

# HAIRY CELL LEUKEMIA: BIOLOGY, CLINICAL DIAGNOSIS, UNUSUAL MANIFESTATIONS AND ASSOCIATED DISORDERS

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*In the present article, we have reviewed all the clinical features of patients suffering from hairy cell leukemia (HCL) and have stressed some of the unusual and rare manifestations of the disease, associations with autoimmune disorders and possible links with other malignancies. Newer data on the biology and epidemiology of HCL are also summarized, while classic morphologic features as seen by light and electron-microscopy, as well as immunophenotypic and molecular genetic data, are provided in some detail. Diagnostic criteria and differential diagnosis are also discussed. It is hoped that this detailed review of the current knowledge available on HCL will serve as a guide to those who are interested in this unusual disease.*

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## HISTORICAL ASPECTS – BACKGROUND

Hairy cell leukemia (HCL) is an uncommon but distinct form of chronic lymphoproliferative disorder characterized by an indolent course, peripheral cytopenias and splenomegaly due to the presence of characteristic neoplastic B lymphocytes in the blood, bone marrow and organs of the “classic” reticuloendothelial system (RES), associated with reticulin-fibrosis of the marrow (Table 1). The diagnosis is based upon the recognition of the characteristic “hairy” nature of the leukemic lymphoid cells in the

peripheral blood smears and the typical appearance and pattern of infiltration in the bone marrow biopsies in association with increased reticulin and eventual fibrosis of the marrow (1, 2). Additional special features include the presence of tartrate resistant acid phosphatase (TRAP) positivity within the cells associated with a specific HCL immunophenotypic profile on flow cytometry and elevated levels of soluble interleukin 2 receptors (solIL-2R) in the peripheral circulation, which are all important features in establishing the diagnosis.

HCL was first recognized as early as the mid 1920's (3) and later in 1956 but was termed leukemic reticuloendotheliosis. Other terms, such as histiocytic leukemia, malignant reticulosis, lymphoid myelofibrosis

*HCL is a B-cell neoplasia in which therapy is extremely effective in controlling the disease and even achieving complete remission, though cell biology, pathogenesis and molecular genetic defects are not well understood.*

**Table 1**  
**Diagnostic features clinically**

- Pancytopenia
- Splenomegaly
- HC in peripheral blood
- Dry tap on aspiration
- Bone marrow reticulin-fibrosis

had all been used, suggesting that the disease had already been recognized earlier as a separate entity (2). However, Bouroncle *et al.* (4) were the first group to describe HCL as a distinct clinical and histopathologic entity in 1958, identifying it as a disorder with an indolent course, characteristic clinical and laboratory features and an excellent prognosis if treated correctly. The beneficial effect of splenectomy had already been noted in earlier reports, yet nomenclature remained problematic and confusing, while no progress was made at that time in terms of identifying the true nature of the neoplastic cells, until the newer immunophenotypic methodologies became available in the mid-1970's (2, 5).

In 1969, Lee *et al.* (6) also described 26 HCL patients, still using the terminology of reticulum cell leukemia, stressing its similarity to chronic lymphocytic leukemia (CLL). In 1966, Schrek and Donnelly were the first to use the term "hairy cell" (HC) (7), noting the fine hair-like cytoplasmic projections under contrast phase microscopy and realizing that their two cases were similar to those described earlier in 1958 (4). Thereafter, the terms HC and HCL were used widely and, once the era of modern immunology developed and immunophenotyping using flow cytometry and FACS became routine procedures, more groups became interested in the true nature and identification of HC and HCL by surface markers, transmission and scanning electron (and immunoelectron) microscopy (8–26). The classic "hybrid-like" morphologic features of lympho-monocytic cells were appreciated and specific ultrastructural features and the complex surface

topography were described in more detail (14, 15, 27–33). Debates still continued on the origin of this unusual cell type, whether it was of macrophage/monocyte or lymphoid origin; however, in the mid-late 1970's, it was clearly shown that these were B lymphocytic in origin. HC showed strongly positive surface immunoglobulin (SIg) (10–12), clear evidence was provided to show that HC were able to synthesize Ig and it was recognized that there were Ig gene rearrangements present in these cells (12, 22, 25).

Other classic features relating to TRAP positivity (13, 17), surface topography, the presence of the IL-2 surface receptor CD25 and of CD11c (18, 23, 24, 34) were soon appreciated as additional diagnostic tools to establish the diagnosis with certainty. This new information led to the more ready recognition and diagnosis of HCL as a special entity which could be quite easily controlled and treated using a number of different therapeutic modalities (21, 35–40). These varied from splenectomy to the successful use of interferon alpha (IFN- $\alpha$ ) in the mid 1980's and the eventual "clinical cure" so readily obtained once the purine analogs (pentostatin and cladribine) became available in the mid 1980's and 1990's (2, 21, 35–40). Inappropriate aggressive therapies were now redundant and the negative results obtained using more aggressive therapy were not repeated (for further information on treatment see accompanying article by M. Tallmann). HCL became a fine example of how a neoplasm could be successfully managed and clinically "cured" by using appropriate drugs, despite the fact that its biology, pathogenesis and etiology are still not understood.

## MORPHOLOGY OF HAIRY CELLS

On light microscopy, these cells are 10–15  $\mu\text{m}$  in diameter and have a solitary slightly

eccentric nucleus which is usually round, ovoid or indented but rarely lobulated (Table 2). The chromatin is dispersed or stippled and nucleoli are not readily seen (Fig 1). The moderately abundant cytoplasm is pale blue-gray and sometimes rod-shaped inclusions may be seen, which are the counterparts of the ribosomal-lamella complex (RLC) seen on electron microscopy (14, 41, 27–29). The typical cytoplasmic outline is irregularly frayed with fine hair-like villi or broader ruffles. Most HC have a strongly staining acid phosphatase reaction resistant to tartrate (TRAP positive) (Fig 2).

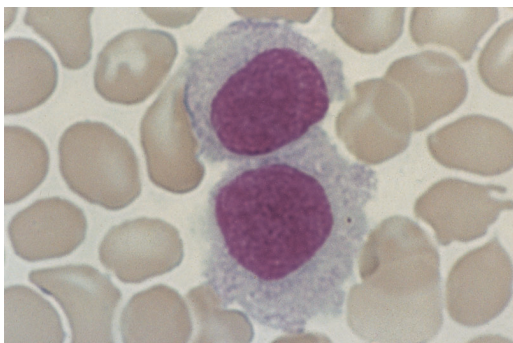
A variant form of the HC has been described which is quite similar to the prolymphocytes seen in B-prolymphocytic leukemia (B-PLL) (42–46). This variant HC has a more central round nucleus with a prominent nucleolus and coarse chromatin pattern (Fig 3). The variant HC also has blue-gray cytoplasm with irregular villous surface projections, but is generally TRAP-negative.

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**Table 2**  
**Hairy cell morphology**

- 10–15  $\mu\text{m}$  in diameter
- Moderate amount of pale-blue cytoplasm
- Central round/oval nucleus
- Stippled/dispersed nuclear chromatin
- Inconspicuous nucleoli
- Fine “hairy” projections
- TRAP positive staining
- Rod-shaped (RLC) inclusions

**Figure 1:** Typical hairy cell leukemia cells in the peripheral blood showing ample cytoplasm with irregular surface and typical nuclear features.

