Hodgkin's Lymphoma: Current Views on the Problem

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Abstract

Lymphogranulomatosis holds a unique position in both oncological and oncohematological studies owing to the extremely polymorphic morphology of tumor tissue, non-specific clinical presentations of the disease, and a high recovery rate ensured by modern treatment protocols. Analysis of the body of literature showed that the development of Hodgkin's lymphoma is associated with malignant B-cell transformation, which is primarily observed in young people.

Histologically, there can be distinguished classical and nodular forms with lymphoid predominance. In the classical form of Hodgkin's lymphoma, Hodgkin's and Reed-Sternberg's cells predominate among tumor cells and are accompanied by reactive inflammation. Modern scientific advances make it possible to perform immunophenotyping of pathological cells and determine the histogenesis of lymphogranulomatosis, however, to the present moment, diagnosing Hodgkin's lymphoma can pose a significant challenge even for experienced professionals, especially in atypical cases.

In most cases, immunohistochemical examination can confirm the diagnosis of classical Hodgkin's lymphoma. A panel comprising CD3, CD20, CD15, CD30, and PAX5 markers is usually enough for its initial identification. Modern treatment standards of the classical form make it possible to achieve remission in over 80% of cases. However, late complications associated with the impact of specific therapy significantly worsen the outcomes of Hodgkin's lymphoma treatment. Therefore, choosing the optimal therapy for this category of patients remains controversial. Chemotherapy and radiation regimens need to be improved, as they are often accompanied by side effects and are difficult for patients to tolerate. At present, there is a need for further studies in prevention, diagnosis, and treatment of Hodgkin's lymphoma.

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Introduction

Lymphogranulomatosis or Hodgkin's lymphoma (HL) is a tumor that primarily affects the lymphatic system[1]. Lymphogranulomatosis holds a unique position in both oncological and oncohematological studies owing to the extremely polymorphic morphology of tumor tissue, non-specific clinical presentations of the disease, and a high recovery rate ensured by modern treatment protocols.

Lymphogranulomatosis had been considered an inflammatory disease for a very long time. Modern advances in cytogenetics, immunology and immunophenotyping of pathological cells have shed light on the histogenesis of lymphogranulomatosis[2]. The disease was first described by Thomas Hodgkin in 1832. According to Russian researchers, the current incidence rate of Hodgkin's lymphoma is

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2.3 per 100,000 population. The pathology affects people of all ages, with the male population having a slightly higher occurrence than the female one[3]. In children, lymphogranulomatosis accounts for about 40% of all lymphoma cases[4], which is why it constitutes a significant oncological problem nowadays.

The present paper aims to analyze the body of scientific literature studying the incidence, diagnosis, and treatment of lymphogranulomatosis nowadays.

Materials and methods

The research was conducted using the bibliosemantic method. 41 modern scientific papers on lymphogranulomatosis were analyzed.

Results

The current incidence of Hodgkin's lymphoma ranges globally from 1.5 to 4.5 per 100,000 population. The peak incidence occurs at 15-40 years, reaching its all-time high at 20-25 years. In the first half of the last century, patients' 5-year overall survival rate was as low as 5%, while timely primary treatment of lymphogranulomatosis today would most likely ensure recovery.

Discussion

The etiology of lymphogranulomatosis is unknown. In the 1970s and 1980s, A. S. Evans and then N. Mueller discovered a correlation between Epstein-Barr virus infection and the incidence of lymphogranulomatosis. According to them, the risk of lymphogranulomatosis was three times higher among infected people than uninfected[2]. Recent studies suggest that Epstein-Barr virus LMP1 oncogene protects lymphoma cells from death through collagen-mediated DDR1 activation[5]. Moreover, patients with Hodgkin's lymphoma who test positive for Epstein-Barr virus have significantly worse survival rates across all age groups[6].

It is currently known that the progression of Hodgkin's lymphoma is associated with the malignant transformation of B cells and is primarily observed in young people. Histologically, there can be distinguished classical and nodular forms with lymphoid predominance. In the classical form of Hodgkin's lymphoma, Hodgkin's and Reed-Sternberg's cells predominate among tumor cells and are accompanied by reactive inflammation[7].

