

# Dynamics of immunological parameters in patients with Hodgkin's lymphoma and favorable outcome of invasive aspergillosis

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## Introduction

Clinical manifestations and outcome of invasive aspergillosis (IA) in hematological patients depend on immunological defects. The immunological features in patients with Hodgkin's lymphoma (HL) are not well understood.

## Methods

We examined dynamics of immunological parameters in 13 adult patients with HL and favorable outcome of IA, the median age - 36 years. For the diagnosis of probable IA criteria EORTS/MSG, 2008 were used. All HL-patients had IA with lung involvement.

The control group included 24 healthy adults, the median age - 29. Immunological parameters were evaluated within 2-6 weeks after IA diagnosis, and in the IA remission before the end of antifungal therapy. Lymphocyte subsets were determined by immunocytochemical method, levels of immunoglobulins in the serum - nephelometric method, blood cell supernatants were tested for IFN- $\gamma$ , IL-17, IL-10, TNF- $\alpha$  and G-CSF by using an ELISA test. Patients were followed for 12 months.

## Results

Before IA prolonged neutropenia had 53% HL-patients, lymphocytopenia - 70%. Etiologic agents were *A.fumigatus* - 60%, *A.niger* - 40%. Other fungal agents (*Aspergillus* spp. plus mucorales or *Pneumocystis jirovecii*) were found in 23% patients.

Complete remission of IA in 12 months follow up period occurred in 92% patients. The 12-month overall survival rate was 100%.

We identified significant immunological defects in patients with HL at the early stage of IA compared with healthy individuals: leukopenia  $<3,5 \times 10^9/L$  - 54%, ( $p=0,02$ ); neutropenia  $<1,5 \times 10^9/L$  - 38%, ( $p=0,02$ ), lymphocytopenia  $<1,0 \times 10^9/L$  - 62% ( $p=0,0001$ ) (Fig.1).

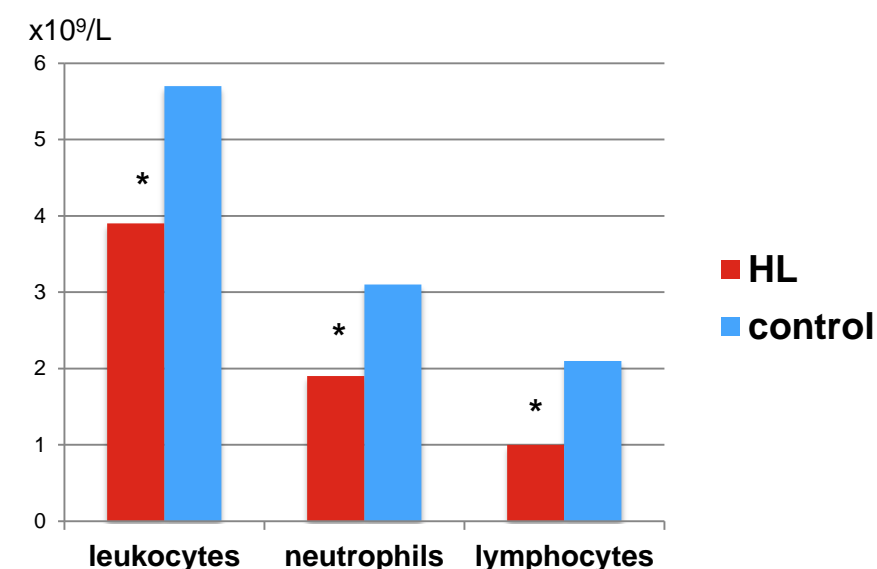


Fig. 1. Risk factors of IA in HL-patients.

We found a positive dynamics of immunological parameters in patients with a favorable outcome of IA: increase in absolute number of lymphocyte subsets: CD4+ ( $0,32 (0,17 \div 0,44) \times 10^9/L$  vs  $0,43 (0,29 \div 0,58) \times 10^9/L$ ),  $p=0,02$ , and CD25+ ( $0,08 (0,04 \div 0,15) \times 10^9/L$  vs  $0,15 (0,10 \div 0,22) \times 10^9/L$ ),  $p=0,07$  (Fig.2).