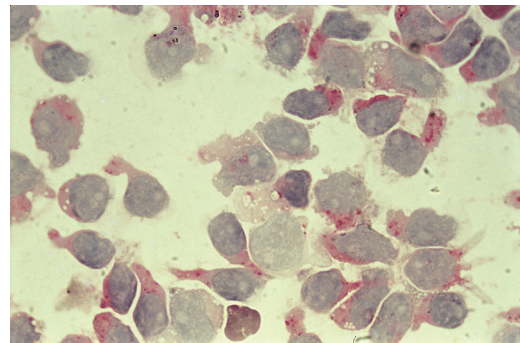


Monocytopenia is typically associated with true HCL and not with the HCL variants. HC surface morphology is best appreciated by phase microscopy of a viable “wet” preparation of moving cells in suspension and here the typical villous nature of the HC are easily appreciated.

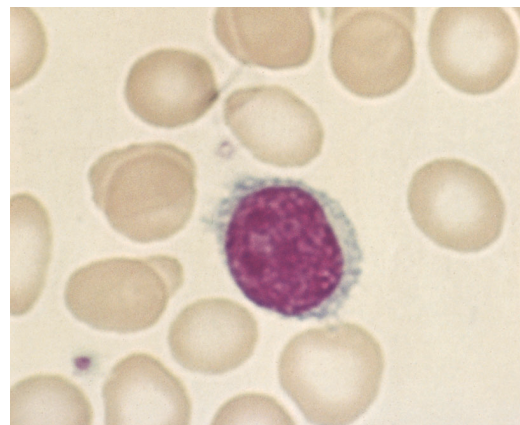
## ULTRASTRUCTURE OF HC

Prior to the era of immunocytochemistry and modern flow cytometry, ultrastructural techniques were used to diagnose HCL with more confidence. Today, neither transmission (TEM) or scanning electron microscopy (SEM) are used routinely in diagnosis. The classic light microscopic features of HC could readily

**Figure 2:** Strong tartrate resistant acid phosphatase (TRAP) positive staining in hairy cell leukemia cells.



**Figure 3:** Hairy cell leukemia variant cell with central round nucleus and nucleolus.

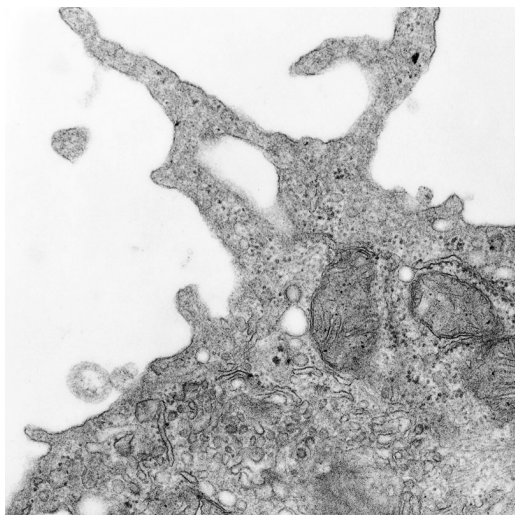


be appreciated on TEM and the long delicate surface microprojections reaching up to 3 μm in length are easily seen and often interdigitate (Fig 4). Pinocytotic activity is seen and peripheral cytoplasmic vesicles and phagocytosis may be evident. Oval mitochondria are quite abundant and dense lysosomal bodies and fine fibrils are present. Cylindric tubular inclusions termed ribosomal-lamellae complexes (RLC) first described in 1972 and 1973 (27–29), are seen in about 50% of HCL cases and in individual cases up to 90% of cells may contain these structures (Fig 5). The Ribosomallamellae complexes (RLC) are typical of HC and their cross and longitudinally sectioned appearance as cylindrical structures

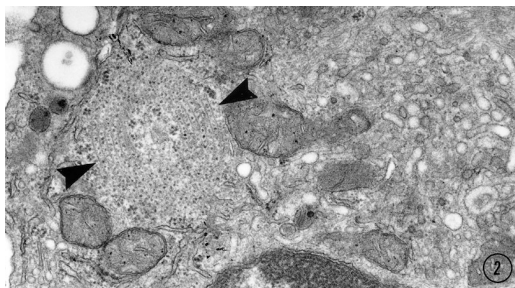
with a hollow central space and an outer sheath of parallel lamellae of fixed sizes filled with ribosome-like granules are unmistakable and their origin still unexplained.

SEM, as well as immune-SEM of HC (15, 30–33), reveals the fascinatingly complex surface topography of the HC, which shows clusters of microvilli scattered between complex broad surface ruffles, an appearance which is a hybrid lymphocyte-monocyte surface (Fig 6). Many of these ruffles are elongated and during movement may alter becoming extremely long as well

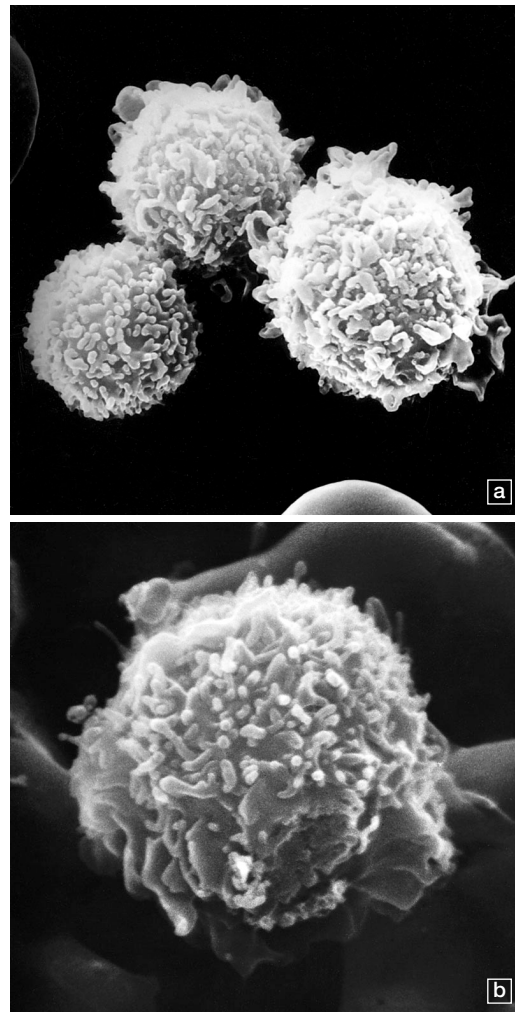
**Figure 4:** High power transmission electron microscopic (TEM) view of elongated surface microprojections so typical of hairy cells.