Classical Hodgkin's lymphoma resembles pathological, molecular, and clinical characteristics of primary mediastinal B-cell lymphoma[8].

It is traditionally believed that lymphogranulomatosis can be diagnosed only morphologically when histological examination reveals specific multinucleated CD30+, CD15+ Reed-Sternberg cells[2]. To the present moment, diagnosing Hodgkin's lymphoma can pose a significant challenge even for experienced professionals, especially in atypical cases. Currently, immunohistochemistry plays a significant role in its diagnosis, which typically uses anti-CD15 and anti-CD30 antibodies[8]. In most cases, immunohistochemical examination can confirm the diagnosis of classical Hodgkin's lymphoma. A panel comprising CD3, CD20, CD15, CD30, and PAX5 markers is usually enough for its initial identification. In case samples do not match the differential diagnosis, additional markers can be used[10].

Multi-parameter flow cytometry is another powerful diagnostic tool that makes it possible to assess the expression of cellular antigens to quickly obtain immunophenotypic information needed to identify non-Hodgkin's and Hodgkin's lymphoma[11].

Among other methods of diagnosis, experts have recently noted positron emission tomography, which is more sensitive than the biopsy and is applied to diagnose bone marrow involvement in the pathological process of Hodgkin's lymphoma[12].

Positron emission tomography has recently become a routine method aiming to directly visualize tumors. However, extensive application of this technique in clinical practice requires conducting an in-depth study of the indications for this diagnostic technique and the interpretation of its results[13]. Positron emission tomography using the radiopharmaceutical agent fluorodeoxyglucose (FDG) is important in examining patients with Hodgkin's lymphoma, both at the onset of the disease and throughout its progression, to assess response to therapy and detect the slightest recurrence. Currently, no international guidelines have been developed concerning the use of positron emission tomography with FDG to monitor the

effectiveness of treatment of lymphoma patients who went into complete remission, and its use to monitor the disease dynamics remains controversial. The first prospective study by scientists from the University of Bologna proved the feasibility of using positron emission tomography with FDG when observing lymphoma patients in complete remission. Researchers have shown that this diagnostic method makes it possible to identify recurrences that were not detected during computed tomography in patients with favorable and unfavorable prognoses[14,15].

Assessing the prognosis and treatment risks in patients with Hodgkin's lymphoma has been a subject of numerous studies. The human multidrug resistance gene (MDR1), which encodes the major transmembrane transporter P-glycoprotein, has been shown to determine tumor susceptibility and response to chemotherapy[16].

Studies of the prognostically significant pretreatment serum cytokine levels in classical Hodgkin's lymphoma have shown that elevated serum cytokine levels prior to therapy increase the risk of disease recurrence and correspond to lower survival rates. Pretreatment cytokine profile, in particular serum levels of IL-6 and IL-2R, can be used to identify patients at high risk of early recurrence[17]. Elevated serum interleukin-6 in Hodgkin's lymphoma correlates with the severity of clinical picture, the way tumor process responds to treatment, as well as adult patients' survival rate. The prognostic value of immunohistochemical studies of interleukin-6 expression in Hodgkin's cells, Reed-Sternberg cells, and bystander reactive cells in pediatric patients is currently being studied. Further prospective studies in children are needed to confirm the applicability of interleukin-6 expression to stratify the treatment of this category of patients[18]. High pretreatment levels of soluble CD30 in the serum in advanced stages of classical Hodgkin's lymphoma can identify patients with a poor prognosis[19].

