Chronic Lymphoid Leukemia: a systematic review of its epidemiological, etiological and genetic aspects

Leucemia Linfoide Crônica: uma revisão sistemática de seus aspectos epidemiológicos, etiológicos e genéticos

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ABSTRACT
Chronic lymphocytic leukemia (CLL) is a lymphoproliferative neoplasm that mainly affects the elderly, being the most common leukemia in western adults. It is estimated the presence of about 191,000 new cases annually in the world. Despite the advances made in the diagnosis and therapeutic management of CLL, its etiological and genetic aspects are still not completely clear. The objective of the article was to address and bring together the main epidemiological and etiopathogenic aspects of CLL, exploring how a greater biological understanding of the disease can improve and generate new therapeutic strategies.

Keywords: chronic lymphoid leukemia, epidemiology, etiology.

RESUMO
A leucemia linfóide crônica (LLC) é uma neoplasia linfoproliferativa que acomete principalmente idosos, sendo a leucemia mais comum em adultos ocidentais. Estima-se presença de cerca de 191.000 novos casos anuais no mundo. Apesar dos avanços obtidos no diagnóstico e no manejo terapêutico da LLC, seus aspectos etiológicos e genéticos ainda não estão totalmente claros. O objetivo do artigo foi abordar e reunir os principais aspectos
epidemiológicos e etiopatogênicos da LLC, explorando como a maior compreensão biológica da doença pode melhorar e gerar novas estratégias terapêuticas.

**Palavras-chave:** leucemia linfóide crônica, epidemiologia, etiologia.

1 INTRODUCTION

Chronic lymphoid leukemia (CLL) is a chronic lymphoproliferative syndrome characterized by generating a malignant disorder of mature and dysfunctional lymphocytes, which accumulate in peripheral blood, bone marrow and lymphoid tissues. This condition predominantly affects B lymphocytes, resulting in a monoclonal proliferation of these cells.

The diagnosis of CLL is established through the analysis of clinical and laboratory characteristics. Complete blood count, morphological analysis and immunophenotyping of peripheral blood are used in the initial analysis. The presence of sustained lymphocytosis associated with immunophenotyping of peripheral blood containing CD5, CD19, CD20, CD23 are some of the markers commonly used in the diagnosis. CLL can also be classified according to its morphology, being divided into typical and atypical cases. In atypical cases, in addition to conventional investigation, genetic and molecular elements should be analyzed to exclude other possible hematological diseases.

The treatment of choice for CLL depends directly on the patient's clinical variables. In the case of young patients or patients with good general clinical status, there is a tendency to opt for more aggressive and curative therapeutic regimes, with allogeneic bone marrow transplantation as the main therapy. For patients with compromised clinical status, palliative treatment should be used, with treatments less likely to induce myelosuppression or infectious risk.

2 OBJECTIVE

The objective of the present study is to gather information through analysis of recent articles on the main epidemiological and etiopathogenic aspects of Chronic Lymphoid Leukemia, synthesizing and exploring its main points.

3 MATERIALS AND METHODS

A literature review was carried out, selecting the main studies and publications indexed through a systematic search in the databases: Medical Literature and Retrieval System on Line (Medline), Scientific Electronic Library Online (Scielo) and PubMed. After the initial search,
the articles were selected according to their greater relevance and adequacy to the theme of the review.

4 EPIDEMIOLOGY

Chronic lymphocytic leukemia (CLL) is the most prevalent form of leukemia in adults in Western countries, accounting for approximately 25 to 35 percent of all leukemias diagnosed in the US. The incidence of CLL shows a predominance in men, with an approximate ratio of 1.5:1 when compared to the involvement in women⁵. The National Cancer Institute (INCA) estimates that for each year of the 2020/2022 triennium, 5,920 new cases were diagnosed in Brazil in men and 4,890 in women. These values correspond to an estimated risk of 5.67 new cases per 100,000 men and 4.56 new cases per 100,000 women ⁶. On a global scale, CLL accounts for about 191,000 cases and 61,000 deaths each year ⁵.

CLL predominantly affects older adults, with an average age of 70 years at diagnosis. Although its incidence gradually increases with age, it is important to note that CLL can also be diagnosed in young adults ⁵. Geographical and racial differences also influence the incidence of CLL. Asian countries such as China and Japan exhibit extremely low incidence rates, estimated to be around 10 percent of those seen in Western countries ⁴.

