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Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: MT-13/00142.

Each attendee should claim THREE CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 43 SLIDE 5 – DECEMBER 2013

LYMPHOPROLIFERATIVE DISORDERS/CLL

Lymphoproliferative disorders are a set of disorders characterized by the abnormal proliferation of lymphocytes into a monoclonal lymphocytosis. The two major types of lymphocytes are B cells and T cells, which are derived from pluripotential hematopoietic stem cells in the bone marrow. Individuals who have some sort of immuno-dysfunction are susceptible to developing a lymphoproliferative disorder because when any of the numerous control points of the immune system become dysfunctional, immunodeficiency or deregulation of lymphocytes is more likely to occur. There are several inherited gene mutations that have been identified to cause lymphoproliferative disorders, however there are also acquired and iatrogenic causes.

B-cell chronic lymphocytic leukemia (B-CLL), also known as chronic lymphoid leukemia (CLL), is the most common type of leukemia. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection by producing antibodies. In CLL, B cells grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells. CLL is a stage of small lymphocytic lymphoma (SLL), a type of B-cell lymphoma, which presents primarily in the lymph nodes. CLL and SLL are considered the same underlying disease, just with different appearances.

CLL is a disease of adults, but, in rare cases, it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men.

Symptoms and signs

Most people are diagnosed without symptoms as the result of a routine blood test that returns a high white blood cell count. Less commonly, CLL may present with enlarged lymph nodes without a high white blood cell count or no evidence of the disease in the blood. This is referred to as small lymphocytic lymphoma. In some individuals the disease comes to light only after the neoplastic cells overwhelm the bone marrow resulting in anemia producing tiredness or weakness.

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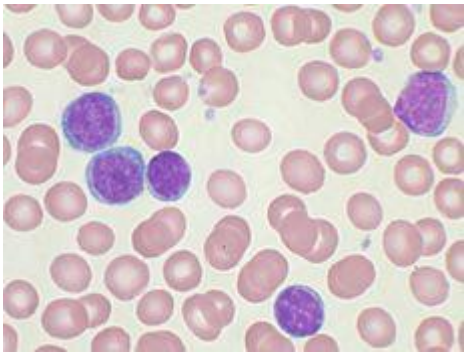
Diagnosis

CLL is usually first suspected by the presence of a lymphocytosis on a complete blood count (CBC) test. Most often the lymphocyte count is greater than $40x10^9/L$, but can be much higher. The presence of a lymphocytosis in an elderly individual should raise strong suspicion for CLL, and a confirmatory diagnostic test, in particular flow cytometry, should be performed unless clinically unnecessary.

The diagnosis of CLL is based on the demonstration of an abnormal population of B lymphocytes in the blood, bone marrow, or tissues that display an unusual but characteristic pattern of molecules on the cell surface. This atypical molecular pattern includes the coexpression of cells surface markers CD5 and CD23. In addition, all the CLL cells within one individual are clonal, that is, genetically identical. In practice, this is inferred by the detection of only one of the mutually exclusive antibody light chains, kappa or lambda, on the entire population of the abnormal B cells. Normal B lymphocytes consist of a stew of different antibody-producing cells, resulting in a mixture of both kappa and lambda expressing cells. The lack of the normal distribution of kappa and lambda producing B cells is one basis for demonstrating clonality, the key element for establishing a diagnosis of any B cell malignancy (B cell non-Hodgkin lymphoma).

The combination of the microscopic examination of the peripheral blood and analysis of the lymphocytes by flow cytometry to confirm clonality and marker molecule expression is needed to establish the diagnosis of CLL. In CLL, the lymphocytes are genetically clonal, of the B cell lineage (expressing marker molecules CD19 and CD20), and characteristically express the marker molecules CD5 and CD23. These B cells resemble normal lymphocytes under the microscope, although slightly smaller, and are fragile when smeared onto a glass slide, giving rise to many broken cells, which are called smudge or smear cells.



Peripheral blood smear showing CLL cells

Related diseases

In the past, cases with similar microscopic appearance in the blood but with a T cell phenotype were referred to as T-cell CLL. These so-called T-cell CLLs, however, are now recognized as a separate disease group and are currently classified as T-cell prolymphocytic leukemias.

CLL should not be confused with acute lymphoblastic leukemia (ALL), a highly aggressive leukemia most commonly diagnosed in children, and highly treatable in the pediatric setting.

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Differential diagnosis

Hematologic disorders that may resemble CLL in their clinical presentation, behavior, and microscopic appearance include mantle cell lymphoma, marginal zone lymphoma, B cell prolymphocytic leukemia, and lymphoplasmacytic lymphoma.

B cell prolymphocytic leukemia (B PLL), a related, but more aggressive disorder, has cells with similar phenotype, but, are significantly larger than normal lymphocytes and have a prominent nucleolus. The distinction is important as the prognosis and therapy differs from CLL.

All the B cell malignancies of the blood and bone marrow can be differentiated from one another by the combination of cellular microscopic morphology, marker molecule expression, and specific tumor-associated gene defects. This is best accomplished by evaluation of the patient's blood, bone marrow and occasionally lymph node cells.

Treatment

CLL treatment focuses on controlling the disease and its symptoms rather than on an outright cure. CLL is treated by chemotherapy, radiation therapy, biological therapy, or bone marrow transplantation. Symptoms are sometimes treated surgically (splenectomy removal of enlarged spleen) or by radiation therapy ("de-bulking" swollen lymph nodes).

Initial CLL treatments vary depending on the exact diagnosis and the progression of the disease, and even with the preference and experience of the health care practitioner. Dozens of agents are used for CLL therapy. An initial treatment regimen that contains fludarabine, cyclophosphamide, and rituximab (known as FCR) has demonstrated higher overall response rates and complete response rates.

References

1. Lymphoma, Non-Hodgkin Author: Sanjay Vinjamaram, MD, MPH, Fellow in Hematology/Oncology, Roswell Park Cancer Institute
2. The leukaemic phase of non-Hodgkin's lymphoma, B J Bain, D Catovsky
3. Essential Haematology edition 4, Hoffbrand, Pettit and Moss
4. http://en.wikipedia.org/wiki/B-cell_chronic_lymphocytic_leukemia

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Questions

1. Define lymphoproliferative disorders.
2. Discuss the possible lab findings in a patient diagnosed with CLL.
3. List and discuss any other hematologic disorders that may resemble CLL.