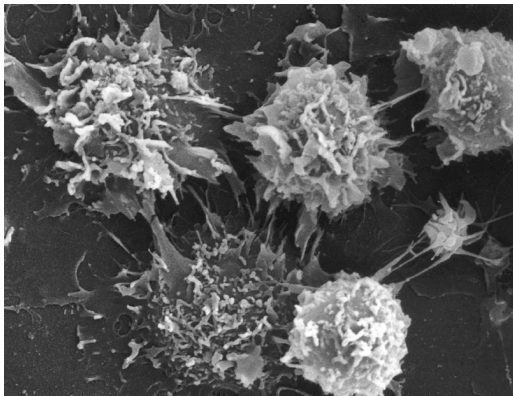
**Figure 5:** High power TEM showing typical ribosomal lamellae complexes (RLC) in the cytoplasm of HCL cells.



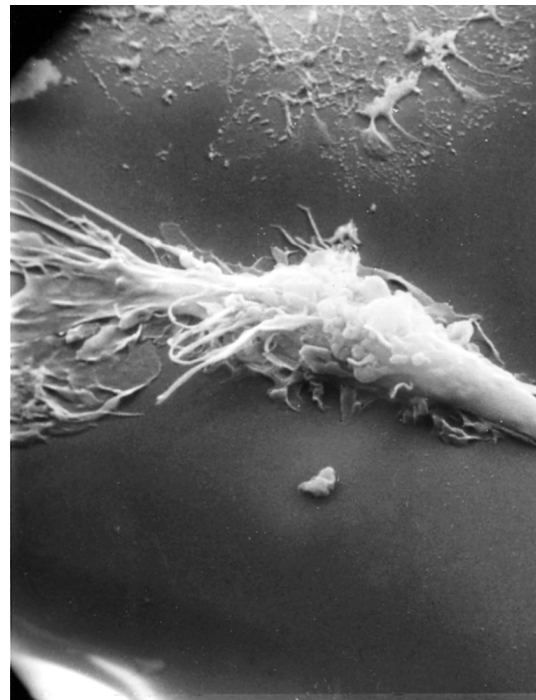
**Figure 6:** Scanning electron microscopy (SEM) of hairy cell leukemia cells showing typical complex surface features with combinations of surface microvilli and broader ruffles.



**Figure 7:** SEM of a group of hairy cells attaching and adhering to an underlying substrate, showing many filamentous cytoplasmic extensions.



**Figure 8:** Glass – adherent HCL cell showing shape change and an elongated “fibroblast” – like appearance as seen by SEM.



as serving as broad cytoplasmic attachments to any underlying substrate (Figs 7 and 8). Immune-SEM shows the distribution of antigenic sites on this complex cell surface, particularly when back-scattered imaging techniques are used. Although sadly, these techniques are seldom used today, it should be stressed that they are specific and diagnostic for HCL.

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### PERIPHERAL BLOOD IN HCL

When the peripheral blood smear is examined, HC are found in almost all instances. In some cases, cells are infrequent and difficult to find and only evident after a long search. Phase microscopy done on concentrated mononuclear cell suspensions or buffy coats will invariably enable cells to be identified, with relative ease. In general, patients will have leukopenia and most will have a white blood cell (WBC) count of  $< 3 \times 10^9/L$ . A few patients may indeed show leukocytosis and very rare cases may have extreme hyperleukocytosis  $> 100 \times 10^9/L$ . This absolute neutropenia may be associated with varying degrees of thrombocytopenia (generally  $> 50 \times 10^9/L$ ) and a normocytic normochromic anemia (1, 5, 16, 19, 20). Monocytopenia is a persistent feature of

**Table 3**  
**Bone marrow pathology**

- Hypercellular marrow, mostly
- Diffuse involvement, but can be “patchy”
- Hypoplasia, focal aplasia, can be seen
- No paratrabecular involvement
- HC merge into background
- “Fried-egg” appearance
- Increased reticulin-fibrosis
- Mast-cell increase
- TRAP + cells on touch smear

HCL (47), while rare cases show increased number of large granular lymphocytes and natural killer (NK) cells.

### BONE MARROW IN HCL

Infiltration of the marrow by HC is seen in all patients with HCL (Table 3). The marrow is classically difficult to aspirate (dry tap) and the biopsy usually shows a hypercellular

picture in most cases with diffuse involvement and increased reticulin fibers eventually causing fibrosis of the marrow (16, 48–52). Nevertheless, focal or patchy and interstitial involvement may also be seen and in a proportion of cases (10–20%) there may even be a hypocellular picture with areas of focal aplasia (51). HC do not show paratrabecular involvement and when the pattern is one of interstitial involvement, the HC are seen to merge in-between the remaining hematopoietic cells and fat tissue. In the hypocellular type of HCL, immunostaining of the HC will make the diagnosis easier to establish (51). In the biopsy sections, HC lose their typical “hairy” appearance and there is shrinkage of the abundant cytoplasm, resulting in the picture of nuclei spaced widely from each other by surrounding empty pale cytoplasm (“fried-egg” appearance). Nuclei appear bland without nucleoli, unlike other packed leukemic marrows (48–52). Mast cell hyperplasia is often present (53).

Another typical feature is the appearance of focal congested areas with widened “angiomatic” vascular lakes, with extravasated erythrocytes, formed by merging of these dilated sinusoids involved by HC (54–57). Increased reticulin-fibrosis is always evident and is often very marked. The latter is due to the secretion of fibronectin-matrix by the HC, eventually resulting in secondary reticulin-fibrosis (56, 57). This is the reason for the difficulty in aspiration and the dry tap encountered in HCL.

### SPLEEN IN HCL

Splenomegaly is usually present in about 80% of the patients (Table 4) (1, 5, 16, 19, 20). HCL is mostly a red pulp disorder with infiltration of the cords and sinusoids (48, 50, 58, 59). HC often replace the endothelial lining cells in the splenic sinusoids and these congested pseudosinususes merge to form

**Table 4**  
**Splenic pathology – HCL**

- Red pulp disease
- Sinusoidal involvement by HC
- Congested red pulp
- Angiomatous lakes form
- White pulp atrophic

congested angiomatous lakes (54), a phenomenon which is characteristic of HCL and which is also seen in the bone marrow. The white pulp can also be replaced by HCL and is often atrophic. Liver involvement is frequent with sinusoidal involvement, congestion and periportal infiltrates as well (48–50, 58–61).

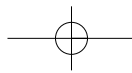
*Typical light microscopic morphology, presence of monocytopenia, immunophenotype, TRAP positivity, ultrastructural features and bone biopsy all contribute to the confident and definitive diagnosis of HCL.*

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### IMMUNOPHENOTYPE OF HAIRY CELLS

HC are B-cell derived and mature, but not terminally, differentiated. B-lineage associated antigens are strongly expressed. SIg and light chain restriction are clearly present. Ig gene rearrangements of both heavy and light chains are found (12, 22, 25). Preferential use of the IgG3 subtype of Ig is the most frequently encountered, but all classes of IgG are expressed, showing that Ig switch has already taken place. There may also be an aberration in class-switching in the constant region of the IgM gene intron.

