012;**13**(71):253-265
- [12] Martinez D, Navarro A, Martinez-Trillos A, Molina-Urra R, Gonzalez-Farre B, Salaverria I, et al. NOTCH1, TP53, and MAP2K1 mutations in splenic diffuse red pulp small b-cell lymphoma are associated with progressive disease. *The American Journal of Surgical Pathology*. 2016;**40**(2):192-201. DOI: 10.1097/PAS.0000000000000523
- [13] Curiel-Olmo S, Mondéjar R, Almaraz C, Mollejo M, Cereceda L,

Marès R, et al. Splenic diffuse red pulp small B-cell lymphoma displays increased expression of cyclin D3 and recurrent CCND3 mutations. *Blood*. 2017;**129**:1042-1045. DOI: 10.1182/blood-2016-11-751024

[14] Baseggio L, Traverse-Glehen A, Callet-Bauchu E, Morel D, Magaud JP, Berger F, et al. Relevance of a scoring system including CD11c expression in the identification of splenic diffuse red pulp small B-cell lymphoma (SRPL). *Hematological Oncology*. 2011;**29**(1): 47-51. DOI: 10.1002/hon.957

[15] Jallades L, Baseggio L, Sujobert P, Huet S, Chabane K, Callet-Bauchu E, et al. Exome sequencing identifies recurrent BCOR alterations and the absence of KLF2, TNFAIP3 and MYD88 mutations in splenic diffuse red pulp small B-cell lymphoma. *Haematologica*. 2017;**102**:1758

[16] Wang R-C et al. Villous lymphocytes in splenic large B-cell lymphoma with diffuse red pulp infiltration. *International Journal of Hematology*. 2019;**109**(2):133-134

[17] Hoehn D, Miranda RN, Kanagal-Shamanna R, Lin P, Medeiros LJ. Splenic B-cell lymphomas with more than 55% prolymphocytes in blood: Evidence for prolymphocytoid transformation. *Human Pathology*. 2012;**43**(11):1828-1838. DOI: 10.1016/j.humpath.2012.01.003

[18] Cheng WY, Zhu YM, Cheng S, Chen YS, Shen Y. Development of B-cell prolymphocytic leukemia in a patient with splenic diffuse red pulp small B-cell lymphoma. *Leukemia & Lymphoma*. 2018;**59**(8):1990-1993. DOI: 10.1080/10428194.2017.1405397

[19] Cawley JC, Burns GF, Hayhoe FG. A chronic lymphoproliferative disorder with distinctive features: A distinct variant of hairy-cell leukaemia. *Leukemia Research*. 1980;**4**(6):547-545

[20] Wang X, Spielberger R, Huang Q. Hairy cell leukemia variant, a new entity of the WHO 2008. *Journal of Clinical Oncology*. 2011;**29**(36):e864-e866

[21] Matutes E, Wotherspoon A, Catovsky D. The variant form of hairy cell leukaemia. *Best Practice & Research. Clinical Haematology*. 2003;**16**(1):41-56. DOI: 10.1016/s1521-6926(02)00086-5

[22] Matutes E. Diagnostic and therapeutic challenges in hairy cell leukemia-variant: Where are we in 2021? *Expert Review of Hematology*. 2021;**14**(4):355-363. DOI: 10.1080/17474086.2021.1908121

[23] Hockley SL, Else M, Morilla A, Wotherspoon A, Dearden C, Catovsky D, et al. The prognostic impact of clinical and molecular features in hairy cell leukaemia variant and splenic marginal zone lymphoma. *British Journal of Haematology*. 2012;**158**(3):347-354. DOI: 10.1111/j.1365-2141.2012.09163.x

[24] Robak T. Current treatment options in hairy cell leukemia and hairy cell leukemia variant. *Cancer Treatment Reviews*. 2006;**32**(5):365-376. DOI: 10.1016/j.ctrv.2006.04.010

[25] Zanelli M, Ragazzi M, Valli R, Piattoni S, Alvarez De Celis MI, Farnetti E, et al. Transformation of IGHV4-34+ hairy cell leukaemia-variant with U2AF1 mutation into a clonally-related high grade B-cell lymphoma responding to immunochemotherapy. *British Journal of Haematology*. 2016;**173**(3):491-495. DOI: 10.1111/bjh.13627

[26] Kanellis G, Garcia-Alonso L, Camacho FI, Garcia JF, Mollejo M, Montes-Moreno S, et al. Hairy cell leukemia, blastic type: Description of spleen morphology and immunophenotype of a distinctive case. *Leukemia & Lymphoma*. 2011;**52**(8): 1589-1592. DOI: 10.3109/10428194.2011.575488

