Chronic Leukemias

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The chronic leukemias—chronic granulocytic leukemia (CGL), chronic lymphocytic leukemia (CLL), and hairy cell leukemia (HCL)—are uncommon diseases characterized by a chronic course and by organ infiltration and bone marrow replacement. Recently our understanding of the pathophysiology of these diseases has improved. Treatment results in symptomatic improvement, although little has been gained in terms of increased survival in these patients.

Chronic Granulocytic Leukemia

Chronic granulocytic leukemia (CGL) has been shown to be a disorder of the hematopoietic stem cell. Cytogenetic and enzymatic evidence has shown CGL to arise from a single clone of cells.[1,2] In over 90% of cases, it is associated with an acquired chromosomal abnormality, the Philadelphia chromosome (Ph^1). The major clinical manifestations are due to overgrowth of granulocytes in the marrow and elsewhere in the reticuloendothelial system. Most cases can be controlled with a variety of agents for two to four years, but 75%–80% of the patients die with an acute terminal phase of their illness, variously called accelerated phase, blast phase, or metamorphosis of CGL.

Clinical Features

CGL accounts for 20% of adult leukemias in the United States (3500 cases/yr).[3] Its peak incidence is at age 40, range 25–60. Proposed etiologic factors include ionizing radiation and certain chemicals and viruses. The onset is usually insidious, with the history being one of evolution of worsening signs and constitutional symptoms over two to six months. At presentation, the patient may have fatigue, decreased exercise tolerance, night sweats, and weight loss. Fever is uncommon at presentation. Bone pain or a sense of fullness in the upper abdomen due to splenic enlargement may occur as the disease progresses. Bleeding manifestations may occur due to abnormalities of platelet number (too many or too few), or abnormalities of platelet function. Generally, at presentation, symptoms are mild and the patient's overall status is good.

Laboratory and Cytogenetic Features

Peripheral blood and bone marrow examination in the chronic phase of CGL reveal characteristic abnormalities. Normal appearing granulocytes in all stages of development are present in the peripheral blood with a mean leukocyte count at presentation over 100,000/mm.[3] The mean hemoglobin is 10 gm%, and platelet count in the normal or elevated range sometimes exceeds one million at diagnosis. In the chronic phase, promyelocytes and myeloblasts do not exceed 10–15% of the total cell population in the peripheral blood or bone marrow. Bone marrow aspirates from any site are hypercellular with marked granulocytic hyperplasia.

Leukocyte alkaline phosphatase (LAP) is a neutrophil enzyme whose precise function and subcellular localization remain unclear.[4] LAP activity is characteristically absent or markedly reduced in patients with uncomplicated CGL in chronic phase. Elevation of LAP is often seen at metamorphosis. The pathophysiology of low LAP scores in chronic phase CGL remains unclear.

CGL is the only human malignancy with a specific chromosomal abnormality, the (Ph^1) chromosome.[5] Since its initial description in 1960 by Nowell and Hungerford,[6] the Ph^1 chromosome has been shown to be present in the bone marrow of 85–90% of all patients with CGL. In most cases, the Ph^1 chromosome is composed of deleted chromosomal material from chromosome 22 which had been translocated onto one of the no 9 chromosomes.

In patients with leukocytosis and a hypercellular marrow, detection of the Ph^1 chromosome is diagnostic of CGL. The detection of Ph^1 chromosome in an

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asymptomatic individual has been described as a marker for development of the disease at a later time.[7] Sporadic cases of acute granulocytic leukemia bearing the Ph[1] chromosome have been reported, but may represent CGL presenting in blast phase without a clinically apparent chronic phase. The Ph[1] chromosome persists throughout the course of the disease. The appearance of multiple Ph[1] chromosomes, or additional chromosomal anomalies may precede, or accompany metamorphosis in CGL.[5] The functional significance of the Ph[1] chromosome is unknown.

Metamorphosis of CGL

Despite effective therapy for the symptoms and signs of chronic phase CGL, 75–80% of patients develop a more acute phase of their disease which is refractory to therapy.[8] This transformation may be sudden, resulting in the death of the patient in a period of weeks, or it may have a more chronic course with resulting death in a period of months, or a year or longer. This change in disease behavior, termed metamorphosis, accelerated phase, or blast crisis, occurs most commonly 2½ to 3 years after diagnosis. As time from diagnosis increases, the risk of metamorphosis increases. Symptoms of metamorphosis frequently resemble symptoms at presentation of disease, but may also include drenching night sweats, bone pain due to lytic bone lesions,[9] myalgias, and arthralgias and signs of meningeal involvement. Lymphadenopathy and recurrent infection, uncommon in the chronic phase, may become prominent in metamorphosis. The symptoms, physical signs, and hematologic picture of metamorphosis of CGL may be out of step with one another.[10,11] Laboratory findings include increased numbers of circulating blasts and progranulocytes in some cases and severe pancytopenia in others. The LAP score may rise to normal levels. Needle aspiration of marrow yields variable results: a left shift in granulopoiesis is more prominent in this phase, but occasionally a normal aspirate may be obtained.