Typical B-cell markers are clearly evident on HC including surface Ig, CD19, CD20, CD22, CD79A, CD40 and FMC7, while CD5, CD21, CD23 are generally not expressed and CD79B is mostly negative. In addition to these conventional B-cell markers, other activation antigens and “specific” HC markers are also expressed, all of which make up the characteristic HC profile,



CD11c, HC-2, CD25 (the IL-2R) as well as CD103 (an  $\alpha$  subunit of the  $\alpha\beta$  integrin molecule). Thus, the association of the above markers constitutes the typical surface immunophenotype for HCL (24, 25). Some of these phenotypic features are indicative of an activated lymphoid cell profile (CD22, CD25, D72 and CD40-ligand) and are strongly expressed, while BCL-2, CD21 and CD24 are only weakly expressed at low levels. HCL variant cells are invariably CD25-negative and CD103-negative (18, 22–25, 34, 62–69).

In the HCL scoring system (66–68) each one of the following markers, CD25<sup>+</sup>, CD11c<sup>+</sup>, HC2<sup>+</sup> and CD103<sup>+</sup> receives one point in the score and the usual score is 3–4,

while other disorders like HCL variant and splenic lymphoma with villous lymphocytes (SLVL) usually have scores of 0–2 (69). Thus, 98% of typical HCL have a high score (3–4) and only 2% have low scores (0–2), while in HCL variant 87% have a low score (0–2) and only 0–13% have a higher score (3–4). Almost all SLVL have a 0–2 score (69). If one uses the scoring system suggested for CLL (65, 66, 70), HCL will always have a low score (ranging from 0 to 1) compared to CLL, which has a score from 3 to 5. The CLL score gives 1 point for the following markers: CD5<sup>+</sup>, CD23<sup>+</sup>, FMC7<sup>-</sup>, SIg weak and CD22/CD79B weakly positive. These scores and the typical full profile for HCL are summarized in Tables 5–7.

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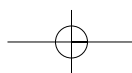
Table 5 Hairy cell scoring system		
	1 point	0 point
CD11c	+	-
CD25	+	-
CD103	+	-
HC2	+	-

HCL score, 3–4 (98%); 4 (86%)  
 HCLv score, 3 (13%); 4 (0%) 1–2 (87%)  
 SLVL score, 3–4 (0%); 0–1 (96%)

Table 6 Scoring system for CLL		
	1 point	0 point
CD5	+	-
CD23	+	-
SIg	±	-
CD22	±	+
CD79B	±	+
FMC7	-	+

CLL score usually 4–5, rarely 3  
 HCL + HCLV score usually 1–3  
 B-cell NHL, score usually 0–2

Table 7 Typical immunophenotype and morphologic features		
Features	HCL	HCL variant
<b>Nucleolus nuclear chromatin</b>	<b>Absent reticular</b>	<b>Present condensed</b>
TRAP	+++ / ++	±
HC2	++	±
CD25	++	±
CD11c	++	++
CD103	++	++
CD20	++	++
CD19	++	++
SIg	++	++
CD22	++	++



## TISSUES – BONE MARROW

On paraffin sectioned tissue material, the monoclonal antibodies used routinely include anti-CD20 (L26) and DBA44 (71, 72). These identify HCL easily and are strongly positive in almost all HC. Positive staining with the antibodies together with the pattern of involvement by HC as seen by light microscopy consolidate the diagnosis of HCL on biopsy sections. Minimal residual disease can also be detected readily by positive immunostaining in patients who are in clinical complete remission (CR) (40, 73, 74). Furthermore, flow cytometry using FACS can also detect residual disease in cell suspension specimens, if a combination of antibodies to HC2, CD11c, CD103 and CD25 is used. Molecular genetic polymerase chain reaction (PCR) techniques to detect Ig heavy chain rearrangements will almost always illustrate residual disease following successful treatment, despite the fact that light microscopic morphology and immunocytochemistry are negative in CR patients.

*The immunophenotypic profile of typical HCL cells show CD5, CD23, CD21 and CD10 negativity, but must show CD11c, CD25, CD103 positivity. The proposed hairy cell scoring system is very useful in the diagnosis of HCL.*

## BIOLOGY – ADHESION RECEPTOR PROFILE AND HOMING RECEPTORS

HC are able to phagocytose and adhere to different substrates preferentially (Table 8). Their complex surface is utilized for these purposes. Furthermore, HC contain F-actin in their active cytoskeletal structure which is employed in signaling activity (26, 56, 75, 76). These highly activated cells are rich in tyrosine-phosphorylated kinases, contain serine and threonine kinases and have pronounced (PKC) activity (26, 76, 77). A variety

**Table 8**  
**Biology of hairy cells**

- Strong expression of F-actin
- VLA-4 ( $\alpha 4\beta 1$  integrin) binds to VCAM-1
- VLA-5 integrin ( $\alpha 5\beta 1$ )
- Fibronectin
- TNF- $\alpha$  (induces endothelial VCAM)
- Vitronectin ( $\alpha V\beta 3$  integrin)
- IL-2 and IL-1 receptors
- GM and M-CSF

of adhesion molecules and homing receptors are present on HC and probably regulate the traffic of HC in the circulation and their homing in the RES (25, 56, 76). These molecules determine their preferential homing sites in the RES. HC do not appear to home to the lymphoid organs, as they lack the lymphoid L-selectin which is probably shed on cell activation. L-selectin enables lymphoid cells to migrate to lymphoid tissues and its absence on HC may explain why HC are not prominent in lymphoid tissues.

HC express adhesion molecules such as CD54/ICAM, CD18, CD49D and the homing receptor CD44. In this respect, homing integrins like VLA-4 play an important role (62, 78). The endothelial cellular ligand of VLA-4 ( $\alpha 4\beta 1$ ), VCAM-1, is present mostly in bone marrow stroma, hepatic and splenic sinusoids, which are in fact the major sites for HC infiltration in patients with HCL (57). VLA-5 ( $\alpha 5\beta 1$ ) is also an important integrin in HC. It binds to fibronectin, which is an extracellular matrix ligand for HCL. Both VLA-4 and VLA-5 bind to fibronectin which is also synthesized and assembled by HC (55, 76). The VNR ( $\alpha V\beta 3$ ) integrin, produced by HC, is linked to the cytoskeleton and also binds to extracellular fibronectin and vitronectin. All these have an important function in cell migration and HC motility, and probably promote their entry into the splenic red pulp circulation (26, 56, 76, 78). HC secrete fibronectin and this may also explain the fine reticulosis and eventual fibrosis seen in the



marrow in HCL. Furthermore, HC integrins, such as VNR ( $\alpha V\beta 3$ ) and VLA-4 ( $\alpha 4\beta 1$ ), are utilized in adhesion and interaction with sinusoidal endothelial cells. After attachment of HC to the endothelium, they eventually replace the lining cells by inducing endothelial cell apoptosis (26, 56, 76, 78).

