HAIRY CELL LEUKEMIA: REVIEW

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Summary

The accumulation of abnormal B-lymphocytes which is an uncommon hematological malignancy is called 'Hairy cell leukemia' because of its hairy appearance under microscope. These malignant cells accumulate in the bone marrow and thus interfere with the production of normal white blood cells, red blood cells, platelets. Complete blood counts, CT scan, bone marrow biopsy are few methods used to diagnose such malignancies. Bone marrow failure and splenomegaly are the primary causes for pancytopenia. The success rates of the first line therapy by purine analogs like pentostatin and cladribin are very high. In certain difficult resistant cases, immunotherapy by administering monoclonal antibodies or interferon-alpha is pursued. Splenoctomy and marrow transplant sutures are supportive treatment options.

Keywords: B-lymphocytes, Blood, Bone marrow, Cancer, Hairy Cell Leukemia, Spleen.

Introduction

Hairy cell leukemia (HCL) is a rare chronic lympho-proliferative disorder typified by the presence of circulating monoclonal B-lymphocytes that have prominent cytoplasmic projections, and which display distinctive infiltration patterns in the bone marrow and spleen. In leukaemia, the normal pattern of white blood cell development is disrupted and too many immature white blood cells are produced. The bone marrow slowly starts the production of the abnormal white blood cells, and so the number of normal white blood cells, red cells, and platelets that can be produced is lowered. Hairy cell leukaemia is an overproduction of one type of white blood cell: the B-lymphocyte.

In hairy cell leukaemia, the abnormal white blood cells build up in the spleen and cause it to enlarge. The enlarged spleen may also cause normal blood cells to be removed from the bloodstream, which can lead to a further lack of red blood cells and lower numbers of normal white blood cells. Hairy cell leukaemia is very rare and only accounts for 2-5 in 100 of all cases of leukaemia. It is found mostly in people aged between 40 and 60, and is more common in men than women. The condition usually develops very slowly, so the term 'chronic' is used to describe it. Hairy cell leukemia was originally described as histiocytic leukemia, malignant reticulosis, or lymphoid myelofibrosis in publications dating back to the 1920s. The disease was formally named leukemic reticuloendotheliosis. Its common name, which was coined in 1966, is derived from the "hairy" appearance of the malignant B cells under a microscope. [1, 2]

Classification [3]

When not further specified, the "classic" form is often implied. However, two variants have been described: Hairy cell leukemia-variant, which usually is diagnosed in men and a Japanese variant. The non-Japanese variant is more difficult to treat than either 'classic' ssHCL or the Japanese variant HCL.

Hairy cell leukemia-variant, or HCL-V, is usually described as a prolymphocytic variant of hairy cell leukemia. While classic HCL primarily affects men, HCL-V is somewhat more evenly divided between males and females. While the disease can appear at any age, the median age at diagnosis is over 70. HCL-V is a more aggressive disease and is less likely to be treated successfully than classic HCL and remissions tend to be shorter. Many treatment approaches, such as Interferon-alpha, CHOP and common alkylating agents like cyclophosphamide provide very little benefit. Pentostatin and cladribine provide some benefit to many HCL-V patients, but with shorter remissions and lower response rates compared to classic HCL. More than half of patients respond partially to splenectomy.

Hairy cell leukemia-Japanese variant or HCL-J: There is also a Japanese variant, which is more easily treated. Treatment with cladribine has been reported.

Stages [4]

Staging is the process used to find out how far the cancer has spread. There is no standard staging system for hairy cell leukemia. The disease is grouped as untreated, progressive, or refractory.

Untreated hairy cell leukemia

The hairy cell leukemia is newly diagnosed and has not been treated except to relieve symptoms, such as weight loss and infections. In untreated hairy cell leukemia, some or all of the following conditions occur:

1. Hairy (leukemia) cells are found in the blood and bone marrow.
2. The number of red blood cells, white blood cells, or platelets may be lower than normal.
3. The spleen may be larger than normal.

Progressive hairy cell leukemia

In progressive hairy cell leukemia, the leukemia has been treated with either chemotherapy or splenectomy (removal of the spleen) and one or both of the following conditions occur:

1. There is an increase in the number of hairy cells in the blood or bone marrow.
2. The number of red blood cells, white blood cells, or platelets in the blood is lower than normal.

