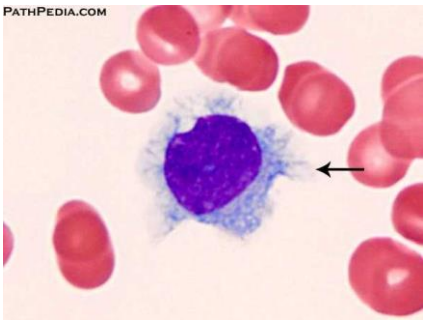
Cancer Association of South Africa (CANSA)

Fact Sheet on Adult Hairy Cell Leukaemia

Introduction

Leukaemia is a cancer of the blood forming system. Most types of leukaemia cause the bone marrow to make abnormal white blood cells. These abnormal cells can get into the bloodstream and circulate around the body.

[Picture Credit: Hairy Cell Leukaemia]



Adult Hairy Cell Leukaemia (HCL)

Hairy cell leukaemia is a rare, slow-growing cancer of the blood in which the bone marrow makes too many B cells (lymphocytes), a type of white blood cell that fights infection. These excess B cells are abnormal and look "hairy" under a microscope. As the number of leukaemia cells increases, fewer healthy white blood cells, red blood cells and platelets are produced.

This disease affects more men than women, and it occurs most commonly in middle-aged or older adults. It is considered a chronic disease because it may never completely disappear, although treatment can lead to remission for years.

Joshi, A., Dhanushkodi, M., Ganesan, P., Radhakrishnan, V., Kannan, K., Mehra, N., Kalaiyarasi, J.P., Krupashankar, S., Sundersingh, S., Ganesan, T.S. & Sagar, T.G. 2020.
"HCL is an uncommon B cell lympho-proliferative disorder with high remission rates. There is paucity of data on the long-term outcome of HCL from India. We retrospectively collected data from individual case records of patients with HCL who were treated in Cancer Institute, Chennai from January 2001 until January 2018. Sixteen patients were diagnosed with HCL and were treated with cladribine (81%), interferon (13%) and one patient received only best supportive care (6%). All the treated patients achieved complete response. More than half of the patients developed febrile neutropenia but there were no treatment related mortality. The 5-year DFS was 77% and 5-year OS was 80%. Relapse of disease was seen in 27%. HCL is a curable malignancy with high remission rates and survival comparable to patient treated in west."

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Zheng, G., Chattopadhyay, S., Sud, A., Sundquist, K., Sundquist, J., Försti, A., Houlston, R., Hemminki, A. & Hemminki, K. 2019.
"Improvement of survival in lymphocytic leukaemia has been accompanied by the occurrence of second primary cancer (SPCs). Based on Swedish Family Cancer Database, we applied bi-directional analyses in which relative risks (RRs) were calculated for any SPCs in patients with chronic lymphocytic leukaemia (CLL), acute lymphoblastic leukaemia (ALL) and hairy cell leukaemia (HCL) and the risks of these leukaemias as SPCs. After CLL, RRs were significant for 20 SPCs, and high for skin squamous cell cancer (24·58 for in situ and 7·63 for invasive), Merkel cell carcinoma (14·36), Hodgkin lymphoma (7·16) and Kaposi sarcoma (6·76). Conversely, 15 CLL cancer pairs were reciprocally increased. The increased risks were reciprocal for ALL and four cancers. RR for ALL was 15·35 after myeloid neoplasia. HCL showed reciprocally increased RRs with non-Hodgkin lymphoma and melanoma. The concordance between RRs for bi-directional associations between CLL and different cancers, and HCL and different cancers was highly significant. For CLL (also for HCL), the bi-directional risks with skin cancers and other immune-related cancers suggest the probable involvement of immune dysfunction. For ALL, treatment may contribute to risks of multiple SPCs. Increased risk of ALL after haematological neoplasms may indicate bone marrow dysfunction. These findings may help guide treatment decisions and prognostic assessment."