*Hairy cells express a variety of adhesion molecules and homing receptors which regulate their traffic and homing within the reticulo-endothelial system.*

### CYTOKINES AND CYTOKINE RECEPTORS

There is evidence suggesting that the proliferation of HC is regulated by different cytokines and growth factors (75, 79–81). These are produced in an autocrine and paracrine fashion, and include tumor necrosis factor (TNF  $\alpha$  and  $\beta$ ), macrophage colony stimulating factor (M-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF). Cells also have high and low affinity receptors for these cytokines, as well as for IL-1 and IL-2. Some of them function as growth and survival factors, and cleaved soluble fractions of the above cytokines circulate in the peripheral circulation and their respective levels in the blood are indeed indicative of the tumor bulk present at any given time in the course of the disease (82–85). Thus, they may indeed serve as an indicator of disease activity in HCL.

TNF $\alpha$  induces VCAM expression on endothelial cells thereby contributing to the adhesion of HC. TNF $\alpha$  can also modify and suppress granulocyte colony stimulating factor (G-CSF) production which may also contribute to the degree of leukopenia encountered in these patients. The CSF cytokines may also influence the adhesion and motility of HC.

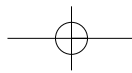
TNF $\alpha$  prolongs the survival and affects proliferation of HC, and HC have both low and high affinity receptors. When these

receptors are cleaved, they circulate in the peripheral blood circulation and in this respect soluble TNF $\alpha$  R80 levels appear to be of more significance in terms of disease status (85–88).

Other cytokines like IL-2 and IL-1 (85–89) have also been shown to be significant in HCL and may indeed affect cell proliferation. Like the levels of TNFR and soluble TNFR, cleaved IL-2R and IL-1R, in soluble form, serve as accurate indicators of tumor bulk and clinical status in HCL, and can be reliably utilized to establish remission or relapse status in HCL. In our own experience, soluble IL-2R levels are a most reliable indicator of disease activity and should always be examined in HCL (85).

### T-cell immunity and susceptibility to infections

The IL are also important as T-cell immunoregulators in HCL and function not only in terms of B-cell proliferation and in response to TNF $\alpha$  secretion (26, 76, 89). Indeed, it is possible that many of the manifestations seen in the peripheral blood in HCL relate to the interactions of these cells with the T-cell system, including monocytopenia and leukopenias (90, 91). There are indeed profound alterations in the T-cell immunity in HCL with the production of a skewed T-cell repertoire. This is reflected in an increase in CD3<sup>+</sup>  $\gamma\delta$  cells as a persistent clonal excess. There is also a recently described severe decrease in peripheral blood dendritic cells in HCL, as well as reported alterations in NK and (large granular lymphocyte) LGL activity (92). All the above no doubt contribute to the well-recognized tendency to infections by intracellular pathogens in HCL. Altered T-cell immunity, profound monocytopenia and impressive decreases in the numbers of antigen presenting dendritic cells known to stimulate the adaptive immune response, all contribute significantly to the infections encountered in this disease.



It is also possible that IL-6, IL-10 and IL-15 (89, 93) may have biologic activities in HCL in terms of regulation of HC proliferation and the immune response. IFN therapy benefits patient and induces CR in HCL; its interaction with cytokines and antigenic receptors is of great interest and still requires further investigation.

*Hairy cell proliferation is regulated by different cytokines and growth factors. There are also associated alterations in T-cell immunity in HCL which contribute to the risk of infection in patients with HCL.*

### Cytogenetics and genetics

Reports on cytogenetic abnormalities in HCL are sparse and relate to the fact that there are not always sufficient cells available for study in the peripheral blood or in the dry-taps obtained after bone marrow aspiration. Brito-Babapulle *et al.* (94–96) probably have the greatest experience in this field and have shown that although clonal abnormalities are present, no specific abnormalities have really been observed. There appear to be distinct multiple clones present in combination with partially unrelated clones (97, 98). The most frequent abnormality encountered seems to be 14q+, sometimes 14q22–24, involving the heavy chain locus of the Ig molecule. These include t(14;18) and t(2;8), while chromosome 12 abnormalities involving 12p, 12q24 and 12a13 have also been seen (99). Other studies (98) showed clonal abnormalities clustered to specific regions, like chromosome 5 (in 40% of studied patients), seen mostly as trisomy 5, pericentric inversions of 5 and interstitial deletions involving 5q13. In the series reported by Hagland *et al.* (98), 8 patients had abnormalities of 11q and 11p, while 6 had 1q42, del12 together with abnormalities in chromosomes 5 and 14. Some studies using fluorescence *in situ* hybridization (FISH) (100, 101) have shown diploidy only for some of the chromosomes examined in HCL, while others had 5–10% of

nuclei which showed three signals for chromosome 12 centromere, suggesting trisomy 12.

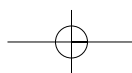
The BCL-1 gene is mapped to band q13 of chromosome 11 encoding for cyclin D1. In a study of 18 HCL patients, BCL-1 gene overexpression was evident but not associated with rearrangement or amplification of BCL-1 (102). Another study of 22 patients also showed increased cyclin D expression, but no 11q13 abnormalities were seen on banding analysis (94, 103), showing that HCL is very different from mantle cell lymphoma, which always shows BCL-1 rearrangements.

Despite the fact that the TRAP gene in HCL has been cloned and thought to be related to storage and transport of iron (104), it is still unclear how the above function of TRAP is linked to the pathogenesis of HCL. This enzyme, so specific for HCL, remains an enigma and requires further study (105). The RAS and RASA genes on chromosome 5 may be of possible significance in HCL, but not enough is known about their role in HCL (94). The gene associated with pp52 and actin, which encodes for cytoskeletal phosphoprotein and binds to F-actin, has also been cloned recently and mapped to chromosome 11p15.5 (106). This leukocyte-specific gene (pp52) should also be investigated in HCL, particularly because of the abnormalities described in the 11p chromosome in HCL and because of the reduction in pp52 mRNA and effects on pp52 transcription (94, 106) occurring after the use of IFN- $\alpha$ , a drug beneficial for HCL. However, a wider study of this phenomenon has not been reported as yet.

## CLINICAL ASPECTS

### Incidence and environmental factors

HCL accounts for about 2% of all the leukemias and occurs at a median age of approximately 50 years, more frequently



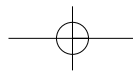


Table 9 Associated malignancies
<ul style="list-style-type: none"> <li>• Multiple myeloma</li> <li>• Monoclonal gammopathies</li> <li>• Lymphoma</li> </ul>
<ul style="list-style-type: none"> <li>• Cutaneous cancers Kaposi sarcoma melanoma</li> <li>• Renal carcinoma</li> <li>• Colon carcinoma</li> </ul>
<ul style="list-style-type: none"> <li>• Acute myeloblastic leukemia</li> <li>• Malignant histiocytosis</li> <li>• Myelodysplasia</li> </ul>

Table 10 Associated non malignant disorders
<ul style="list-style-type: none"> <li>• Myelofibrosis</li> <li>• Polycythemia vera</li> <li>• Bone marrow aplasia</li> <li>• Amyloidosis (AA)</li> <li>• Porphyria cutanea tarda</li> <li>• Granulomatous diseases</li> <li>• Sarcoid</li> <li>• Mastocytosis</li> <li>• Large granular lymphocytosis</li> </ul>

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in males than in females (4.2:1). This male:female ratio may vary from country to country and in Japan it is close to 1:1 (107–110).