Causes [5]

As with many cancers, the cause of hairy cell leukemia is **unknown**. Exposure to tobacco smoke, ionizing radiation, or industrial chemicals (with the possible exception of diesel) does not appear to increase the risk of developing HCL. Farming and gardening appear to increase the risk of HCL in some studies. Human T-lymphotropic virus 2 (HTLV-2) has been isolated in a small number of patients with the variant form of HCL. In the 1980s, HTLV-2 was identified in a patient with a T-cell lymphoproliferative disease; this patient later developed hairy cell leukemia (a B cell disease), but HTLV-2 was not found in the hairy cell clones. There is no evidence that HTLV-II causes any sort of hematological malignancy, including HCL. [6]

Signs And Symptoms [6, 7]

Since hairy cell leukaemia normally develops slowly, it may not cause symptoms for a long time, and may often only be diagnosed after a blood test has been taken for other reasons.

1. **Symptoms**
    a. Bone pain (e.g. Hip Pain) if bone lesions present
2. **Signs**
    a. Defining features
        i. Splenomegaly (75%)
    b. Vasculitis associated findings
        i. Erythema Nodosum
        ii. Cutaneous Nodules
    c. Rare findings
        i. Lymphadenopathy
        ii. Hepatomegaly [12]

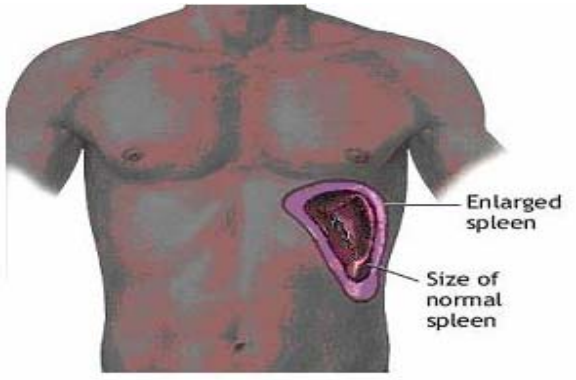

Figure 1: Enlarged spleen

These and other symptoms may be caused by hairy cell leukemia. Other conditions may cause the same symptoms.

1. Weakness or feeling tired.
2. Fever or frequent infections.
3. Easy bruising or bleeding.
4. Shortness of breath.
5. Weight loss for no known reason.
6. Pain or a feeling of fullness below the ribs.
7. Painless lumps in the neck, underarm, stomach, or groin.

Diagnosis-Lab Tests [8]

Labs: The following tests and procedures may be used.

1. Physical exam and history
2. Complete Blood Count
    a. Pancytopenia
    b. Leukocyte count normal or low

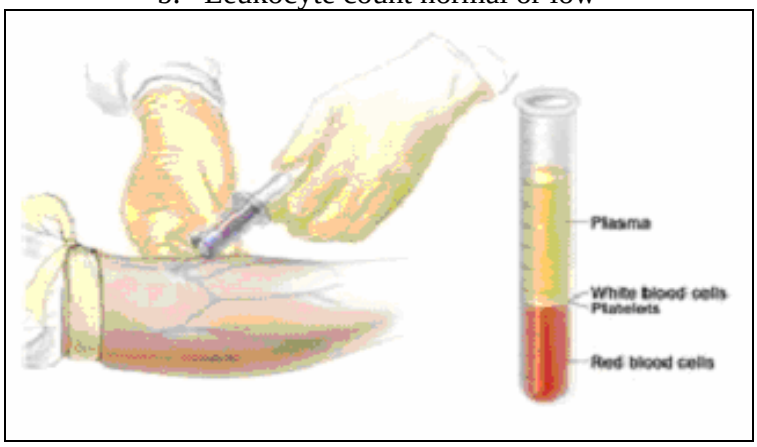

Figure 2: Complete Blood Count

Peripheral Smear

1. Hairy appearing Leukocytes (cytoplasmic projections)
    a. Size: 15 to 20 um in diameter
    b. Eccentric nucleus with foamy cytoplasm