Therapy and Prognosis

Multiple agents are available that control signs and symptoms of chronic phase CGL. Although busulfan remains the most widely used chemotherapeutic agent in CGL,[12] enthusiasm for its use has waned due to its pulmonary toxicity and cases of severe myelosuppression related to its use. Hydroxyurea may be effective in chronic phase or in early metamorphosis and is especially useful in cases where rapid reduction in white cell count is necessary. Myelosuppression due to hydroxyurea is rapidly reversible upon discontinuation of therapy, a feature not seen with busulfan. None of these agents, however, have altered the natural history of CGL.

Radiation therapy, once popular in this disease, is currently reserved for palliative treatment of symptomatic splenomegaly, or control of extramedullary tumors composed of granulocytic precursors, so called "chloromas." The median survival of patients in most series is approximately 3–3½ years; but varies widely. Most patients who develop an accelerated phase die due to infection or because of bleeding.[13] No cures of CGL by chemotherapy or radiation therapy have been reported.

Therapy of metamorphosis in CGL has been extremely disappointing. Because the clinical and hematologic manifestations of this phase of the disease are variable, new forms of therapy have been difficult to evaluate. Since metamorphosis has been so refractory to current therapeutic efforts, recent attempts at eradication of CGL in the chronic phase, before the emergence of a refractory disease state, have been made. These have included intensive combination chemotherapy,[14] elective splenectomy in the chronic phase, leukapheresis, immunotherapy, and, in a few cases, autologous marrow infusion or allogeneic bone marrow transplant.[15,16] All of these approaches must presently be regarded as investigational.

These therapeutic maneuvers are being made to change the course of disease, and thereby the survival of patients with CGL. Of the current methods being tried, autologous marrow infusion or bone marrow transplantation while in chronic phase following high dose chemotherapy, may offer the most promise. It is too early yet to say whether or not intensive chemotherapy given in the chronic phase of the disease will change its course.

Chronic Lymphocytic Leukemia

A disease of unknown etiology, CLL is the most common leukemia seen in the Western countries. Its course is variable but in general is characterized by gradual accumulation of mature appearing lymphocytes in marrow and RES. Eventual involvement of other organ systems occurs, ie, skin, liver, lung, and GI tract. These well-differentiated lymphocytes are now well characterized as abnormal, immunologically inert B cells in the majority of cases, although T cell variants have been described.[17] Major advances in our understanding of the pathogenesis of CLL have occurred recently, but have not been accompanied by major therapeutic advances. Median survival in most series is in the range of five years. Recently, staging systems for CLL have been introduced which should help evaluate efficacy of therapy in comparable groups of patients.

Clinical Features

The presenting features in CLL vary widely. Twenty-five to 30% of patients are asymptomatic at diagnosis. Other patients may develop signs and symptoms of anemia, or they may discover an enlarged lymph node which leads to diagnosis. Less common presentations include bleeding due to thrombocytopenia, skin infiltration or erythroderm, bony pain, or symptomatic splenomegaly.

The physical examination is most striking for generalized lymphadenopathy. Hepatosplenomegaly is frequently present, but marked hepatosplenomegaly is rarely a presenting feature without lymphadenopathy. Infectious complications of CLL may bring the patient to medical attention. Fever is nearly always due to infection rather than to the disease itself. Persistant fever should suggest infection; rarely it may indicate emergence of another lymphoproliferative process such as diffuse histiocytic lymphoma ("Richter's syndrome"), which may coexist with CLL. Bacterial infections are common; fungal infections and infections with pneumocystis and other opportunists may be seen in patients treated with corticosteroids.