MicroRNA-SNP studies can provide useful prognostic information on treatment-related toxicity and clinical outcomes in HL. This information can be used to identify patients with signs of chemoresistance or recurrence[20]. The diagnostic value of survivin, a protein encoded in humans by the BIRC5 gene, a cell-cycle regulator, and an apoptosis inhibitor, was also studied. It is actively expressed during fetal development, but is absent in most differentiated tissues of adults, except for elements of the immune system such as B and T lymphocytes. Survivin expression is observed in all types of carcinoma; with regard to lymphoma, this issue still remains understudied. Recent studies have shown that although survivin is expressed in Hodgkin's tumor cells, it may not play a major role in the progression of classical Hodgkin's lymphoma and thus cannot be viewed as a biomarker of its progression, as opposed to most carcinomas[21].

Modern treatment standards of the classical form make it possible to achieve remission in over 80% of cases. However, late complications associated with the impact of specific therapy significantly worsen the outcomes of HL treatment. Therefore, choosing the optimal therapy for this category of patients remains controversial. In particular, this discussion is diagnostically important for evaluating the results of positron emission tomography and using brentuximab vedotin (conjugate of antibodies with a drug that delivers an antineoplastic agent to CD30-positive tumor cells, leading to apoptotic cell death), nivolumab, and pembrolizumab (anticancer monoclonal antibodies). The issue of identifying patients who need allogeneic stem cell transplantation has not been resolved[7,22-24].

Significant clinical effect with a controlled safety profile in patients with relapsed or resistant Hodgkin's lymphoma proves the effectiveness of prescribing brentuximab vedotin[25].

Brentuximab vedotin is a conjugated antibody that induces sustained responses in patients with recurrent or resistant Hodgkin's lymphoma and systemic anaplastic large cell lymphoma. Applying consolidative allogeneic stem-cell transplantation in 15 patients followed by brentuximab vedotin treatment at a dose of 1.8 mg/kg every 3 weeks for up to 16 cycles showed a two-year progression-free survival in 66% of cases. The overall two-year survival rate was 80%[26].

Blocking programmed death-1 (PD-1) pathway using monoclonal antibodies has led to the development of an antitumor response with lower toxicity levels compared to immunotherapy using interleukin-2 and ipilimumab in clinical trials. Thus, nivolumab, an anti-PD-1 antibody, should be applied when treating groups of patients with refractory HL[27]. As the PD-1 pathway inhibitor,

nivolumab can also be used to treat recurrent Hodgkin's lymphoma. Its use has proven to be more effective compared to other drugs in the long-term treatment of patients with recurrent and refractory conditions. Adverse effects of nivolumab are manageable and have a high safety profile[28,29]. According to recent studies, prescribing anti-PD-1 immunotherapy followed by radiation therapy in patients with Hodgkin's refractory lymphoma is quite appropriate and shows promising results. Toxic lung lesions associated with radiation therapy went into remission in all patients after applying antibiotic therapy[30].

At the same time, the analysis of the long-term outcomes of 89 patients with relapsed or refractory classical Hodgkin's lymphoma who were prescribed total lymphoid irradiation and high-dose chemotherapy followed by autologous stem cell transplantation showed that the treatment failed in 20 patients in 6.1 months following the transplantation. The 5-, 10-, and 15-year overall survival rates were 72.3%, 67.5%, and 57.8%, respectively. Eight patients developed secondary malignancies, five being hematological and three being solid tumors[31].

Hodgkin's lymphoma is a relatively chemosensitive malignancy[32]. There are several treatment strategies available for adults with late-stage Hodgkin's lymphoma, therefore, two alternative chemotherapy standards have been evaluated in the studies (increasing the doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone in escalated BEACOPP regimen and doxorubicin, bleomycin, vinblastine, and dacarbazine in ABVD). Six escalated BEACOPP regimen cycles significantly improve overall survival rate compared to ABVD and other regimens, and therefore the authors recommend this treatment strategy as the standard of care for patients, provided that appropriate supportive care is available[33]. Bendamustine is effective in patients with refractory or recurrent forms of Hodgkin's lymphoma and can be used in combination with other drugs for initial therapy[34].