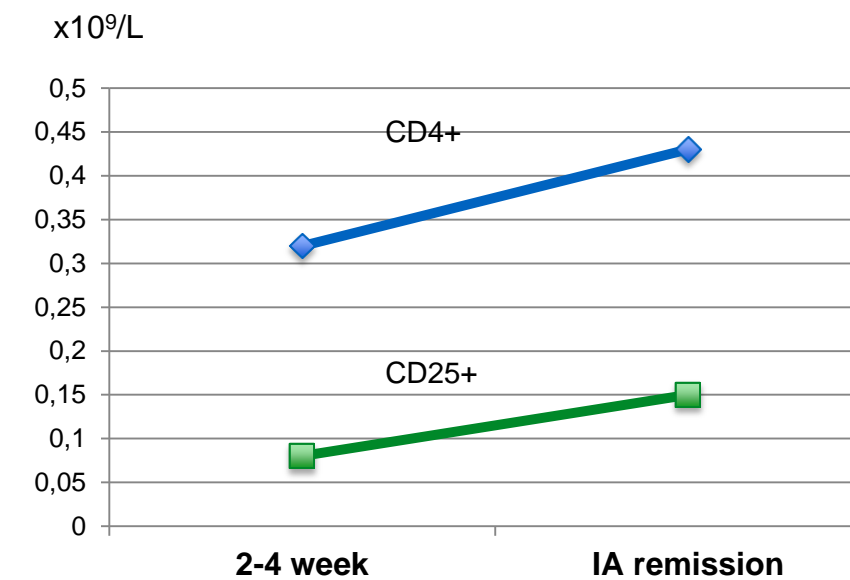


Fig. 2. Lymphocyte subsets dynamics.

We identified an increase in leukocytes production of TNF- $\alpha$  ( $400 (274 \div 419)$  pg/ml vs  $450 (405 \div 466)$  pg/ml),  $p=0,01$ ; IFN- $\gamma$  ( $452 (302 \div 641)$  pg/ml vs  $867 (354 \div 1549)$  pg/ml),  $p=0,01$ ; and IL-17 ( $37 (15 \div 56)$  pg/ml vs  $72 (30 \div 138)$  pg/ml),  $p=0,02$  in patients with a favorable outcome of IA (Fig.3).

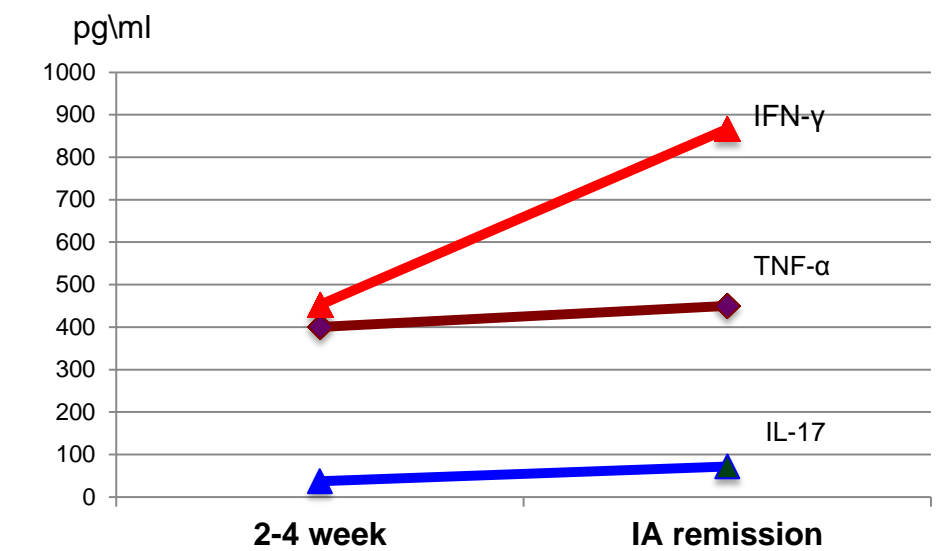


Fig. 3. Dynamics of cytokine production

At the time of the establishment of IA remission in patients with HL we found the recovery of basic immunological parameters. Only numbers of B-cells and immunoglobulins levels stayed significantly low.

## Conclusions

Immunological features of invasive aspergillosis in patients with Hodgkin's lymphoma were reduction of absolute numbers of lymphocytes subsets, decrease of immunoglobulin levels, and significant inhibition of key cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-10, IL-17) production. Increase in absolute CD4 + number, and ability of blood cells to produce IFN- $\gamma$ , TNF- $\alpha$ , and IL-17 are necessary for successful outcome of invasive aspergillosis in patients with Hodgkin's lymphoma.