Best Practice & Research Clinical Haematology 28 (2015) 180–192

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Clinical features and diagnosis of hairy cell leukemia

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Keywords:
Hairy cell leukemia
Clinical features
Diagnosis
Immunophenotyping
BRAF V600E

A B S T R A C T

Significant advances in the diagnosis and treatment of hairy cell leukemia (HCL) have recently been made. Improved distinction of HCL from its mimics though clinical presentations, morphologic and immunophenotypic features, and more recently molecular biology, has highlighted marked differences in treatment response and overall prognosis between these disorders. As our understanding of the unique pathobiology of HCL has grown, exciting new avenues of treatment as well as insight into immune function have been obtained. This review provides an overview of the clinical features and diagnostic attributes of HCL, with contrast to other mature B cell lymphoproliferative disorders with overlapping features.

Introduction

Hairy cell leukemia (HCL) is a chronic B-cell disorder, initially described as leukemic reticuloendotheliosis by Bouroncle et al., in 1958 [1]. The disease is characterized by the presence of typical "hairy cells" – monocytoid lymphocytes featuring circumferential villous projections - in the peripheral blood and marrow, pancytopenia, and a variable degree of splenomegaly. The disease has always aroused interest, initially over the unique morphological and clinical features of HCL, subsequently over dramatic advances in treatment, and presently as the pathobiology of the disease is being elucidated.

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http://dx.doi.org/10.1016/j.beha.2015.10.017
1521-6926/

The malignant cells of HCL are mature B-lymphocytes, characteristically demonstrating coexpression of CD11c, CD25, CD103, and CD123. The malignant B lymphocytes are usually IgVH-mutated, and appear derived from a unique maturation stage which is closely related to memory B-cells, although the hairy cells are unique in being able to express multiple immunoglobulin (Ig) isotypes [2–4]. More recently, it has been demonstrated that most cases of HCL contain a mutated active form of the BRAF gene (V600E), a feature that is specific for HCL amongst the B lymphoproliferative disorders and can be targeted for therapy [4–6].

Clinical findings

The median age of HCL patients at diagnosis is approximately 55 years (range, 18–95 years), with the male-to-female ratio being 4:1 [1,7,8]. Classically, these patients present with weakness and fatigue, and the symptoms can usually be related to pancytopenia and splenomegaly (Table 1). Early studies demonstrated splenomegaly in greater than 90% of patients, which was often massive, but this has become a less prominent feature, possibly due to earlier diagnosis through routine blood work. Peripheral lymphadenopathy is uncommon, though significant abdominal lymphadenopathy may be observed upon imaging studies, and correlates with the duration and extent of disease [9]. The incidence of adenopathy at presentation is 17%, but increases to 56% at relapse after chemotherapy [10]. Less frequently, mediastinal node enlargement may also be observed [11].

Patients commonly present with pancytopenia at presentation, related to marrow infiltration, suppression of hematopoiesis, and hypersplenism. Marrow failure is related to replacement of marrow by hairy cells and reticulin fibrosis, and to the inhibition of myelopoiesis by cytokines, such as TNF-α, released by the hairy cells [2,3]. Splenomegaly in HCL may also contribute to pancytopenia by sequestration of blood cells. Finally, autoimmune thrombocytopenia or autoimmune hemolytic anemia can occur rarely in HCL [12,13].

Infections

Prior to the development of effective treatments for HCL, infections were a major problem and the leading cause of death [7,14,15]. Thus, many of the studies dealing with infections in HCL were carried out over thirty years ago, prior to the development of effective therapies. Interestingly, although there is an initial increase in the risk of infections with pentostatin or cladribine, this risk will resolve when the disease goes into remission and there is recovery of the chemotherapy-induced lymphopenia. Nowadays, approximately one-third of patients will develop an infection during the course of their disease and two thirds of these will be serious [14]. Fever is rarely a manifestation of the underlying HCL; when present, it should prompt a careful search for an infectious process. Approximately 30% of patients present with infection, and 70% have either documented or suspected infections during the

Table 1
Clinical features of hairy cell leukemia.

Manifestation	Incidence (%)
Weakness, easy fatigue	80
Fever, sweats, weight loss, anorexia	20–35
Infection	20–30
Easy bruising, bleeding	20–30
Left upper quadrant abdominal discomfort	25
Autoimmune disorders	15–30
Splenomegaly	80–90
Hepatomegaly	30–40
Ecchymoses, petechiae	20–30
Peripheral lymphadenopathy	<5
Lytic bone lesions	3
Skin involvement	5
Splenic rupture	<5
Other organ dysfunction	<5