There is some controversy relating to occupational and environmental risk factors and a number of case-control studies in HCL are available from the US, UK, Sweden and France, some suggesting a role for exposure to organic solvents, ionizing radiation, farming, pesticides, petroleum products, woodwork, sawdust and some professions (107–114). An interesting and striking negative correlation with smoking has been reported in four different studies (107, 112). There is, however, a difference of opinion in relation to the significance of these findings in the different studies.

Familial factors also play a role in HCL and it seems that type-1 (human leukocyte antigen) HLA groups were identical for the blood relatives affected by HCL and those affected by the same disorder or another malignant blood disorder such as CLL (111). Reported data support a genetic predisposition for HCL with an odds ratio of 2.1 for any relative having a blood disorder and of 3.6% in first-degree male relatives.

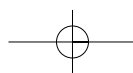
**Increased risk of associated malignancies.** Several reports have suggested a borderline association with an increased risk of solid cancers in patients with HCL, but this

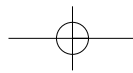
has also become a controversial issue for quite some time (Table 9). In a report involving 350 HCL patients there appeared to be no significant excess of solid tumors compared to the expected incidence; however, an increased number of cases of myeloma and lymphoma were documented (107, 115–117). In some series, however, it has been suggested that renal carcinoma, colon carcinoma and skin cancers may show a borderline increase in incidence (118, 119). When comparing this study to others, it appears that the only true increase relates to lymphoma and myeloma. An association of HCL with other hematopoietic malignancies, including polycythemia vera, myelofibrosis, Hodgkin's disease, myelodysplasia and acute myeloblastic leukemia has been reported, but these are not statistically significant.

A list of other non-malignant disorders seen with HCL is also summarized in ref. 119 and given in Table 10.

**Clinical features**

The classic diagnostic trial for HCL includes varying degrees and combinations of cytopenias, usually splenomegaly and the recognition of circulating HC with bone marrow reticulin fibrosis due to involvement by HC. About 50% of patients have pancytopenia, while the remaining cases indeed show varying combinations of anemia, neutropenia and thrombocytopenia. Many of the patients present with symptoms secondary to pancytopenia, including fatigue and weakness due





to anemia, bleeding tendency related to low levels of thrombocytes and infections due to neutropenia (1, 2, 4, 5, 19, 20, 26, 39). Other patients will be asymptomatic and the correct diagnosis will only be made due to the chance finding of splenomegaly or abnormal blood counts. About 25% of patients will present with symptoms and signs due to the enlarged spleen, with early satiety, abdominal or left upper quadrant discomfort or pain.

Splenomegaly is present in close to 90% of patients, while hepatomegaly is rarer and found in about a third of the patients. Lymphadenopathy is indeed not regarded as a feature of HCL, but has been described in about 20% of cases. If abdominal computed tomography (CT) scans are used in the investigation, unexpected sites of bulky disease may be encountered in up to 15–20% of cases (119–123).

*HCL is rare, affecting middle-aged males more than females, manifesting with cytopenias and splenomegaly associated with a dry bone marrow tap due to increased reticulin/fibrosis. There are some suggestions that occupational/environmental and familial factors play a role in pathogenesis. A possible increased risk of associated malignancy is still controversial.*

**Blood findings.** In general, varying combinations of cytopenias are evident. Up to 30% will have neutropenia ( $< 0.5 \times 10^9/L$  neutrophils) with characteristic monocytopenia. In most patients, HC are readily seen in the peripheral blood film, but in about 10% of cases HC are not evident in the blood at all. In these patients, buffy coat or mononuclear cell preparations will invariably show HC, particularly if phase microscopy is done, routinely when HCL is suspected or if TRAP staining is performed. In about 20% of patients, a frank leukemic phase may be seen with higher WBC counts and in these cases identification of HC is easy. When patients have excessive leukocytosis, the diagnosis of HCL variant should always be

considered and special attention should be paid to the HC morphology (42–46).

In rare cases, there may be an associated large granular lymphocytosis or an increase in NK cells (124). An increase in CD3 positive  $\gamma\delta$  lymphocytes may also be detected in these cases.

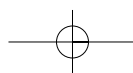
Polyclonal and monoclonal gammopathy can occur in 20–30% of patients (119, 125). These may be related to the presence of an associated myeloma or lymphoma (124, 126–129) or to the presence of autoimmune phenomena or disorders, including rheumatoid arthritis, periarteritis nodosa, leukocytoclastic vasculitis or Raynaud’s disease (130–135).

Laboratory tests may show altered liver function in a proportion of cases who have liver involvement, while sol IL-2R levels are markedly increased (82–85) in the presence of normal serum  $\beta 2$ -microglobulin levels.

**Associated infections.** Because of the combination of monocytopenia, neutropenia (136), decreased numbers of dendritic cells (1, 47, 92) and an imbalanced immune T-cell function (90, 91), infections are common (120, 137–139). These opportunistic infections increase with progression of the disease and some patients present with opportunistic infections as a major manifestation of HCL (Table 11). These include Legionella pneumonia, fungal and myco-

**Table 11**  
**Opportunistic infections**

- Listeria, Legionella
  - Mycobacterial disease  
  Kansasii, avium
  - Candidiasis
  - Cryptococcosis
  - Toxoplasmosis
- 
- Torulopsis
  - Aspergillosis
  - Sporothrix
  - Rhizopus
- 
- EBV – Japanese HCL



bacterial infections. *Mycobacterium kansasii* (5–10% of mycobacterial disease in HCL), *Pneumocystis carinii*, aspergillosis, histoplasmosis, cryptococcosis and toxoplasmosis are all candidate infections (137–149).

*The combination of neutropenia, monocytopenia, decreased dendritic cells and compromised T-cell immunity all contribute to the increased tendency to infection seen in HCL.*

### UNUSUAL MANIFESTATIONS AND COMPLICATIONS

In 1987, Bouroncle *et al.* (150) recorded a cohort of 116 patients with HCL emphasizing the unusual clinical manifestations, which may be encountered (Table 12). Other rare associations have also been reported and summarized by different authors (119).

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#### Skeletal lesions

Osteolytic lesions occur in about 3% of patients, but vary from 0–13% in different studies (119, 150, 151). Bone pain may occur, but is rare. Lytic lesions are reported in the axial skeleton or in long bones, as well as the hip joint, particularly the head and

neck of the right femur. These bone lesions can occur as part of progressive disease or when the patient is in partial or even complete response (152, 153). Radiologically, these are mostly lytic in nature, but diffuse osteoporosis, focal osteoblastic changes or sclerosis, as well as mixed patterns, can also be seen (154). According to the above, compression fractures of vertebrae and spontaneous or traumatic fractures of the head of the femur have also been reported. Aseptic necrosis of the femoral head may occur and rare arthralgia accompanied by joint swelling can be seen. MRI or bone scan may be helpful to detect possible sites of fracture. True cut needle bone biopsy of the lesions will provide diagnosis in these cases. Coexistence of multiple myeloma should always be excluded and rare cases associated with Gaucher's disease may have to be biopsied. HCL bone lesions are sensitive to systemic therapy, particularly IFN- $\alpha$  and of course to local radiotherapy (15–30Gy).

