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RESEARCH ARTICLE

Epidemiological data and diagnosis pitfalls in aggressive extranodal non-Hodgkin's lymphomas: current issues

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What is not yet known on the issue addressed in the submitted manuscript

Despite the development of new methods of diagnosis and treatment with antineoplastic agents, the results of aggressive non-Hodgkin lymphomas treatment remain modest, with frequent relapses and primary refractory forms.

The research hypothesis

A study was carried out, which assumed the narrative synthesis of the literature to identify the current epidemiological characteristics and the difficulties in establishing the diagnosis of aggressive extranodal non-Hodgkin lymphomas.

The novelty added by manuscript to the already published scientific literature

Conducting a broad literary synthesis to demonstrate the importance of continuing research in the field of aggressive extranodal non-Hodgkin lymphomas, which remains a prevalent issue in modern haemato-oncology and public health.

Abstract

Introduction. Non-Hodgkin's lymphoma is a group of malignant tumors that develop from hematopoietic cells located outside the medullary. They are one of the most common forms of hemoblastosis. Non-Hodgkin lymphoma develops in people of all ages. Morbidity of non-Hodgkin lymphoma increases with age reaching its highest level in people over 50 years of age.

Material and methods. A study was carried out through a narrative review of the literature in the form of a synthesis article. The article summarized and systematized various primary studies, dedicated to the epidemiological and diagnostic aspects of aggressive extranodal NHL.

Results. Aggressive extranodal NHL remains a major problem, with a fairly large increase in incidence globally. This trend is observed in several countries of the world, thus morbidity increases by 3% annually for women and by 4% for men. Globally, aggressive non-Hodgkin's lymphoma continues to affect the working-age population. Although patients with primary extranodal NHL tend to report to a medical specialist at a lower stage than those with primary ganglion disease, the number of those addressing in advanced stages continues to be increased.

Conclusions. Although diagnosing NHL does not involve great impediments, primary care physicians often detect patients in the late stages of the disease either because of delayed referral to the doctor or because of incorrect diagnosis. Despite the development of new methods of diagnosis and treatment, aggressive extranodal NHL continues to be a current problem of clinical medicine and public health, requiring increased managerial and financial efforts.

Key words: aggressive non-Hodgkin's lymphomas, extranodal, morbidity, diagnosis

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignant tumors of B-, T-and, less commonly, NK-cellular origin that may primarily affect any organ and tissue that contains lymphoid cells [1]. Currently, NLH is considered the most common group of malignant hemopathies, it ranks 7 as morbidity by malignant tumors and 6 as mortality by cancers [2]. Worldwide, there is a clear increase in the incidence of NHL by about 80% more than in the early 1970s [3]. Annually, 287.000 new cases of NLH are diagnosed worldwide [4]. The incidence of NHL varies significantly depending on the geographical region; these differences may be related to demographics, environmental

differences and other factors such as lifestyle and health-care systems [5]. A higher incidence is found in males, especially in Israel (17.6 cases per 100k), in white Americans (14.5 per 100k), in Australia (15.3 per 100k), Canada (13.7 per 100k) and Portugal (13.3 per 100k) [6]. Similar geographical particularities were observed in females, with a higher incidence recorded in the population of Israel (13.0 per 100k), white Americans (10.4 per 100k), Canada (10.0 per 100k), Australia (12.3 per 100k) and lower in Central Africa (2.8 per 100k), South Africa (1.6 per 100k), Vietnam (3.5 per 100k), India (3.6 per 100k) [7]. The NHL morbidity index in the Republic of Moldova constitutes 4.1 per 100 000 people [8].

The aim of the study was to identify current epidemiological patterns and difficulties in establishing diagnosis in aggressive non-Hodgkin's extranodal lymphomas.

Material and methods

A study was carried out through a narrative review of the literature in the form of a synthesis article. The article summarized and systematized various primary studies, dedicated to the epidemiological and diagnostic aspects of aggressive extranodal non-Hodgkin lymphoma. The accumulation of information for this research was carried out by analyzing data from specialized international bibliographic sources and official statistics on the respective malignant myeloproliferative neoplasm. To achieve this, scientific medical publications were searched through Google Search, PubMed, Z-Library, NCIB, Medscape, Hinari database, using the following keywords: „non-Hodgkin lymphoma”, „aggressive”, „extranodal”, „mortality”, „survival”, „incidence”, „prevalence”, „diagnosis”. More than 50 reference bibliographic sources have been studied to conduct the qualitative research. In order to diversify the conclusions, the results of foreign studies were supplemented by research data published from the Republic of Moldova.

Results and Discussion

Aggressive extranodal NHL remains a major problem today, with a clear increase in incidence globally. The evolution and survival rate depend largely on the type and subtypes of lymphoma, the stage and severity of the disease, the age of the patient at the time of the diagnosis and comorbidities. Although patients with primary extranodal NHL tend to see a specialist at a lower stage than those with primary ganglion disease, the number of those who address in advanced stages continues to be high. At the moment, contemporary diagnostic methods allow accurate stabilization of the diagnosis and subsequent initiation of treatment according to the type of lymphoma.

