

ON THE PROBLEM OF TIMELY AND PRECISE DIAGNOSTICS OF LYMPHOPROLIFERATIVE DISEASES

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The rise of malignant neoplasm morbidity rate is partially due to morbidity rate increase of Hodgkin's disease (HD) and, especially, of non-Hodgkin lymphomas (NHL). Classical clinical manifestations related to application of antibiotics and corticosteroids and present lymphadenomegaly are changing their kind to a certain extent. New concepts concerning pathogenesis (mainly of HD) together with therapeutic results achieved in local stages of these diseases make the problem of early and timely diagnosis, of specifying of morphological variant and clinical stage both extraordinarily actual, indeed.

The purpose of the present paper is to summarize our experience concerning timely and precise diagnosis of lymphoproliferative diseases.

Material and Methods

Diagnostic terms were examined in a total of 412 patients with HD and NHL.

With a view to timely diagnostics and specifying of morphological variant a comparative cyto-histomorphological and ultrastructural investigation of lymph node biopsies from 116 patients was carried out. Preliminarily, lymph puncture was performed and after biopsy an imprint for cytological and cytochemical investigation was taken. The following cytochemical methods were used: express staining with acridine-orange, staining for nucleoli (in our own modification), for non-specific esterase after Undritz and for acid esterase, as well as direct immunofluorescence.

A new biochemical criterion with high information value for evaluation of the activity of the disease was introduced, namely blood histamine level (determined spectrophotofluorimetrically after the method of W. Lorenz et al. (1970)).

A complex programme for patients' examination was elaborated. It included routine paraclinical and roentgenological methods, bone-marrow investigation, trepanobiopsy, echographic investigation of abdomen, endoscopic methods (fibrobronchoscopy and rectoromanoscopy), parameters for evaluation of both cell-mediated and humoral immunity as well.

Data were processed after the method of variation and non-parametric analyses. A mathematical method for probability evaluation of discriminative capacity of a given criterion was applied.

Results and Discussion

1. Time limits for diagnosis

Diagnostic stages are followed-up by means of inquiries with 324 HD patients and 92 NHL ones. The first stage – from initial manifestations of the illness until seeking physician's aid – is at the average 3.33 ± 0.25 months long. There is a reliable difference of duration for 1st–

IInd stage ($p < 0.05$) and, especially, for Ist–IIIrd and Ist–IVth one ($p < 0.001$) in the clinical course of the disease. The second stage – from the first physician's examination until diagnosing – is at the average 3.38 ± 0.22 months long and provides information about oncological purposefulness of physicians from the public health services. The most important, third stage – from initial complaints to diagnosing – which does not present any summation of the first two ones, is at the average 5.86 ± 1.76 months long. It is shorter in patients of 1st and 2nd clinical stage – 5.26 ± 1.76 months and 4.97 ± 0.70 months, respectively, but longer – 6.94 ± 0.53 months in patients of 3rd stage, especially of 4th one – 8.48 ± 0.87 months ($P < 0.001$). This stage is the longest one with patients of lymphoexhausted variant ($p < 0.001$). Data presented show that in Bulgaria, like in other countries (1, 2, 4, 5) HD is diagnosed averagely half a year after initial clinical manifestations, i.e. after a period of undoubted progress of the disease. More than half the patients (57.67. per cent) are diagnosed during generalized 3rd and 4th stages. The reasons for late diagnosis of HD patients are as follows: non-timely seeking physician's aid on the occasion of lymphadenomegaly, incorrect initial clinical diagnosis (in 54.49 per cent of the cases) (fig. 1), existence of so-called "masks of disease", performing of antibiotic and corticohormonal treatment inducing false fade-away of symptoms, and more seldom – a morphological error (in 6.12 per cent of the patients).

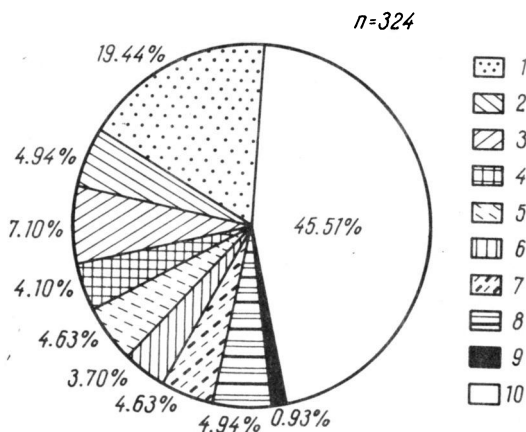


Fig. 1. Incorrect initial diagnosis of lymphoproliferative diseases
 1 – lymphadenopathy; 2 – tbc; 3 – lung disease; 4 – thyroid gland disease; 5 – respiratory diseases, sepsis; 6 – dermatoses; 7 – radiculitis; 8 – surgical disease; 9 – cardiovascular disease; 10 – normal

The mean time limit for diagnosis is 10.5 ± 0.92 months in NHL patients with low malignancy degree but 2.3 ± 0.031 months in NHL ones with higher malignancy degree. Clinical symptoms are rather more manifested in these patients which has made them seek earlier physician's aid and thus a more timely diagnosis of their disease.