At presentation, the lymphocyte count varies from 5,000/mm^3 on upwards, and counts greater than 100,000/mm^3 are not unusual. Mild to moderate anemia is present at diagnosis in up to 50% of patients. Anemia is usually normochromic and normocytic; the Coomb's test is positive in one-third of cases. Mild thrombocytopenia is common at diagnosis. Five percent of patients have a detectable monoclonal paraprotein on protein electrophoresis. In other patients depressed serum globulin levels may be present. In advanced CLL, factors which may complicate decreased host defenses and low serum globulins include malnutrition, protein losing enteropathy, or chemotherapy. Variable defects in cellular immunity have been described that may contribute to a tendency toward infection, especially infection of skin, respiratory tract, and genitourinary tract.

Variability in clinical features and course in CLL have made analysis of survival data difficult until recently. Rai et al have introduced a clinical staging system useful in assessing prognosis.[18] According to their system, the duration of survival for patients with CLL is related inversely to "stage" of disease (Table 1). Such "staging systems" may allow stratification of patients for more accurate comparisons of effects of treatment on survival. Other prognostic indicators are currently being evaluated.

Most cases of CLL are B-cell disorders as defined by membrane receptors on the malignant cells, but recently several reports have appeared in the literature describing patients whose proliferating cells are T cells.[19] Some of these latter patients have had unusual clinical presentations, characterized by massive splenomegaly without lymphadenopathy, and prominent neutropenia, and in many cases by skin involvement. It is as yet unclear whether T-cell CLL carries a different prognosis than B-cell CLL.

Therapy and Prognosis in CLL

It remains unclear whether or not antileukemic therapy in CLL changes survival. Indications for initiating therapy vary, and many patients are observed from months to years after diagnosis before they begin treatment. Since no form of therapy has unequivocally been shown to alter the prognosis in CLL, the goal of treatment is palliation of symptoms and signs of disease activity. Unlike in CGL, where an acute phase occurs in the majority of cases, acute termination is very rare in CLL. Radiotherapy may be useful in occasional patients with large lymph node masses and painful splenomegaly, although chemotherapy is useful in these settings as well. Systemic benefit from splenic or thymic irradiation or total body irradiation has been reported, but these modes of therapy remain controversial.

Alkylating agent therapy with or without corticosteroids remains the most widely used treatment for patients with CLL who require treatment. Chlorambucil given daily on a sliding scale or in higher doses biweekly, has been an effective and well-tolerated agent. Cyclophosphamide and melphalan appear to be

TABLE 1.

	Clinical Stage vs Survival	Median Survival in Months
Stage 0	Absolute lymphocytosis >15,000/mm^3	>150
Stage 1	Absolute lymphocytosis plus lymphadenopathy	105
Stage 2	Absolute lymphocytosis and lymphadenopathy, plus enlarged liver and/or spleen	71
Stage 3	Absolute lymphocytosis and lymphadenopathy, plus anemia (hemoglobin >11 g/dl)	19
Stage 4	Absolute lymphocytosis and lymphadenopathy, plus thrombocytopenia (platelet count 100,000/mm^3)	19

as effective as chlorambucil. In most series 70% or more of patients will improve in terms of general sense of well-being, decrease in lymphadenopathy and splenomegaly, decrease in lymphocyte count, and, in about 50% of patients, increase in hematocrit. Corticosteroids, in doses of 15–50 mg/day of prednisone, are effective as a temporary measure to reduce many of the symptoms and signs of CLL, but side effects of long-term steroids are numerous. Complete remissions (complete disappearance of signs and symptoms of disease) with single agents or corticosteroids are rare. Combination chemotherapy,[21,22] effective in lymphomas and myelomas, has been tried in CLL with some promising results, but all of these studies are small and use historical controls. Controlled, randomized studies are needed.

The incidence of second malignancies in CLL is difficult to estimate but most authors agree that it has increased. In some series, the incidence is up to 15–20% (including skin cancer). Unlike in Hodgkin's disease or myeloma, there appears to be no clear-cut relationship between therapy and emergence of second malignancy in CLL.

Although our understanding of the pathophysiology of CLL has improved, therapeutic advances have been slow. Combination chemotherapy may achieve complete responses, however, at present the overall effect of complete remission on duration of survival cannot be assessed. Careful randomized studies using concurrent controls must be done utilizing clinical staging of patients. The place of other therapeutic modalities, such as total body irradiation, organ irradiation, or extracorporeal irradiation remains unclear.

