THE ROLE OF CYTOKINES IN THE FORMATION OF MORPHOLOGICAL CHANGES IN THE SKIN WITH LEPROSY

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ABSTRACT — Sixty leprosy patients aged 65 to 80 years were examined. Of these, 45 are with multibacterial MB (multybacillary — MB) and 15 are with low-bacterial PB (paucibacillary — PB) forms of leprosy. The process was in a state of steady regress in the patients examined. In all patients, the plasma concentration of pro-inflammatory cytokines — IL-1β, IL-8 and tumor necrosis factor-alpha (TNF-α) was studied and a histological examination of the biopsies of affected skin sites was performed. The results of the study indicate that a significantly higher content of IL-1β and IL-8 in the blood of patients with low-bacterial forms of leprosy in comparison with multibacterial forms. When studying the content of TNFα, an opposite trend was observed. At the same time, morphological changes are more pronounced in patients with low-bacterial forms of leprosy.

KEYWORDS — leprosy, cytokines, hepatitis, morphology, skin biopsy, macrophages.

Leprosy is a spectral disease, the severity of which varies from localized, or tuberculoid, to disseminated, or lepromatous, forms with intermediate variants. Symptoms of leprosy depend on the difference in the immune status of infected individuals [1]. At the tuberculoid pole, the disease is more limited, and bacteria tend to accumulate in well-defined granulomas. At the lepromatous end, the disease is characterized by diffuse multi-bacillary lesions, where numerous bacteria are found mainly in tissue macrophages, particularly the skin, in Kupffer cells of the liver, as well as in Schwann cells of peripheral nerves. Cytokine activation is critical for inducing protective inflammatory immunity by macrophages and polymorphonuclear leukocytes (PMN) in the infection site in the initial stages of infection to form granulomas and to limit the spread of the disease. Thus, the spectrum of the immune response to M. leprae serves as a model for studying the role of cytokines in the pathogenesis of the leprosy process [2].

In the formation and flow of the process, the main role belongs to the degree of susceptibility of the macroorganism, which is due to the level of cellular immunity in relation to the pathogen. Most people are resistant to leprosy and therefore the comparative ease of transmission is combined with a relatively low incidence.

To date, the literature has accumulated enough evidence that the pathological deviations of the immune response are associated with impaired cytokine production. Among the cytokines that play a key role in coordinating immune responses, a special place is occupied by pro-inflammatory cytokines, which are the main mediators of development, both local inflammatory reaction and acute response at the body level.

Methods:

Materials from 60 leprosy patients aged 65 to 80 years were examined. Of these, 45 — with multibacterial MB (multybacillary — MB) and 15 with low-bacterial PB (paucibacillary — PB) forms of leprosy. The average duration of the disease was about 35 years. Specific manifestations on the skin of patients were practically absent or had a residual character. The results of the bacterioscopy of the skin were negative. At the same time, the majority of the subjects observed neurological disorders characteristic of leprosy with motor, sensory and trophic disorders. 15 patients with MB forms of the disease had clinical signs of liver failure, manifested as a syndrome complex, characteristic of chronic persistent hepatitis. Morphological and functional disorders of the liver in this contingent of patients are chronic and associated with at least several etiological causes. Among them — in the first place — a long-term systemic mycobacteriosis (due to the tropicity of Mycobacterium leprae to Kupffer cells of the liver), as well as the autoimmune factors associated with it. The long-term impact on the liver of antibacterial chemotherapeutic drugs and, in some cases, the concomitant infection with HCV or HBV viruses, is of definite importance. These patients, together with etiotropic treatment received hepatoprotectors — "Carlsil", "Essentiale" and Vitamin Complexes. In all patients, the plasma concentration of pro-inflammatory cytokines-IL-1β, IL-8 and tumor necrosis factor-alpha (TNF-α) was investigated using test kits of "Protein Contour" (St. Petersburg, Russia).