2. Cyto-, histomorphological and ultrastructural study

The comparison between cytological and histological examination reveals a coincidence between cytological and histological diagnosis in 79.80 per cent of the patients. Total in coincidence percentage of 20.20 is mainly due to fine-needle aspiration biopsy (in 12.3 per cent) while that due to imprints is only 7.9 per cent. Histological diagnosis has not been possible without cytological investigation in 1.98 per cent of the cases. On the one hand, cytochemical methods enable specifying of morphological variant, especially in NHL patients, and, on the other hand, establishing of malignancy degree.

The ultrastructural study of lymph nodes from HD and NHL patients reveals specific differences in dependence on their histological variant. Cellular atypia increases with pathological process advancing. It is particularly well-expressed in patients with evolution course of the disease. Ultrastructural peculiarities of lymph node metastases from tumours of epithelial origin (desmosomes, basal bodies) can be used as additional criteria in the differential diagnosis of lymphoproliferative diseases.

3. Blood histamine level

In relation to recent data about an eventual role of histamine in numerous diseases characterized by disturbances of the immune system (10) and, more concretely, about its immunomodulating role in HD (6), we followed-up blood histamine level in a total of 116 patients, of which 73 with HD and 43 with NHL. It was established that this level is about 3 times lower as compared with that of healthy individuals (i.e. 0.031 ± 0.002 mkg/ml and 0.072 ± 0.002 mkg/ml, respectively) only in HD patients with active pathological process. After treatment, however, blood histamine level increases and during remission this level reaches the normal limits (0.089 ± 0.005 mkg/ml). We calculated the discriminative capacity of this criterion and it was 0.040 mkg/ml. This means that at borderline states blood histamine reduction below 0.040 mkg/ml is an alarming finding. The information value of newly-introduced parameter "blood histamine level" is compared with laboratory indexes commonly used at present (according to Ann Arbor Classification, 1971) (9). By using of a method for probability modelling of states of biological activity and remission the maximal recognition capacity of combinations of laboratory indexes concerning these two states is determined (8). This enables timely starting of treatment in relapse of the disease as well as its cessation. Other authors (3) also report a search for new additional criteria for evaluation of HD patients' state and for determining the prognosis of the illness.

4. Complex programme for patient's examination

This programme elaborated by us consisting in the methods mentioned above for specifying of pathological process generalization caused stage change with 38 per cent of HD and NHL patients.

We can conclude that diagnostic specifying of lymphoproliferative diseases is a responsible and difficult physician's task. While at the beginning the question is posed at the early and proof morphological diagnosis, later on the specifying of clinical stage is required. Maximal shortening of diagnostic time limits, introduction of modern methods for evaluation of generalization and activity of the pathological process contribute to increasing effectivity of treatment and to prognostical improvement of these diseases.

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К ВОПРОСУ О СВОЕВРЕМЕННОЙ И ПРЕЦИЗИОННОЙ ДИАГНОСТИКЕ ЛИМФОПРОЛИФЕРАТИВНЫХ ЗАБОЛЕВАНИЙ

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Р Е З Ю М Е

С целью ранней и своевременной диагностики лимфопролиферативных заболеваний, а также для прецизирования их морфологического варианта и клинического стадия, изучены сроки диагностирования больных болезнью Хочкина и больных не-хочкиновыми лимфомами. Применены сравнительные цитоморфологическое, гистоморфологическое и ультраструктурное исследования биопсий лимфатических узлов. Применен также дополнительный биохимический критерий (уровень гистамина в крови) с целью оценки активности заболевания при болезни Хочкина. Разработана наряду с этим расширенная программа исследования больных.

Обобщенные данные показывают, что диагностирование лимфопролиферативных заболеваний требует комплексного подхода, включающего клинико-морфологические, ультраструктурные, биохимические и инструментальные исследования, с целью проведения адекватной терапии и определения прогноза заболеваний.