5 ETIOLOGY

To date, there are no clearly identifiable occupational or environmental factors that predispose individuals to CLL. For example, survivors of radioactive accidents did not show an increase in the incidence of CLL, despite an increase in other types of leukemia ⁶. Although there are some reports associating CLL with farmers, exposure to benzene and heavy solvents, there is still no consensus on the influence of environmental factors on the appearance of CLL. In turn, genetic factors seem to play a significant role in explaining CLL. pathological genesis of CLL ⁷.

In addition, it is observed that CLL, as well as other lymphoid and hematological tumors, occurs more frequently among first-degree relatives of sick patients ². It is estimated that up to 17 percent of first-degree relatives of patients with CLL have monoclonal B-cell lymphocytosis (BMCL) detected by flow cytometry³. The phenomenon of genetic anticipation is also noted in cases of CLL, making the disease tend to develop at an earlier age in successive generations.
6 PATHOGENESIS

6.1 VARIABLE IMMUNOGLOBULIN HEAVY CHAIN (IGHV)

To try to explain the origin of CLL, studies that investigated specific rearrangements of the immunoglobulin heavy chain variable region gene (IGHV), suggest that cells from patients with chronic lymphocytic leukemia (CLL) who use wild-type IGHV come from cells B conventional, without previous treatment. That is, they have gene expression distinct from conventional B cells. However, gene expression studies in cells from patients with CLL show that those expressing both wild-type and mutated IGHV share a common gene expression profile, suggesting a common origin for both variants.

Analysis of mutations in the IGHV genes revealed that CD5+ blood B cells are clonally expanded and contain a small number of B cells derived from the germinal center, evidencing the existence of two classes of CLL defined by the presence or absence of IGHV hypermutation. Accordingly, researchers now believe that CLL cells with wild-type IGHV originate from mature CD5+ CD27- B cells with wild-type IGHV, whereas mutated cells are derived from a distinct subset of CD5+ CD27+ central germline B cells with mutated IGHV. These findings advance our understanding of the pathogenesis of CLL and highlight the importance of alterations in the IGHV genes in the origin and development of this disease. Knowledge of these mechanisms may be critical for the development of more specific and effective therapeutic approaches for the treatment of CLL.

6.2 GENETIC ASPECTS

Next-generation sequencing (NGS) has revealed the complexity of the chronic lymphocytic leukemia (CLL) genetic panel, in which the accumulation of mutations or genetic combinations is associated with disease progression and resistance to treatment. Common copy number changes seen in CLL include focal chromosome 13q deletion, trisomy 12, and chromosome 11q (ATM) or 17p (TP53) deletion. High recurrence of mutations in specific key genes is observed in patients with CLL. Key ones include the splicing factor SF3B1, the microenvironmental receptor NOTCH1, DNA damage response proteins such as TP53 and ATM, genes for B cell developmental pathways such as IRF4 and IKZF3, NFkB signaling proteins, as BIRC3, and the MYC and MGA pathway gene. These genetic alterations, in addition to playing a fundamental role in the pathogenesis of CLL, influence behavior and response to disease treatment.

It is noted that the CLL genetic panel is dynamic, changing with selected somatic events being enriched after therapeutic relapse and resistance to chemotherapy or inhibitors of specific
pathways. This observation highlights the existence of preferred evolutionary trajectories taken by CLL cells during disease progression and after treatment, contributing to therapeutic challenges.\(^9\)\(^{-11}\)

Additionally, CLL cells are characterized by disordered local methylation patterns, identified as a hallmark of the disease. Altered methylation patterns are associated with an increased adaptive capacity for clonal evolution, potentially driving the development of more aggressive and treatment-resistant CLL subclones.\(^11\)

\section*{7 CONCLUSION}

It is concluded that the pathogenic etiology of CLL is still not fully known. Thus, the identification of these genetic and epigenetic aspects in CLL not only improves our understanding of the biology of the disease, but also opens up new perspectives for personalized therapeutic strategies. Targeting specific gene mutations and altered pathways holds promise to develop more effective treatments and improve treatment outcomes in patients with CLL. Continued research efforts are essential to uncover the full complexity of the CLL genetic landscape and pave the way for precision medicine approaches to this challenging hematologic malignancy.
REFERENCES