Incidence of Adult Hairy Cell Leukaemia in South Africa
In providing the incidence figures of Leukaemia in South Africa, the outdated National Cancer Registry (2017) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the 'Frequency of Histologically Diagnosed Cancer in South Africa' Section of the Registry .

According to the National Cancer Registry (2017) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	338	1:634	0,85%
Asian males	7	1:1 000	1,72%
Black males	151	1:1 357	1,12%
Coloured males	29	1:862	0,58%
White males	151	1:209	0,72%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	230	1:1 289	0,55%
Asian females	8	1:1 010	0,62%
Black females	106	1:2 410	0,56%
Coloured females	25	1:1 074	0,53%
White females	91	1:455	0,52%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	82	21	29	33	54	61	42	16
Asian males	0	0	3	1	1	1	1	0
Black males	66	10	19	16	16	19	4	1
Coloured males	7	2	1	4	8	3	6	1
White males	9	9	6	12	31	38	3	14

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	40	17	20	28	31	39	37	18
Asian females	1	1	0	6	2	3	1	0
Black females	32	10	17	12	15	14	2	4
Coloured females	1	3	0	5	4	6	5	1
White females	6	3	3	11	10	16	29	13

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Signs and Symptoms of Adult Hairy Cell Leukaemia

The causes of Hairy Cell Leukaemia (HCL) are unknown. It is not infectious and cannot be passed on to other people. Because this disease usually develops slowly, it may not cause any symptoms for quite some time. It is sometimes discovered by chance when a blood test is taken for another reason, for example as part of a routine health check.

These and other signs and symptoms may be caused by adult hairy cell leukaemia or by other conditions:

- Weakness
- Feeling tired
- Fever
- Frequent infections
- Easy bruising or bleeding
- Weight loss for no known reason.
- Pain or a feeling of fullness below the ribs.
- Painless lumps in the neck, underarm, stomach, or groin.

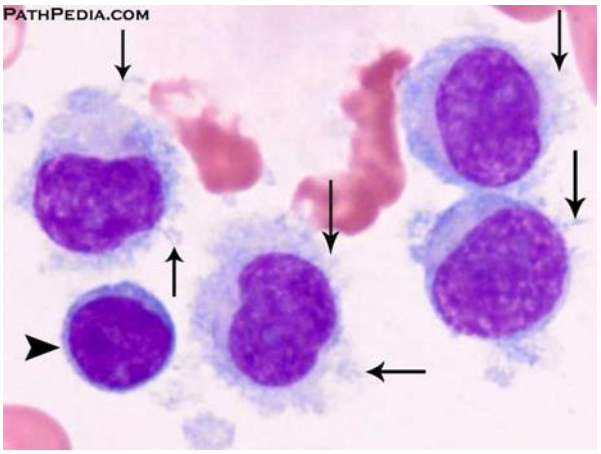
Streu, E. 2016.

Hairy cell leukemia is a relatively rare but distinct B-cell lympho-proliferative disorder of the blood, bone marrow, and spleen that accounts for only 2% of all adult leukemia cases. The median age at presentation is 50-55 years, with a 4:1 male to female predominance. Although considered uncommon, a number of unusual clinical presentations have been noted in the literature, including the presence of peripheral lymphadenopathy, lytic bone lesions, skin involvement, organ involvement, and central nervous system involvement. Unlike the clinical management of other hematologic malignancies, no current system is used to stage hairy cell leukemia.

Diagnosis of Adult Hairy Cell Leukaemia

The best approach to establishing the diagnosis of hairy cell leukaemia usually includes careful examination of blood and bone marrow biopsy specimens to identify cells with the morphologic

features of hairy cells and to demonstrate that the neoplastic cells have an antigenic profile that is characteristic for hairy cell leukaemia.



