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Historical overview of hairy cell leukemia

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A B S T R A C T

Since its discovery in 1923 and further characterization in 1958, hairy cell leukemia (HCL) has undergone enormous advances in the understanding of the biology and treatment of the disease. Initially a uniformly fatal disease, new therapies in rapid succession transformed HCL into a chronic disease with a normal life expectancy in many cases. More recently, the identification of BRAFV600E mutations in the majority of patients with classic HCL have enabled targeted therapies as a therapeutic option. Additional discoveries into the biology of the disease have identified new subtypes of HCL. Modern approaches to the evaluation and treatment of HCL include detailed molecular analysis which informs therapeutic options, which may consist of traditional therapies such as purine nucleoside analogs, or targeted therapies with antibodies, BTK inhibitors, or BRAF inhibitors, or combination therapy. Because HCL is a rare disease, continued progress depends on patients being enrolled on clinical trials whenever possible.

Introduction

For almost 100 years, hematologists have recognized the existence of a unique hematologic malignancy characterized by pancytopenia and splenomegaly. In 1923, Ewald first coined the term

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"leukemic reticuloendotheliosis" to describe a hematologic disorder characterized by splenomegaly, pancytopenia, and circulating monocytic cells [1]. This entity was later recognized as most likely describing acute monocytic leukemia, however this first attempt at characterization led to further study of this clinical syndrome of unknown cellular origin. Using only microscopy to guide classification, Fieschi [2] described three additional subtypes of this entity: 1) reticuloendotheliosis with primitive cells, 2) reticuloendotheliosis with monocytoid cells, and 3) reticuloendotheliosis with lymphoid cells.

The most detailed investigation to follow was performed by Gosselin and colleagues, who studied a series of 49 patients who had been treated at the Mayo Clinic for leukemic reticuloendotheliosis from 1944 to 1953 [3]. The authors examined the clinical course as well as the peripheral blood, bone marrow, and tissue aspirates of these patients. Three typical cells of leukemic reticuloendotheliosis were described by the authors, including a primitive cell type, a monocytic type (Schilling's monocytic leukemia), and a lymphocytic type. These corresponded to three general clinical manifestations including an acute type which was rapidly progressive and similar in course to acute leukemia, a subacute type which consisted of low grade systemic manifestations followed by an acute exacerbation leading to death, and a chronic type characterized by a prolonged disease course. In any case, the course was found to be uniformly fatal due to hemorrhage or infection. The authors identified five typical clinical features which included a history of a flu-like syndrome preceding diagnosis, constitutional symptoms, a short history of splenomegaly and occasionally hepatomegaly, variable lymphadenopathy, and in many patients, cutaneous manifestations consisting mostly of popular eruptions, nodules, and erythroderma. Splenomegaly was the most consistent physical exam abnormality, seen in 73% of patients. These authors correctly identified severe anemia as a late and poor prognostic factor. In one of these patients, treatment with nitrogen mustard was attempted, but the patient rapidly died from complications of agranulocytosis.

The first definitive work to more fully characterize the disease occurred in 1958, when Bouroncle and colleagues authored a paper identifying leukemic reticuloendotheliosis as a distinct entity, in which the typical hairy cell was first described [4]. This was also the first study to describe the demographics of the disease, identifying this as a rare disease with an overall incidence of approximately 2% of all leukemias treated at Ohio State annually. The authors also described the usual male predominance. The authors studied in detail the clinical course and hematopathological findings in 26 patients treated at their institution. The most common presenting signs and symptoms were related to cytopenias, constitutional symptoms, and infection. Splenomegaly was the most common clinical manifestation, with infection being a frequent complication. Survival on average was short, with the majority of the patients surviving fewer than 5 years and only one patient surviving as long as 15 years. The clinical courses of each of the 26 patients were meticulously documented. Ten patients were treated with nitrogen mustard without response. Splenic radiotherapy was observed to result in clinical improvement, as did steroids alone or in combination with triethylene melamine. Splenectomy was reserved for the chronic forms, and when used in patients with predominately splenic involvement achieved excellent results.

These investigators utilized supravital, hematoxylin & eosin, and Wright's stains to examine the peripheral blood, bone marrow, or bone from the spinous processes. The malignant cells were isolated and described as "free reticulum cells" or "histiocyte." On supravital staining, these cells were noted to have pseudopods protruding from the cytoplasm which resulted in a serrated border. The authors published photographs of these cells which are now recognized to be the classic "hairy cells," once and for all characterizing the malignant cell underlying the disease which would later be termed "hairy cell leukemia." [5].

Despite this progress, even as late as 1974 there was no scientific consensus regarding the name of the disease, criteria for diagnosis, cell of origin, or classification among hematologic malignancies. Catovsky and colleagues undertook a review of the literature which included 170 published reports, and studied 30 cases from their own center, utilizing the modern techniques of cytochemical staining that included tartrate-resistant acid phosphatase (TRAP) and periodic acid Schiff (PAS) [6]. The cells were also examined using electron microscopy. Their seminal work determined was that this disease should be characterized as a lymphoproliferative disorder. Criteria for diagnosis included the presence of "hairy" cells in the peripheral blood or bone marrow which were negative for myeloperoxidase,