#### Bulky tumors nodes in mediastinum and abdomen

Lymphadenopathy and particularly bulky lymphadenopathy are not classical features of HCL, but abdominal and mediastinal nodes may be seen in about 15% of cases, particularly in an era where CT scans are done routinely more often than before (119–123). Cases with massive lymphadenopathy have been reported and are sometimes associated with progressive disease and resistance to standard therapy. Rarely ascites (sometimes chylous in nature), pleuro-pericardial effusions and even large mediastinal masses have also been documented (155, 156).

#### Cutaneous lesions

In a series reported by Carsuzaa *et al.* (157), about half of the patients had some cutaneous manifestations. Specific involvement by HCL seems to be extremely rare, but in

Table 12 Unusual clinical manifestations
<ul style="list-style-type: none"> <li>• Bulky abdominal lymphadenopathy</li> <li>• Tumor masses in mediastinum</li> <li>• Paravertebral masses</li> <li>• Pleural effusions and ascites</li> <li>• Painful lytic bone lesions</li> <li>• Skin involvement</li> <li>• GIT involvement – oesophageal, gastric, protein-losing enteropathy</li> <li>• Neurological – meningeal and CNS cord compression</li> <li>• Ocular – corneal involvement, uveitis, retinal artery thrombosis</li> <li>• Liver lesions – simulating "hepatitis" Cavernous hemangioma</li> <li>• Solitary lung lesions</li> </ul>

other series about 8% had specific involvement. These lesions may appear as nodules, plaques or be maculopapular in nature, with rare specific HCL infiltration. Infections of the skin are the most frequent cutaneous finding in HCL, including fasciitis, cellulitis and pustular lesions with pyogenic bacteria. Fungal lesions with granulomatous responses indicative of sepsis have also been recorded (119). Vasculitis, Sweet's syndrome and pyoderma gangrenosum may occur as presenting manifestations or develop in parallel with the evolution of systemic disease (119, 132). Rare instances of vitiligo and scleroderma have also been reported (158, 159).

### Ocular manifestations

These are uncommon, but panuveitis with visual disturbances can occur in HCL. Rare individuals with central retinal artery occlusion, perhaps related to hypergammaglobulinemia, have been recorded in HCL (160–162).

### Gastrointestinal involvement

Infiltration of the gastrointestinal tract (GIT) rarely results in symptomatic disease which is readily diagnosed. However, rare cases of protein-losing enteropathy due to HCL infiltration and esophageal involvement with perforation have been reported (119, 150, 163). Very rare instances of pulmonary HCL have also been seen (163).

### Central nervous system

Isolated cases of meningeal involvement, paravertebral or vertebral tumor invasion of the cord with spinal cord compression or radicular infiltration have also been reported (165, 166). Rare patients with sensory and motor neuropathy have also been seen. However, many of the cases with central nervous system (CNS) manifestations were in

fact patients with opportunistic infections, such as cryptococcosis and CNS toxoplasmosis, while others had hemorrhagic phenomena related to a bleeding tendency (119).

*Unusual clinical presentations may include skeletal and cutaneous lesions, bulky abdominal and mediastinal lymphadenopathy, while ocular, gastro-intestinal tract and CNS manifestations are very rare. Angiomatous lakes and hemangiomas may develop in the reticulo-endothelial system organs.*

### Liver involvement

Liver involvement with gross hepatomegaly sometimes occurs in HCL with progressive disease (60, 119, 167). Some cases with large “cavernous” hemangiomas of the liver have been seen on CT scan and at autopsy (163). These large vascular tumors probably originated from the “angiomatous” lakes which develop in the organs of the RES in HCL (54, 60).

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## AUTOIMMUNE DISORDERS

HCL can be associated with autoimmune phenomena and some autoimmune disorders with the following approximate order of frequency (Table 13) (119, 131–135, 159, 163, 168–175).

- 1) Vasculitis – periarteritis nodosa, leukocytoclastic vasculitis. These tend to occur relatively early in the development of the disease and can manifest as fever, arthralgia, erythema nodosum, cutaneous phenomena and peripheral neuropathy. Isolated organ phenomena, such as nephritis or cerebral and testicular involvement, may occur.
- 2) Temporal arteritis, cryoglobulinemia.
- 3) Glomerulonephritis.
- 4) Autoimmune hemolytic anemia and immune thrombocytopenia (ITP).
- 5) Rheumatoid arthritis, scleroderma, CREST syndrome.

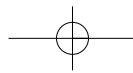


Table 13 Auto (immune) associations	
• Vasculitis	
• Leukocytoclastic vasculitis	
• Periarteritis nodosa	
• Erythema nodosum	
• Temporal arteritis	
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• Scleroderma	
• Rheumatoid arthritis	
• Polymyositis	
• Lupus anticoagulants	
anticardiolipin	
anti factor 8 antibody	
• Coombs + & hemolysis	
• ITP-like syndrome	
<hr/>	
• CREST	
• Myasthenia gravis	
• Glomerulonephritis	
• Pernicious anemia	
• Thyroiditis	
• Ulcerative colitis	

myelofibrosis with splenomegaly, mastocytosis if the mast cell hyperplasia is prominent in the marrow biopsy and peripheral blood, and with bone marrow hypoplasia or aplasia if this finding is present when only patchy HCL infiltrate is evident (50–53).

Clinically and morphologically, other hemato-oncologic disorders must be distinguished from HCL and these in fact are the major diseases to be excluded by the treating physician, because they also present with splenomegaly, marrow involvement and varying degrees of lymphocytosis of the peripheral blood (Table 14).

*Differential diagnosis is important and includes exclusion of HCL variant, SLVL, B-PLL and very rarely MCL or atypical CLL. HCL most often does not show obvious leukocytosis.*

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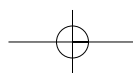
- 6) Polymyositis, thyroiditis, myasthenia gravis, pernicious anemia, ulcerative colitis, anticardiolipin syndrome, anti-factor 8 antibody with von Willebrand-like disorder.