- [27] Cessna MH, Hartung L, Tripp S, Perkins SL, Bahler DW. Hairy cell leukemia variant: Fact or fiction. *American Journal of Clinical Pathology*. 2005;**123**(1):132-138. DOI: 10.1309/8qytyq1clqmhq9cl
- [28] Matutes E, Wotherspoon A, Brito-Babapulle V, Catovsky D. The natural history and clinico-pathological features of the variant form of hairy cell leukemia. *Leukemia*. 2001;**15**(1):184-186. DOI: 10.1038/sj.leu.2401999
- [29] Alapat D, Coviello-Malle J, Owens R, Qu P, Barlogie B, Shaughnessy JD, et al. Diagnostic usefulness and prognostic impact of CD200 expression in lymphoid malignancies and plasma cell myeloma. *American Journal of Clinical Pathology*. 2012;**137**(1):93-100. DOI: 10.1309/AJCP59UORCYZEVQO
- [30] Matutes E. Immunophenotyping and differential diagnosis of hairy cell leukemia. *Hematology/Oncology Clinics of North America*. 2006;**20**(5):1051-1063. DOI: 10.1016/j.hoc.2006.06.012
- [31] Hockley SL, Morgan GJ, Leone PE, Walker BA, Morilla A, Else M, et al. High-resolution genomic profiling in hairy cell leukemia-variant compared with typical hairy cell leukemia. *Leukemia*. 2011;**25**(7):1189-1192
- [32] Zhang R, Wu Y, Wang X, Lu X, Li Y, Li S, et al. Difference of genomic copy numbers alterations between hairy cell leukemia-variant and classical hairy cell leukemia: A pilot retrospective study in Chinese. *International Journal of Medical Sciences*. 2020;**17**(3):325-331. DOI: 10.7150/ijms.39307
- [33] Laurini JA, Aoun P, Iqbal J, Chan W, Greiner TC. Investigation of the BRAF V600E mutation by pyrosequencing in lymphoproliferative disorders. *American Journal of Clinical Pathology*. 2012;**138**:877-883
- [34] Tiacci E, Schiavoni G, Forconi F, Santi A, Trentin L, Ambrosetti A, et al. Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. *Blood*. 2012;**119**(1):192-195. DOI: 10.1182/blood-2011-08-371179
- [35] Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, et al. BRAF mutations in hairy-cell leukemia. *The New England Journal of Medicine*. 2011;**364**(24):2305-2315. DOI: 10.1056/NEJMoa1014209
- [36] Waterfall JJ, Arons E, Walker RL, Pineda M, Roth L, Killian JK, et al. High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias. *Nature Genetics*. 2014;**46**(1):8-10. DOI: 10.1038/ng.2828
- [37] Dufresne SD, Felgar RE, Sargent RL, Surti U, Gollin SM, McPhail ED, et al. Defining the borders of splenic marginal zone lymphoma: A multiparameter study. *Human Pathology*. 2010;**41**(4):540-551. DOI: 10.1016/j.humpath.2009.09.007
- [38] Shehata M, Schwarzmeier JD, Hilgarth M, Hubmann R, Duechler M, Gisslinger H. TGF-beta1 induces bone marrow reticulin fibrosis in hairy cell leukemia. *The Journal of Clinical Investigation*. 2004;**113**(5):676-685. DOI: 10.1172/JCI19540
- [39] Yoshida T, Mihara K, Sugihara S, Arihiro K, Mino T, Sasaki N, et al. Splenectomy followed by administration of rituximab is useful to treat a patient with hairy cell leukemia-variant. *Annals of Hematology*. 2013;**92**(5):711-713. DOI: 10.1007/s00277-012-1612-1
- [40] Kreitman RJ, Wilson W, Calvo KR, Arons E, Roth L, Sapolsky J, et al. Cladribine with immediate rituximab for the treatment of patients with variant hairy cell leukemia. *Clinical Cancer Research*. 2013;**19**(24):6873-6881. DOI: 10.1158/1078-0432.CCR-13-1752

- [41] Kreitman RJ, Wilson WH, Bergeron K, Raggio M, Stetler-Stevenson M, FitzGerald DJ, et al. Efficacy of the anti-CD22 recombinant immunotoxin BL22 in chemotherapy-resistant hairy-cell leukemia. *The New England Journal of Medicine*. 2001;**345**(4):241-247. DOI: 10.1056/NEJM200107263450402
- [42] Telek B, Batár P, Udvardy M. Atipusos vonásokot mutató hajas sejtes leukémiavariáns sikeres alemtuzumab- (Campath 1H) kezelése [Successful alemtuzumab treatment of a patient with atypical hairy cell leukaemia variant]. *Orvosi Hetilap*. 2007;**148**(38): 1805-1807. DOI: 10.1556/OH.2007.28169
- [43] Troussard X, Grever MR. The revised guidelines for the diagnosis and management of hairy cell leukaemia and the hairy cell leukaemia variant. *Br J Haematology*. 2021;**193**(1):11-14. DOI: 10.1111/bjh.17201
- [44] Turakhia S, Lanigan C, Hamadeh F, Swerdlow SH, Tubbs RR, Cook JR. Immunohistochemistry for BRAF V600E in the Differential Diagnosis of Hairy Cell Leukemia vs Other Splenic B-Cell Lymphomas. *Am J Clin Pathol*. 2015 Jul;**144**(1):87-93. DOI: 10.1309/AJCP5WVXJ2KTLODO. PMID: 26071465
- [45] Flatley E, Chen AI, Zhao X, Jaffe ES, Dunlap JB, Pittaluga S, et al. Aberrations of MYC are a common event in B-cell prolymphocytic leukemia. *American Journal of Clinical Pathology*. 2014;**142**(3):347-354. DOI: 10.1309/AJCPUBHM8U7ZFLOB
- [46] Cook JR, Aguilera NI, Reshmi S, Huang X, Yu Z, Gollin SM, et al. Deletion 6q is not a characteristic marker of nodal lymphoplasmacytic lymphoma. *Cancer Genetics and Cytogenetics*. 2005;**162**(1):85-88