The results of the study indicate a significantly higher content of IL-1β and IL-8 in the blood of patients with PB forms of leprosy in comparison with MB patients (36.7±3.3 pg/ml to 23.6±3.7pg/ml and 12.2±4.3 pg/ml to 4.3±0.8 pg/ml, respectively). Concerning TNF-α, the opposite tendency was observed: in patients with BP form of leprosy, the concentration was 38.5±9.6 pg/ml, and in patients with MB form of leprosy was 52.6±11.5 pg/ml. The analysis of the cytokine level dependence on the fact that the patient has leprosy chronic persistent hepatitis showed that if there were practically no differences between patients with and without hepatitis with regard to IL-1β and IL-8, then TNF-α significantly exceeded its level in patients With a violation of hepatic function up to 102.6±2.1 pg/ml.

The relatively high levels of IL-1β and IL-8 in patients with PB form of leprosy, compared with patients with MB form of leprosy, apparently reflects differences in the state of cellular immunity in these forms of the disease. For PB form of leprosy is characterized by a high level of cellular immunity with respect to M.leprae, while for Mb form of leprosy the intensity of cellular responses to M. leprae is variable and practically absent in lepromatous leprosy. Elevated levels of TNF-α in patients with MB form of leprosy may be due to a higher prevalence among them of lesions of visceral organs, especially the liver, which is associated with the persistence of M. leprae in their body for many years.

Patients with MB forms in the biopsy specimens from the affected skin had numerous, merging infiltrates lying in the deep layers of the dermis, consisting of non-vacuolizing macrophages with a small admixture of scattered lymphoid cells and single polymorphonuclear leukocytes (fig. 1).

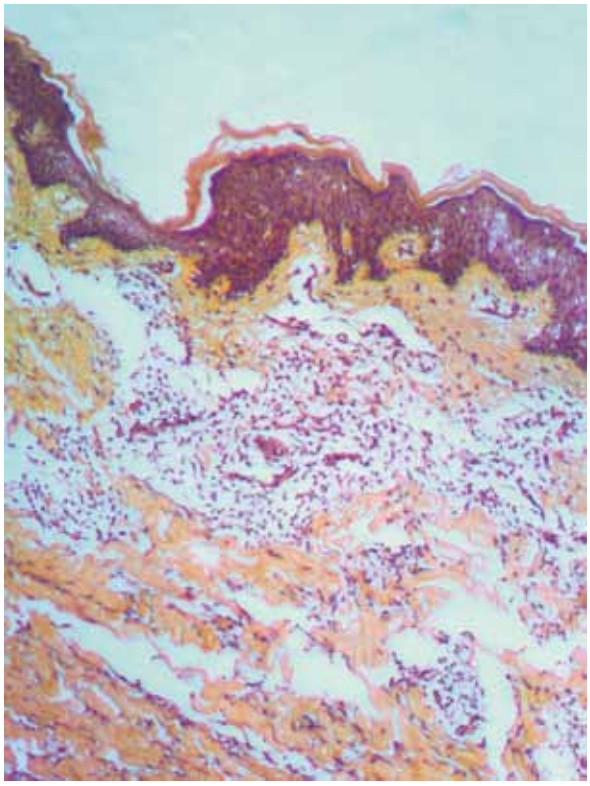

Fig. 1. *Numerous, confluent infiltrates, lying in the deep layers of the dermis. Staining with hematoxylline and eosin. In.100.*

Macrophages contained fat dispersions scattered throughout the cytoplasm, colored with Sudan III in various shades from brownish-yellow to orange-yellow in color. In most of the described drugs, nerve damage was not detected. The content of mycobacteria was determined during staining according to Tsil-Nielsen.

In patients with PB form in the sections of biopsy specimens of skin lesions, there were multiple large infiltrates without clear foci and moderately pronounced infiltration sites around vessels, nerves and sebaceous

and sweat glands, consisting of epithelioid cells and a small number of lymphocytes. On some drugs, the number of lymphocytes predominated over the number of epithelioid cells. Single multinucleated cells with large vacuoles were encountered. Between the epidermis and granuloma there was a very narrow free zone. Occasionally, infiltrated, mainly lymphocytes, nerves containing single mycobacteria granular or homogeneous infiltrated the field of vision.

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