The treatment of 69 children with relapses and 11 children with primary resistance who received therapy under a standardized protocol of 4-6 EPIC chemotherapy cycles (etoposide, prednisolone, ifosfamide, and cisplatin) was analyzed. Radiation therapy was recommended for all relapses. High-dose stem cell therapy was recommended for patients with poor response. The 5-year overall survival and progression-free survival in relapse cases were 75.8% and 39.9%, respectively. The first remission duration closely correlates with overall survival; the risk of death was reduced by 53% in patients who relapsed 3-12 months after the end of the treatment (compared to <3 months) and reduced by 80% in patients who relapsed over 12 months after the end of the treatment. The results of treatment in children with primary Hodgkin's lymphoma leave a lot of room for improvement[35].

Applying either combination modal therapy or chemotherapy by itself in the early stages of Hodgkin's lymphoma remains controversial in the United States. However, prescribing combination modal therapy makes it possible to achieve better survival rates in this category of patients compared to chemotherapy[36].

Side effects of anticancer drugs should be taken into account when conducting chemotherapy. In particular, chemotherapeutic agents used to treat Hodgkin's lymphoma are teratogenic[37]. They are also the most common toxic agents for peripheral nerves. For example, vincristine is a vinca alkaloid used when treating some malignancies in combination with other chemotherapeutic agents. Intravenous vincristine infusion of over 5 mg causes neuropathy accompanied by sensory symptoms, and exceeding the cumulative doses of approximately 30 to 50 mg leads to the development of motor symptoms. There is a clinical case of a Hodgkin's lymphoma patient developing severe polyneuropathy following the administration of 2 mg of vincristine[38]. In general, neurological disorders in patients with HL may be associated with the tumor spreading directly to the nervous system, exposure to chemotherapy or radiation, secondary compression of the tumor, infection, and paraneoplastic syndromes. Paraneoplastic neurological syndromes are rare in patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma. The exceptions are paraneoplastic cerebellar degeneration in Hodgkin's lymphoma and dermatopolymyositis in Hodgkin's lymphoma and non-Hodgkin's lymphoma. Other paraneoplastic syndromes occur rarely and are reported only as isolated cases or in short series. In particular, a case of a Hodgkin's lymphoma patient who developed symptoms of bilateral motor and sensory axonal neuropathy of the

lower extremities was reported[39].

Therefore, given the possible side effects, researching the properties of new chemotherapeutics necessitates studying their safety. Evaluation of the efficacy and safety of gemcitabine combined with oxaliplatin in 27 lymphoma patients after two or more previously unsuccessful chemotherapy regimens showed higher efficacy and better tolerability of this regimen. Efficacy was assessed in 24 patients. Complete response was observed in 4 people (16.7%), partial response in 7 patients (29.1%), a stable process in 6 cases (25.0%), and disease progression in 7 cases (29.1%), the overall response rate was 45.8%. Thus, this chemotherapy regimen proves to be quite effective, it is possible to achieve long-term survival in some patients with lymphoma[40]. A study of the effectiveness of ifosfamide and vinorelbine chemotherapy in pediatric practice for treating recurrent and resistant Hodgkin's lymphoma has shown that it is a safe and effective regimen that makes it possible to perform hematopoietic stem cell transplantation in most patients in the future[41].

Conclusions

Nowadays, Hodgkin's lymphoma remains an urgent oncological problem, because the disease is quite common in clinical practice, affects mainly young people, and it is characterized by polymorphic morphological picture of tumor tissue and nonspecific clinical manifestations of the disease. Modern scientific achievements allow immunophenotyping of pathological cells and determine the histogenesis of lymphogranulomatosis, but even nowadays the diagnosis of Hodgkin's lymphoma can be difficult even for experienced professionals, especially in atypical cases.

Modern timely primary treatment of lymphogranulomatosis (Hodgkin's disease) with highly possibility makes a complete recovery, but the efficacy of the therapy in refractory and recurrent cases remains insufficient. Chemotherapy and radiation regimens require the improvement, whereas they are often accompanied with side effects and they are hard to tolerate by patients. Nowadays, prevention, diagnosis, and treatment of Hodgkin's disease require further study.

Declaration of Interest

The authors declare no conflict of interest regarding this article.

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