**Hairy cell leukemia variant.** This entity has been mentioned earlier in this review and is a disorder intermediate between HCL and B-PLL (Fig 9) (42–46). The morphology of HCL variant is different from HCL and these differences have been described earlier. Cells have a different chromatin network and contain a central nucleolus. The immunophenotype is different to HCL and HCL variant cells have a lower HCL score (usually 0–2) than HCL (3–4). CD25, CD103 and TRAP staining are generally

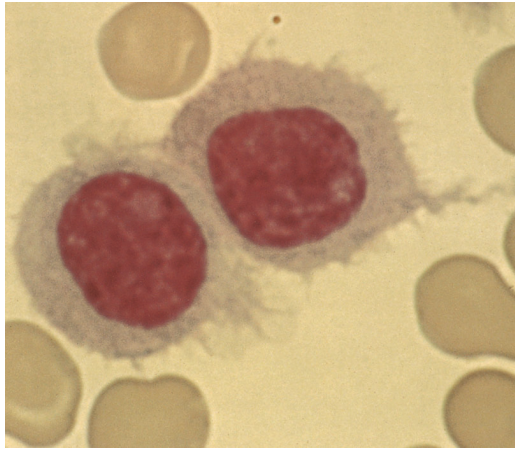
**DIFFERENTIAL DIAGNOSIS**

Sometimes the bone marrow biopsy findings in HCL may be confused with idiopathic

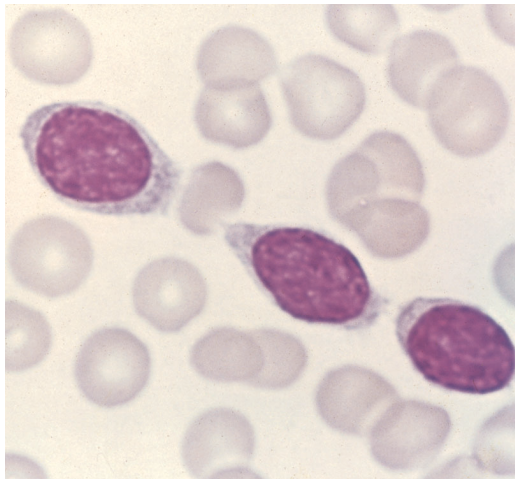
Table 14 Differential diagnosis of HCL immunophenotype					
	HCL	HCLV	SLVL	PLL	CLL
Slg	+++	++	+++	+++	+/-
CD5	-	-	-/+	+/-	++
CD23	-	-	-/+	-	++
FMC7	++	++	++	++	-/+
CD22	++	++	++	+	-/+
CD79B	++	++	++	++	-/+
<hr/>					
CD103	+++	++	+/-	-	-
HC2	++	+/-	+/-	-	-
CD25	++	+/-	+/-	-	-
CD11c	+++	++	+	+/-	+/-
TRAP	++	-/+	+/-	-	-



**Figure 9:** HCL variant cell with central nucleus and nucleolus with irregular cytoplasmic projections.



**Figure 10:** SLVL – splenic lymphoma with villous lymphocytes – cell with spindle shaped appearance and plasmacytoid features.



negative, while HC2 and CD11c are always positive. HCL variant patients have prominent splenomegaly with excessive leukocytosis. High WBC and HCL counts are the rule as opposed to HCL. The classic monocytopenia seen in HCL is also lacking. In contrast to typical HCL, the bone marrow is usually aspirable and patients do not respond to conventional HCL therapy with IFN- $\alpha$  and purine analogs (65–69). Splenectomy is probably the treatment of choice. The Japanese variant of HCL is similar to

HCL variant but there is often large granular lymphocytosis associated with the Japanese variant.

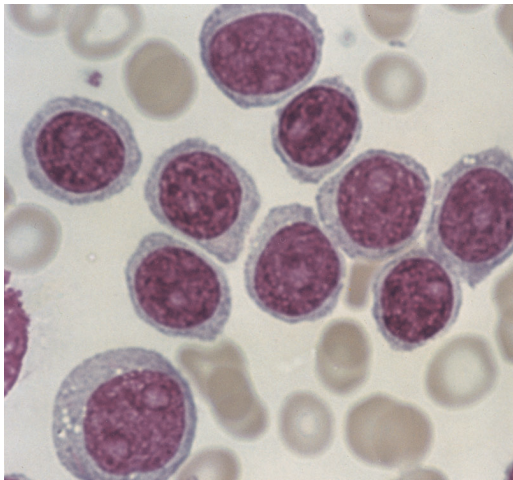
**Splenic lymphoma with villous lymphocytes (SLVL).** This disorder can readily be confused with typical HCL (Fig 10) (46, 65–69, 176, 177). Patients present with splenomegaly and varying combinations of lymphocytosis and cytopenias. There is usually no associated lymphadenopathy. In general, the WBC is modestly elevated and circulating lymphoid cells with “hairy” cell features are evident. These round cells are generally smaller than the regular HC and have a coarse chromatin pattern with occasional nucleoli. Cytoplasm is usually scanty and basophilic. Cells may be elongated with a spindle-shape and villous surfaces often polarized while plasmacytoid forms are also seen.

The HC score is usually low and most cases (> 90%) have a score of 0–1, while only a few have a score of 2–3. Almost no SLVL cases have a higher score of 3–4. Accordingly, the immunophenotype is of great help in the diagnosis of these cases – HC2, CD25, CD103 and CD11c are generally negative. CD5 and CD23 are most frequently negative, but can sometimes be expressed, while FMC7 and CD22 are strongly expressed in most SLVL cases. Cells are almost always TRAP negative. The bone marrow is aspirable in most cases with only modest involvement by SLVL and without reticulin fibrosis. Splenic involvement is in the white pulp and the red pulp is not prominently involved. Splenectomy appears to be the treatment of choice in these cases.

**B-prolymphocytic leukemia (B-PLL)** (Fig 11). This entity is most frequently encountered in elderly males with prominent splenomegaly and very high WBC counts (44, 65–69). It can be confused with the HCL variant, but not with HCL. B-PLL cells are round and larger in size with a monomorphic picture. These prolymphocytes contain condensed chromatin with a prominent



**Figure 11:** Typical prolymphocytic leukemic cells (PLL) with characteristic central nucleus and chromatin with obvious nucleolus.



nucleolus and no cytoplasmic villi are present. Cells are TRAP-negative and the HC score is very low (0–1). CD25, CD11c, CD103 and HC2 are all negative, while FMC7 and SIg are strongly positive. CD5 and CD23 are usually negative. The prognosis is generally very poor.

**Occasionally MCL, lymphoplasmacytic lymphoma in leukemic phase and atypical CLL** may have to be considered in the differential diagnosis, but this is rarely if ever a problem. In these cases, the morphology of the cells, their immunophenotype, TRAP negative staining and bone marrow aspiration findings with the lack of reticulin-fibrosis and a dry tap, make the different diagnosis relatively easy. Furthermore, these disorders, unlike HCL, have frequent lymphadenopathy and are seldom confused with HCL.

## CONCLUSIONS

Despite all the advances in the field of biology and molecular genetics achieved in

recent years with regard to B-cell disorders and in particular to the indolent lymphoproliferative diseases, the etiology, basic biology, cellular origin and basic molecular defects involved in HCL have still defied clear definition. However, despite this therapy is most successful for this disorder and the majority of patients will achieve sustained complete clinical and hematologic response after receiving relatively simple therapy and remain disease free and in good general condition for most of their lives. These dramatic responses after therapy will be detailed in the following report and are remarkable when compared to the results of therapy for other indolent disorders of B-cell origin. Thus, this extensive review purposely concentrated on many of the features of HCL which may not be of common knowledge to all physicians currently involved in treating HCL today. Particular emphasis was placed on clinical features, notably unusual manifestations, association with autoimmune phenomena and other malignancies and occupational hazards in HCL. Novel biologic data on the hairy cell and its relation to the underlying stroma and cellular matrix are provided, while classic ultrastructural and immunophenotypic features and differential diagnosis are discussed. This review has attempted to highlight all the knowledge we have on this most unusual disorder.

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