Hairy Cell Leukemia

Bouroncle et al[23] described another chronic leukemia, hairy cell leukemia (HCL) or leukemic reticuloendotheliosis. Unlike in CGL and in CLL where leukocytosis is the rule, HCL patients frequently present with pancytopenia. The importance of distinguishing HCL from the other chronic leukemias and from the lymphoproliferative disorders lies in the fact that most patients with HCL have shown little response to the usual therapeutic maneuvers for these disorders. Therefore, efforts have been directed toward more precisely characterizing the "hairy cell" and the clinical presentation and course of this disease.

Clinical Manifestations

Bouroncle described clinical findings in 82 patients, which she followed for up to 20 years.[23] Her series of patients with HCL comprised only 2% of all leukemias seen in a tertiary referral hospital. Men predominate in ratios of between 4 : and 7 : 1 in most series. Onset of the disease is usually in the sixth decade, but cases have been described ranging from age 20–70.

The onset of HCL is insidious with malaise, fatigue, and abdominal fullness due to splenomegaly being the most common complaints. Other presenting symptoms include bleeding in 15–30%, symptoms related to massive splenomegaly in 15%, and infection 15%. Fever, chills, and extreme weight loss are uncommon at diagnosis. Occasionally the diagnosis of HCL may be made as an incidental finding on routine hemogram.

Massive splenomegaly is the most characteristic sign at diagnosis. Hepatomegaly is present at diagnosis in 20–50% of patients in various series, but lymphadenopathy is unusual. Skin lesions due to HCL are uncommon, encountered in 10% of cases, which helps to separate HCL from Sezary syndrome and T cell lymphoma also characterized by abnormal appearing circulating mononuclear cells.

Laboratory Findings

Routine laboratory values except for the hemogram are nonspecific. In contrast to CLL, serum protein abnormalities are rare. Most patients present with pancytopenia. Mild to moderate normochromic, normocytic anemia is common. Hemolytic anemia may occur due to hypersplenism and is usually Coomb's negative. Leukopenia and thrombocytopenia are frequently more pronounced than anemia. At presentation, 50–60% of patients have white counts $<3000/mm^3$. White blood counts exceeding $50,000/mm^3$ are unusual except after splenectomy. The percent of circulating hairy cells varies widely. Absolute granulocytopenia and monocytopenia are exceedingly frequent findings. At diagnosis, half of the patients have thrombocytopenia with platelet counts $<100,000/mm^3$. The diagnosis of HCL is confirmed by finding the characteristic mononuclear "hairy" cell with its multiple cytoplasmic projections in peripheral blood and bone marrow smears. Phase contrast microscopy of hairy cells, which may demonstrate the distinctive slender hair-like projections, has been very helpful in diagnosis. Electron microscopy may also be helpful. The bone marrow is virtually always involved in hairy cell leukemia. Attempts at bone marrow aspiration are unsuccessful ("dry tap") in up to 50% of cases.

The use of the cytochemical acid phosphatase stain has been helpful in the diagnosis of HCL. In 90% of cases, hairy cells contain the tartrate resistent isoenzyme of acid phosphatase (TRAP) in their cytoplasm.[24] Although characteristic of HCL, TRAP, is not specific. It has been reported as uncommon in CLL, infectious mononucleosis, lymphoblastic lymphoma and rare in "reactive lymphocytosis," but the intensity of the staining in all of these cases is less than that seen in hairy cell leukemia.

Clinical Course

HCL is a chronic disease with a variable course. Some patients succumb early to infection, and other may survive over 20 years. In general, the course is one of slow progression over months to years with progressive organ and marrow infiltration with hairy cells eventually leading to organ failure. The majority of patients are able to live relatively normal lives until late in their course. Infections, particularly pneumonia and septicemia due to gram negative organisms and staphylococcus are common during the course of the disease.[25] Tuberculosis and infection with atypical mycobacteria have been reported, as have fungal pneumonias. Pneumocystis is uncommon except in patients treated with steroids. In most published series, infection is the cause of death in one-half to three-quarters of patients. Because the infectious complications in HCL are so frequent and so severe, as a rule it is assumed that any fever in these patients is due to infection.

The origin of neoplastic cells in HCL remains controversial. Morphologic appearance alone suggests origination from monocytes or lymphocytes. Surface marker and functional studies have not been conclusive and it has variously been suggested that the cell of origin for the "hairy cell" is a lymphocyte, a monocyte, or a hybrid cell. The cell from which the "hairy cell" originates, and the factors determining the direction of its differentiation are unknown. No variation in clinical course or survival has been demonstrated for any particular cellular characteristic demonstrated by the malignant cell.