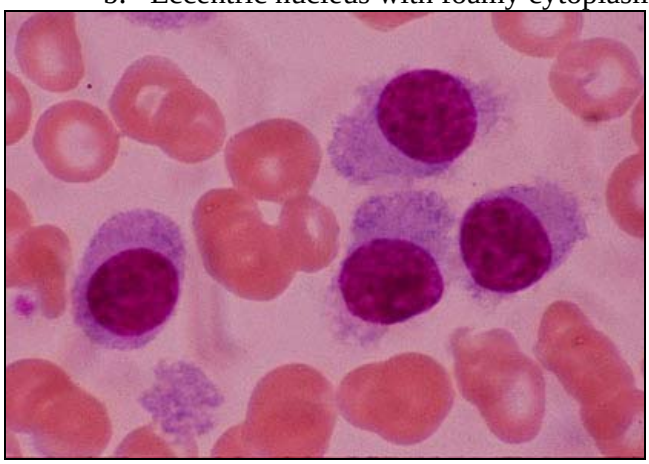

Figure 3: Peripheral Blood

Tartrate-resistant Acid Phosphatase (TRAP) staining

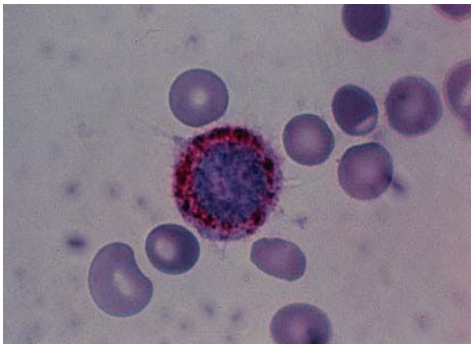

Figure 4: TRAP stain

Bone Marrow Aspiration

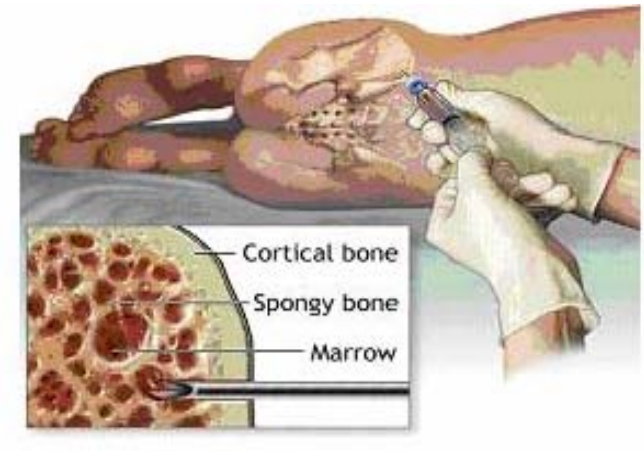

Figure 5: Bone marrow aspiration

2. Difficult due to reticulin fibrosis
3. Mononuclear cells replace normal architecture.

5. Immunophenotyping
6. CT scan

2. Differential Diagnosis

1. Chronic Lymphocytic Leukemia
2. Waldenstrom's Macroglobulinemia
3. Acute Leukemia
4. Aplastic Anemia

3. Cytogenetics

Cytogenetics is the examination of the leukemia cells for chromosome (long strands of genes) abnormalities. It helps doctors confirm the diagnosis and may help to determine the person's prognosis (chance of recovery). Some tests may also determine which treatments may be the most effective. Doctor may consider these factors when choosing a diagnostic test:

1. Age and medical condition
2. The type of cancer suspected
3. Severity of symptoms
   Previous test results.

Pathophysiology [9]

