CLL:
Calling Out a Common Leukemia

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Chronic lymphocytic leukemia (CLL) is the most common kind of leukemia in adults over the age of 65. The incidence is three cases per 100,000 with the majority of patients being over age 50 with a median age of 65 years. The male to female ratio is 2:1.

It is more common in Caucasians than in people of Chinese ancestry.

There is no definite toxic etiology, although, occasionally, there is clustering in a family.

How does CLL present?

CLL is diagnosed in over 70% patients as an incidental finding on routine laboratory testing. CLL can also present with progressive, painless lymphadenopathy. Patients can also develop splenomegaly, presenting with early satiety symptoms or vague fullness in the left upper quadrant.

In more advanced cases, patients have B symptoms, which include fatigue, weight loss and night sweats. In advanced stages with extensive bone marrow infiltration, patients can present with signs and symptoms of cytopenias (anemia, thrombocytopenia and neutropenia). At any time in their course, patients with CLL can develop autoimmune phenomena, including autoimmune hemolytic anemia and immune thrombocytopenic purpura.

What investigations are required?

The laboratory diagnosis of CLL requires a lymphocytosis greater than $5x10^9$/L on the peripheral blood

Henry's Worry

- Age: 50
- He presents complaining of six months of fatigue, weight loss and increasing constipation.
- CBC:
  - Hemoglobin: 85 g/L
  - MCV: 65 fl
  - WBC: 20,000 $x10^9$/L
  - Lymphocytes: 15,000 $x10^9$/L
  - PMN: 5,000 $x10^9$/L
  - Platelets: 600,000 $x10^9$/L
- Peripheral blood film:
  - Hypochromic
  - Microcytic RBC
  - Increased lymphocytes and smudge cells

Henry is referred to Gastroenterology for a colonoscopy, which confirms a sigmoid carcinoma that is subsequently resected. He is referred to Hematology to discuss his lymphocytosis.

For more on Henry, go to page 78.

CBC: Complete blood cell
MCV: Mean cell volume
WBC: White blood cell
PMN: Polymorphonucleotide
RBC: Red blood cell

film. The lymphocytes appear well-differentiated and smudge cells may be seen.

Immunophenotyping is typically performed on all patients requiring treatment and confirms chronic lymphocytic leukemia as opposed to other low-grade lymphoproliferative disorders. CLL cells express weak monotypic surface immunoglobulin, CD5, CD19, CD23 and weak or absent CD79B, CD22 and FMC7.

Additional investigations that may be helpful either at presentation or during the course of the disease include a direct antiglobulin test (DAT). This is essential in all patients who are anemic and before starting treatment with fludarabine. If the DAT is positive in an anemic patient, one must consider autoimmune hemolytic anemia and confirm with additional tests, including low haptoglobin, elevated lactate dehydrogenase and bilirubin plus spherocytes and polychromasia on the blood film. Patients also require renal and liver biochemistry pre-therapy.

A bone marrow aspirate and trephine biopsy are not essential for the diagnosis of CLL, but can be useful for determining the cause of cytopenia, providing prognostic information and also assessing response to therapy. Additional radiologic procedures are typically necessary during the patient's treatment phase and would include a chest X-ray, ultrasound and computed tomography scan.

Early-stage CLL patients may be observed for more than 12 years before therapy is even needed.

How should patients be managed initially?

The overall median survival for CLL is seven years. Early-stage CLL patients may be observed for more than 12 years before therapy is even needed. Hence, initial education and reassurance for these patients with a hematologist or oncologist is very important.

What else are CLL patients at risk for?

Patients with chronic lymphocytic leukemia have an increased infective risk, particularly for encapsulated organisms and varicella zoster. The increased risk is due to multiple factors, including neutropenia, hypogammaglobulinemia and decreased cell-mediated immunity. Asplenia

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adds additional risks.

In patients with repetitive sino-pulmonary infections and documented hypogammaglobulinemia, monthly intravenous immune globulin therapy can be effective.

Preventative strategies, including an annual influenza vaccine and pneumococcal vaccine every five to 10 years, are recommended. With herpes zoster, it is imperative for patients to be assessed and anti-virals to be initiated to reduce the risk of dissemination, pneumonitis and post-herpetic neuralgia.

Patients with CLL also have an increased risk of secondary malignancies, particularly carcinoma of the lung, colon and skin. There is also a risk of transformation to a large cell lymphoma in approximately 5% of patients or, more uncommonly, prolymphocytic leukemia. This would be heralded by a rapid progression of adenopathy, splenomegaly or increased B symptoms.

Following-up with Henry

- Henry has no significant lymphadenopathy or organomegaly.
- His hemoglobin has returned to normal with a course of iron therapy.
- He has stage 0 chronic lymphocytic leukemia and is asymptomatic.
- No therapy is recommended.
- He has returned to his family physician with recommendations for blood work at six months intervals and annual hematology assessments.

To find out what happened to Henry, go to page 79.

What about treatment?

CLL is incurable, with the exception of selected young patients

who qualify for a bone marrow transplant. Hence, indications for treatment are limited to symptomatic patients. This would include:

- progressive marrow failure with the development of significant anemia (less than 100) or thrombocytopenia (less than 100,000) or
- progressive symptomatic lymphadenopathy or splenomegaly.

Patients with progressive lymphocytosis with a doubling time less than six months typically require therapy, as well as patients with severe systemic symptoms, including:

- progressive weight loss,
- fevers,
- extreme fatigue or
- night sweats.

Hyperviscosity due to extreme lymphocytosis is very rare and there is no absolute lymphocyte count that would

More on Henry

Seven years later, Henry becomes symptomatic with drenching sweats, weight loss and bulky adenopathy.

- Hemoglobin: 110 g/L
- WBC: 200,000 x 10^9/L
- PMN: 5,000 x 10^9/L
- Platelet count: 110,000 x 10^9/L

His direct antiglobulin test is negative and he is started on oral fludarabine.

After a planned six cycles, his blood counts have returned to normal.

His night sweats and lymphadenopathy have all resolved. He continues well for one year, post fludarabine therapy.

dictate therapy.

Treatment strategies for CLL require careful consideration for patient-related factors, including:

- age,
- performance status,
- co-morbidity and
- patient's wishes.

There are a variety of therapies currently available for CLL, including well-tolerated alkylating agents, such as chlorambucil or cyclophosphamide. Fludarabine, a nucleoside analogue, given either orally or intravenously, alone or in combination with cyclophosphamide, is often very effective in younger patients without evidence for autoimmune phenomena. More costly monoclonal antibodies with rituximab and alemtuzumab are generally not used for initial therapy of CLL outside a clinical trial setting.

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Rai staging system in CLL

Rai stage	
0	Lymphocytosis only
I	+ lymphadenopathy
II	+ splenomegaly
III	Hemoglobin < 100 g/L
IV	Platelet < 100 x 10^9/l

CLL: Chronic lymphocytic leukemia