[Picture Credit: Hairy Cell Leukaemia 2]

The cell is characterised by an eccentrically located nucleus with fine chromatin, indistinct nucleoli, and an abundant amount of grey-blue cytoplasm with shaggy margins.

The following tests and procedures may be used:

- Physical examination and history
- Complete blood count (CBC)
- Peripheral blood smear
- Blood chemistry studies
- Bone marrow aspiration
- Immunophenotyping
- Flow cytometry
- Cytogenetic analysis
- CT scan (CAT scan)

Cross, M. & Dearden, C. 2020.
Purpose of review: To summarise diagnostic clinical/laboratory findings and highlight differences between classical hairy cell leukaemia (HCLc) and hairy cell leukaemia variant (HCLv). Discussion of prognosis and current treatment indications including novel therapies, linked to understanding of the underlying molecular pathogenesis.
Recent findings: Improved understanding of the underlying pathogenesis of HCLc, particularly the causative mutation BRAF V600E, leading to constitutive activation of the MEK/ERK signalling pathway and increased cell proliferation. HCLc is caused by BRAF V600E mutation in most cases. Purine nucleoside analogue (PNA) therapy is the mainstay of treatment, with the addition of rituximab, improving response and minimal residual disease (MRD) clearance. Despite excellent responses to PNAs, many patients will eventually relapse, requiring further therapy. Rarely, patients are refractory to PNA therapy. In relapsed/refractory patients, novel targeted therapies include BRAF inhibitors (BRAFi), anti-CD22 immunoconjugate moxetumomab and Bruton tyrosine kinase inhibitors (BTKi). HCLv has a worse prognosis with median overall survival (OS), only 7-9 years, despite the combination of PNA/rituximab improving front-line response. Moxetumomab or ibrutinib may be a viable treatment but lacks substantial evidence.

Naing, P.T. & Acharya, U. 2020.
“Hairy cell leukemia (HCL) is a relatively rare chronic B-cell malignancy that involves the bone marrow, spleen, and peripheral blood. The complete blood count may reveal pancytopenia including monocytopenia. Median age at diagnosis is approximately 55. Poor prognostic features, while somewhat variable in the literature, may include age, hemoglobin less than 10 g/dL, platelets less than 100, ANC less than 1000, the presence of lymphadenopathy, and massive splenomegaly. Differential diagnosis includes other B-cell lymphoproliferative disorders, including splenic marginal zone lymphoma. A distinct entity is known as hairy cell leukemia variant (HCL-V), which is biologically unique from HCL also exists. Response to typical HCL in this disease is poor. The variant can be identified by immunophenotypic differences, lack of *BRAF* mutation, and lack of monocytopenia.

HCL accounts for 2% of all leukemias with approximately 1000 new cases being reported in the United States each year."

Suneel, R., Rajasekaran, S., Kaur, H., Mallik, N., Garg, D., Jain, A. & Dey, P. 2020.
Background: Hairy cell leukaemia (HCL) is a rare lymphoproliferative disorder of B cell origin, and uncommonly it affects the lymph node. Fine needle aspiration cytology (FNAC) of lymph node of HCL has rarely been described.
Case description and diagnosis: A 41-year-old man presented with pallor, fever, tachycardia, generalized lymphadenopathy, and massive splenomegaly. The FNAC of the cervical lymph node was done. The smears showed many atypical lymphocytes with a plasmacytoid appearance. There were many large cells with round to reniform shaped nuclei having with hair-like cytoplasmic processes. Flow cytometry (FCM) revealed a clonal B cell population with light chain restriction and positive CD20, CD79b, CD22, CD11c, CD25, CD103, CD123, and CD200 markers.
Conclusion: The characteristic cytological features such as atypical lymphoid cells, large cells with hairy projections along with FCM findings, are helpful in the diagnosis of HCL.