Pancytopenia in HCL is caused primarily by marrow failure and splenomegaly. Bone marrow failure is caused by the accumulation of hairy cells and reticulin fibrosis in the bone marrow, as well as by the detrimental effects of dysregulated cytokine production. Splenomegaly reduces blood counts through sequestration, marginalization, and destruction of healthy blood cells inside the spleen.Hairy cells are nearly mature B cells, which are activated clonal cells with signs of VH gene differentiation. They may be related to pre-plasma marginal zone B cells or memory cells. Cytokine production is disturbed in HCL. Hairy cells produce and thrive on TNF-alpha. This cytokine also suppresses normal production of healthy blood cells in the bone marrow.Unlike healthy B cells, hairy cells express and secrete an immune system protein called Interleukin-2 receptor (IL-2R). In HCL-V, only part of this receptor is expressed.As a result, disease status can be monitored by measuring changes in the amount of IL-2R in the blood serum. The level increases as hairy cells proliferate, and decreases when they are killed. Although uncommonly used in North America and northern Europe, this test correlates better with disease status and predicts relapse more accurately than any other test. Hairy cells respond to normal production of some cytokines by T cells with increased growth. Treatment with Interferon-alpha suppresses the production of this pro-growth cytokine from T cells.A low level of T cells, which is commonly seen after treatment with cladribine or pentostatin, and the consequent reduction of these cytokines, is also associated with reduced levels of hairy cells. There are a few genomic imbalances in the hairy cells, such as trisomy 5. The expression of genes is also dysregulated in a complex and specific pattern. The cells underexpress 3p24, 3p21, 3q13.3-q22, 4p16, 11q23, 14q22-q24, 15q21-q22, 15q24-q25, and 17q22-q24 and overexpress 13q31 and Xq13.3-q21. It has not yet been demonstrated that any of these changes have any practical significance to the patient. [11, 12]

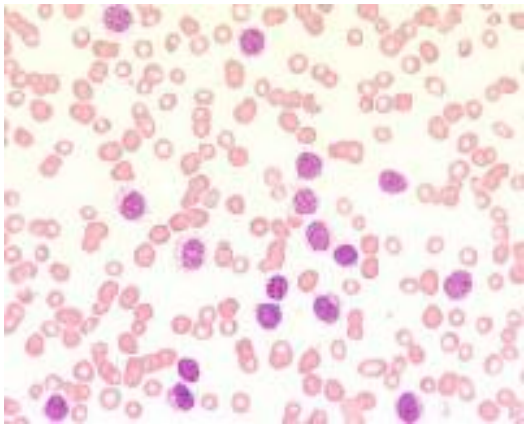

Figure 6: Pathophysiology

Treatment [10, 11, 12]

The aim of treatment for hairy cell leukaemia is to bring about a remission, which means that, although it may still be present, the disease is inactive or dormant. The remission may last for several years. However, as hairy cell leukaemia usually comes back. There are different types of treatment for patients with hairy cell leukemia.

1. Five types of standard treatment are used:
    a. Watchful waiting
    b. Chemotherapy
    c. Biologic therapy
    d. Surgery
    e. Targeted therapy
2. Patients may want to think about taking part in a clinical trial.
3. Patients can enter clinical trials before, during, or after starting their cancer treatment.
4. Follow-up tests may be needed. .

First-line therapy: purine analog chemotherapy

Chemotherapy: is the use of drugs to kill cancer cells. Systemic chemotherapy is delivered through the bloodstream, targeting cancer cells throughout the body. Chemotherapy is given by a medical oncologist, a doctor who specializes in treating cancer with medication, or a hematologist, a doctor who specializes in treating blood disorders. Some people may receive chemotherapy in their doctor's office or outpatient clinic; others may go to the hospital. A chemotherapy regimen (schedule) usually consists of a specific number of cycles given over a specific time. Cladribine (2CDA) and pentostatin (DCF) are the two most common first-line therapies. They both belong to a class of medications called purine analogs, which have mild side effects compared to traditional chemotherapy regimens.

Second-line therapy: immunotherapy

Immunotherapy: (also called biologic therapy) is designed to boost the body's natural defenses to fight the cancer. It uses materials either made by the body or in a laboratory to bolster, target, or restore immune system function. Immunotherapy for HCL includes recombinant interferon alpha (Alferon N, Intron A, Roferon-A). If a patient is resistant to either cladribine or pentostatin, then second-line therapy is pursued. Interferon is a type of immunotherapy, which means that it boosts the body’s own immune system. The exact way in which interferon works in hairy cell leukaemia is not fully understood, but it is thought that it may help to activate the body’s immune system and that it may also work directly against the cancer cells. The drug is usually given three times a week, as an injection under the skin. The most common side effects are flu-like symptoms such as chills, a high temperature, and aching joints. Simple medicines such as paracetamol can often relieve these effects. [7]

Targeted therapy: is a treatment that targets specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. Monoclonal antibodies are a type of targeted therapy. In particular, monoclonal antibodies target specific proteins on the surface of the cancer cell. Rituximab (Rituxan) is an antibody directed against the surface protein CD20. BL22 immunotoxin is an antibody attached to a toxin that is designed to attach to the surface protein, CD22, and deliver the toxin to the cancer cell..