NHL develops and disseminates at different rates, being divided according to histopathological and clinical-evolutionary features into indolent and aggressive [9]. Aggressive lymphomas are a heterogeneous group of malignant tumors that reflect a variety of clinical, biological, and pathological characteristics [16]. They refer to those rapidly growing subtypes (KI-67 proliferation index >40%) and would often

be lethal within a few months without appropriate therapy [10]. According to data from the American Hematology Society in 2015, aggressive lymphoma accounted for about 60% of all cases of NHL in the United States [11].

There are different types and subtypes of aggressive NHL. In order to be able to apply effective treatment, it is essential to determine the type and subtype of lymphoma. Sometimes more than one type of lymphoma can be detected at the same patient [22]. Initially, it will be determined what is the initial cell from which the disease developed [19]. B-cell lymphoma is the most common - about 90% of people in Western countries are diagnosed with B-cell lymphoma. Lymphomas that have their onset from T cells make up about 10%, which are more common in Asian countries, while NK cell lymphoma affects less than 1% of people [23]. The most common subtype of aggressive NHL that develops from type B cells is diffuse large B-cell lymphoma (DLBCL) [25]. 30% of NLH in the United States is DLBCL type, which tends to develop extranodally in about 40% of cases [24]. Type B cells also have their starting point in mantle cell lymphoma, which affects 5 to 7 percent of people with lymphoma. It usually develops in people over the age of 60 and is much more common in males than females, commonly involving the bone marrow in the process [3]. Primary mediastinal lymphoma with large B-cells is an aggressive form of DLBCL. It often complicates with superior vein syndrome. This subtype of lymphoma is most commonly established in females between the ages of 30 and 40, and about 2.5% of people with NHL have this subtype [2].

From the subtypes that develop from T and NK cells, peripheral T cell lymphoma, not otherwise specified (PTCL, NOS) is most common. This is an aggressive form of lymphoma that is often in advanced stages when doctors detect it [26]. It mainly affects people over the age of 60 and accounts for about 6% of all lymphomas in the United States and Europe. Another subtype of aggressive lymphoma is anaplastic lymphoma, which accounts for about 2% of all lymphomas and about 10% of all childhood lymphomas [30].

The tumor originating from the extranodal tissue is called primary extranodal lymphoma (PENL), while the hematogenous spread of the disease from lymph nodes to extranodal tissue is secondary extranodal lymphoma [12]. The incidence of PENL is constantly increasing in recent years; there are many factors that „favor” this increase: HIV infection, the increasing use of immunosuppressive therapy, and indolent viral infection [27]. The primary extranodal sites of NHL constitutes 30-48%, with more frequent damage to the Waldeyer lymphatic ring (19-21%) followed by the gastrointestinal tract (17-19%) and spleen (4-6%) [13]. In other organs and tissues (soft tissues, skin, bones, pleura, lung tissue, central nervous system, orbit, mammary gland, ovary, uterus, prostate, and others) NLH develops rarely (from 0.8 to 3-4%) [14]. Worldwide, it has been observed that patients with primary extranodal NHL tend to present themselves at a lower stage than those with primary ganglion disease.

The only method to confirm the diagnosis of NHL remains excisional biopsy of the tissue with subsequent morphological, immunohistochemical, flow-cytometry, FISH for histological determination of the lymphoma subtype.

However, the most common causes of late diagnosis are late referrals to the specialist doctor, as well as misdiagnosis by other doctors, often treating the disease as an inflammatory/reactive process, and redirecting the patient to the hematologist after several attempts of treatment with anti-inflammatory drugs/antibiotics; this ultimately leads to an increase of patients detected in stages III-IV.

Worldwide, NHL caused 6.8 million DALYs (disability-adjusted life-years) in 2016 [21]. Despite the development of new antineoplastic agents, the outcome of aggressive NHL treatment remains poor, with frequent relapses and primary refractory forms [17]. The survival of patients differs depending on the stage at the time of diagnosis, the type, and subtype of lymphoma, severity of the disease, age of the patient at the time of the diagnosis and comorbidities [28]. According to a study conducted in the UK between 2004 and 2016, 60 out of 100 patients with DLBCL survive 5 years and longer after diagnosis. While 55 in 100 patients with Burkitt lymphoma survive about 5 years, and only 35 in 100 patients with T cell lymphoma survive up to 5 years after diagnosis [29].

The increase in morbidity and disability of the working-age population, the large number of cases diagnosed in the late stages of NHL and the poor results of the treatment of aggressive histopathological types remain a current problem of clinical medicine and public health, imposing increased policy changing and financial efforts [19, 20].

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Conclusions

1. NHL is in the first place in the morbidity among malignant hemopathies, the incidence of which attests a continuous increase in the last years.
2. Worldwide, there is an increase of aggressive NLH morbidity indices for the working-age population as well as an increase in the degree of disability.
3. Although the diagnosing NHL does not have great obstacles, patients are often detected in the advanced stages of the disease either because of late referral to the specialist or because of misdiagnosis by primary care physicians.
4. Despite the development of new methods of diagnosis and treatment, aggressive extranodal NHL continues to be a current issue of clinical medicine and public health, requiring increased managerial and financial efforts.

Declaration of conflicting interests

Nothing to declare.

Authors' contributions

DU studied the bibliographic reference sources, summarized, and systematized the data of published research, studies, and clinical recommendations, structured and drafted the article. VM, MR, NSB, LM, VM conceptualized the manuscript, summarized and systematized the data of published research and studies and revised the draft of the article.

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