Treatment of Adult Hairy Cell Leukaemia
Not all patients will require treatment immediately after the diagnosis is made and can be monitored until it is needed. This 'watch and wait' surveillance approach can be difficult for patients and their families and may generate a lot of anxiety. However, unlike other types of cancer, leukaemias do not spread or metastasise and so waiting to start treatment until there are clear signs that it is indicated is usually perfectly safe and has the advantage of not exposing a patient to drugs, which may have side effects, earlier than is necessary.

PDQ Adult Treatment Editorial Board. 2020.
"The initial therapies of choice for hairy cell leukemia are either cladribine (2-chlorodeoxyadenosine, 2-CdA) or pentostatin. These drugs have comparable response rates but have not been compared in phase III trials. Cladribine is administered as a one-time continuous infusion or series of subcutaneous injections and is associated with a high rate of febrile neutropenia. Rarely, more than one course of treatment is required to induce a desirable response. Treatment should be discontinued once complete remission or stable partial remission with normalization of peripheral blood counts is reached. The presence of residual disease may be predictive of relapse but does not seem to affect survival."

Dearden, C. & Iyengar, S. 2020.
"For a disease initially described in 1958 as a leukaemic reticulo-endotheliosis associated with poor outcomes, we have come a long way in our understanding of Hairy cell leukaemia. The vast majority of patients diagnosed with this rare, often diagnostically challenging, leukaemia can now expect a lifespan that is similar to the general population. This article covers some of the highlights from the last 6 decades that have led to our current understanding of this fascinating leukaemia - from elucidation of its B-cell origin to discovery of the almost universal occurrence of the BRAF V600E mutation; from the initial successes reported with splenectomy to the more recent development of targeted therapies such as Vemurafenib and Moxetumomab Pasudotox. It also pays tribute to some of the outstanding research in this field focusing particularly on the significant contributions made by the clinical and scientific community in the UK."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.
For additional information, please visit: www.sanctr.gov.za/

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Sources and References Consulted or Utilised

Cancer Research UK
http://www.cancerresearchuk.org/about-cancer/type/hairy-cell-leukaemia/about/the-blood-and-hairy-cell-leukaemia

Cross, M. & Dearden, C. 2020. Hairy cell leukaemia. *Curr Oncol Rep*. 2020 Apr 16;22(5):42.

Dearden, C. & Iyengar, S. 2020. Hairy cell leukaemia: from hairy beginnings to a BRAF New World. *Br J Haematol*. 2020 Nov;191(4):527-534.

Divino, V., Karve, S., Gaughan, A., DeKoven, M., Gao, G., Knopf, K.B. & Lanasa, M.C. 2017. Characteristics and treatment patterns among US patients with hairy cell leukemia: a retrospective claims analylsis. J Comp Eff Res. 2017 Sep;6(6):497-508. doi: 10.2217/cer-2017-0014. Epub 2017 May 9. PMID: 28485619.

Hairy Cell Leukaemia
http://www.pathpedia.com/education/eatlas/histopathology/blood_cells/hairy_cell_leukemia_classic.aspx

Hairy Cell Leukaemia 2
http://mymedicaltexts.blogspot.co.za/2016/01/hematology-tips-4-hematological.html

Hairy Cell Leukemia Foundation
https://www.hairycellleukemia.org/about-hcl/treatment/

Joshi, A., Dhanushkodi, M., Ganesan, P., Radhakrishnan, V., Kannan, K., Mehra, N., Kalaiyarasi, J.P., Krupashankar, S., Sundersingh, S., Ganesan, T.S. & Sagar, T.G. 2020. "Hairy Cell Leukemia (HCL): 'Real World' Outcome". *Indian J Hematol Blood Transfus*. 2020 Apr;36(2):267-270.