Therapy

Therapy in HCL has been difficult to evaluate because of the variability of the disease, and no controlled studies are available. As a result, treatment remains uncertain. Splenectomy remains the mainstay of therapy, with most investigators in agreement that splenectomy is appropriate when complications due to pancytopenia become a management problem. The surgical morbidity and mortality is acceptable but great care must be taken to avoid infection. In cases where splenectomy or pancytopenia is asymptomatic, the value of early splenectomy is debated. In most series, 75–90% of patients undergoing splenectomy show improvement in hemogram, usually within the first few weeks postsplenectomy.

Many of the patients who initially respond to splenectomy require additional therapy after varying periods of time. Recent series stress the poor results obtained with either corticosteroid therapy or cytotoxic therapy, especially when they are given prior to splenectomy.

Clinical experience with combination chemotherapy in HCL is limited. Sporadic responses to aggressive combination chemotherapy for splenectomy failures have been reported. The results of leukaphoresis in one remarkable case have recently been described by Fay et al.[26] Golomb[27] has suggested what is currently the prevailing approach: (1) observe the rate of progression of disease and the degree of pancytopenia; (2) recurrent infections due to neutropenia, refractory anemia, or thrombocytopenia may necessitate treatment with splenectomy as the initial therapy; (3) if response to splenectomy is poor or the patient relapses after an initial response, chemotherapy may be indicated; and (4) other therapeutic interventions may show promise but at present are investigational (leukaphoresis, monocyte infusions). Definitive recommendations for therapy await further delineation of the specific nature of the disease and cooperative studies of treatment.

Conclusion

In summary, the chronic leukemias are relatively uncommon malignancies of variable course. Etiology and pathogenesis remain obscure. Although clinical remissions can be obtained, a definite impact of treatment on survival has not been clearly demonstrated. Trials of more aggressive therapy in all the chronic leukemias, including autologous and allogeneic bone marrow infusion in CGL, are underway.

Drug Names

busulfan: Myleran
chlorambucil: Leuxeran
cyclophosphamide: Cytoxan
hydroxyurea: Hydrea
melphalan: Alkeran

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On Fleas

On the basis of attachment to hosts, Harwood and James (1979) segregated fleas into 4 groups. *C. canis* belongs to that group of fleas that easily leave their hosts and may transfer to other hosts of the same or a different species. A massive build-up of flea population probably occurred in the soil under plant cover around the house prior to their movement into the house. In a humid climate (such as Nigeria's) immature stages and adult fleas may be quite abundant outdoors and around homes. This inordinate rise in flea population is made possible because in *C. canis* there is no reproductive synchronisation with host factors as occurs for the rabbit flea, *Spilopsyllus cuniculi* which undergoes ovarian maturation only on pregnant dogs or in response to corticosteroids. This also explains the observation of a massive build-up of *C. canis* in a disused sheep house about 12 months after the sheep had been removed.

One consequence of this human infestation was severe itching which followed the flea bites. There was development of indurated popules and skin rashes. Generally, there was anxiety, restlessness and insomnia. There were more skin lesions on the backs especially just above the waist and lower limbs. These cutaneous manifestations had been shown to be due to the salivary secretions of allergenic materials by fleas.

There are other possible consequences of this anthropophilic deflection of the dog flea. There are at least 8 species of fleas that can transmit *Pasteurella pestis* to man (Lechleitner, 1962) and the number is increasing. If it is proved that *C. canis* can transmit plague bacillus, then its vectorial importance becomes immense. It should be noted that Dipeolu and Ayoade, 1981 b, Akinboade *et al.*, 1981 found *C. canis* on rats (Rattus rattus) in Nigeria and these are regarded as reservoirs of plague bacillus. In the epidemiology of plague it has been established that fleas from dogs can be a problem as was in the case of a woman in California, U.S.A. who had been in contact with a dog in a camp-ground. Also, following an outbreak of plague among Navajo Indians and Prairie dogs *(Cynomys gunnisoni)* in Utah, Southern Colorado, Arizona and New Mexico, 48% of domestic dogs tested had significant titres for *P. Pestis* antibodies (Schwabe, 1969). Furthermore Adams, Emmons and Brooks (1970) are of the view that *Ctenocephalides* sp. may serve as the agent of transfer of Rickttsial infections to man. It should also be noted that *Hymenolepis nana* a tapework of man which also occurs in rats has among its intermediate hosts *C. canis.—Fagbemi BO, Ogunji F, Dipeolu OO: Anthropophilic Deflection of* Ctenocephalides canis *(Dog Flea). Int J Zoonoses 8: 97, 1981*