Alemtuzumab (Campath) is an antibody that targets the surface protein CD52 and has been used in the treatment of PLL.

Monoclonal antibodies the most common treatment for cladribine-resistant disease is infusing monoclonal antibodies that destroy cancerous B cells. Rituximab is by far the most commonly used. Most patients receive one IV infusion over several hours each week for four to eight weeks. Rituximab has successfully induced a complete response in Hairy Cell-Variant. Rituximab's major side effect is serum sickness, commonly described as an "allergic reaction", which can be severe, especially on the first infusion. Serum sickness is primarily caused by the antibodies clumping during infusion and triggering the complement cascade. Although most patients find that side effects are adequately controlled by anti-allergy drugs, some severe, and even fatal, reactions have occurred. Consequently, the first dose is always given in a hospital setting, although subsequent infusions may be given in a physician's office. Remissions are usually shorter than with the preferred first-line drugs, but hematologic remissions of several years' duration are not uncommon.Other B cell-destroying monoclonal antibodies such as Alemtuzumab, Ibritumomab tiuxetan and I-131 Tositumomab may be considered for refractory cases.

Other Treatment Options

Splenectomy can produce long-term remissions in patients whose spleens seem to be heavily involved, but its success rate is noticeably lower than cladribine or pentostatin. Splenectomies are also performed for patients whose persistently enlarged spleens cause significant discomfort or in patients whose persistently low platelet counts suggest Idiopathic thrombocytopenic purpura. For some people who have an enlarged spleen, removing it can help to reduce symptoms. However, the illness will still be present and further treatment is usually necessary. In a small number of people no treatment will be needed following splenectomy .Splenectomy may be done for some patients by a surgical oncologist, a doctor who specializes in treating cancer using surgery.

Stem cell transplantation/bone marrow transplantation: A stem cell transplant is a medical procedure in which diseased bone marrow is replaced by highly specialized cells, called hematopoietic stem cells. Hematopoietic stem cells are found both in the bloodstream and in the bone marrow. Today, this procedure is more commonly called a stem cell transplant, rather than bone marrow transplant, because blood stem cells are typically what is being transplanted, not the actual bone marrow tissue.

Bone marrow transplants are usually shunned in this highly treatable disease because of the inherent risks in the procedure. They may be considered for refractory cases in younger, otherwise healthy individuals. "Mini-transplants" are possible.
Patients with anemia or thrombocytopenia may also receive red blood cells and platelets through **blood transfusions**. Blood transfusions are always irradiated to remove white blood cells and thereby reduce the risk of graft-versus-host disease. Patients may also receive a hormone to stimulate production of red blood cells. These treatments may be medically necessary, but do not kill the hairy cells.

Complications [13]

Infection (most common cause of death)

1. Legionella pneumonitis
2. Toxoplasmosis
3. Mycobacterium tuberculosis
4. Atypical Mycobacterium Disease
5. Nocardiosis
6. pyrogenic infection

Prevention/ Screening [2]

Because the cause is unknown, no effective preventive measures can be taken. As the disease is rare, routine screening is not cost-effective. Pneumococcal Vaccines can be given as a preventive measure.

Epidemiology [14]

This disease is rare, with fewer than 1 in 10,000 people being diagnosed with HCL during their lives. Men are four to five times more likely to develop hairy cell leukemia than women. In the United States, the annual incidence is approximately 3 cases per 1,000,000 men each year, 0.6 cases per 1,000,000 women each year.
Most patients are white males over the age of 50, although it has been diagnosed in at least one teenager. It is less common in people of African and Asian descent compared to people of European descent.It does not appear to be hereditary, although occasional familial cases that suggest a predisposition have been reported, usually showing a common Human Leukocyte Antigen (HLA) type.

Conclusion

More than 95% new patients are treated well or at least adequately by Cladribine and Pentostatin. Survivors of solid tumors are declared cured after a span of 2-5 years, but Hairy cell leukemia patients are “never” cured as relapses occur even after continuous remissions. Patients are even at a risk of developing other kind of cancer like lung and colon cancer at some point in their lives. Risks of autoimmune disease are high.

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