Kreitman, R.J., Dearden, C., Zinzani, P.L., Delgado, J., Karlin, L., Robak, T., Gladstone, D.E., le Coutre, P., Dietrich, S., Gotic, M., Larratt, L., Offner, F., Schiller, G., Swords, R., Bacon, L., Bocchia, M., Bouabdallah, K., Breems, D.A., Cortelezzi, A., Dinner, S., Doubek, M., Gjertsen, B.T., Gobbi, M., Hellmann, A., Lepretre, S., Maloisel, F., Ravandi, F., Rousselot, P., Rummel, M., Siddiqi, T., Tadmor, T., Troussard, X., Yi, C.A., Saglio, G., Roboz, G.J., Balic, K., Standifer, N., He, P., Marshall, S., Wilson, W., Pastan, I., Yao, N.S. & Giles, F. 2018. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia*. 2018 Aug;32(8):1768-1777. doi: 10.1038/s41375-018-0210-1. Epub 2018 Jul 20. PMID: 0030507.

Levy, I. & Tadmor, T. 2017. Time to cure hairy cell leukemia. *Turk J Haematol*. 2017 Dec 1;34(4):289-290. doi: 10.4274/tjh.2017.0296. Epub 2017 Aug 25. No abstract available. PMID: 28840848.

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Leukaemia/Hairycellleukaemia.aspx

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/hairy-cell-leukemia/basics/definition/con-20026432

Medscape
http://emedicine.medscape.com/article/200580-differential

Naing, P.T. & Acharya, U. 2020. Hairy cell leukemia. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Aug 10.

National Cancer Institute
http://www.cancer.gov/about-cancer/treatment/clinical-trials
http://www.cancer.gov/types/leukemia/patient/hairy-cell-treatment-pdq

NCBI
http://www.ncbi.nlm.nih.gov/books/NBK13250/

PDQ Adult Treatment Editorial Board. 2020. Hairy Cell Leukemia Treatment (PDQ®): Health. ***In***: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002–2020 Dec 17.

PDQ Adult Treatment Editorial Board. PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-2018 May 18.

Sarvaria, S., Topp, Z. & Saven, A. 2016. Current therapy and new directions in the treatment of hairy cell leukaemia: a review. *JAMA Oncol*. 2016 Jan;2(1):123-9. doi: 10.1001/jamaoncol.2015.4134.

Streu, E. 2016. Hairy cell leukemia and bone pain. *Oncol Nurs Forum*. 2016 Jan;43(1):18-21. doi: 10.1188/16.ONF.18-21.

Suneel, R., Rajasekaran, S., Kaur, H., Mallik, N., Garg, D., Jain, A. & Dey, P. 2020. Diagnosis of hairy cell leukaemia by fine needle aspiration cytology of lymph node. *Diagn Cytopathol*. 2020 Oct 1.

Troussard, X. & Cornet, E. 2017. Hairy cell leukemia 2018: Update on diagnosis, risk-stratification, and treatment. *Am J Hematol*. 2017 Dec;92(12):1382-1390. doi: 10.1002/ajh.24936. PMID: 29110361.

Wierda, W.G., Byrd, J.C., Abramson, J.S., Bhat, S., Bociek, G., Brander, D., Brown, J., Chanan-Khan, A., Coutre, S.E., Davis, R.S., Fletcher, C.D., Hill, B., Kahl, B.S., Kamdar, M., Kaplan, L.D., Khan, N., Kipps, T.J., Lancet, J., Ma, S., Malek, S., Mosse, C., Shadman, M., Siddiqi, T., Stephens, D., Wagner, N., Zelenetz, A.D., Dwyer, M.A. & Sundar, H. 2017. Hairy cell leukemia. Version 2.2018, NCCN clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017 Nov;15(11):1414-1427. doi: 10.6004/jnccn.2017.0165. PMID: 29118233.

Zheng, G., Chattopadhyay, S., Sud, A., Sundquist, K., Sundquist, J., Försti, A., Houlston, R., Hemminki, A. & Hemminki, K. 2019. Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukaemia. *Br J Haematol*. 2019 Jan 31. doi: 10.1111/bjh.15777. [Epub ahead of print]. PMID: 30706458.