MODERN ASPECTS OF PATHOGENESIS OF BRUCELLOSIS

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The pathogenesis of brucellosis in humans is determined by the characteristics of the pathogen, particularly the absence of classic virulence factors such as endotoxins or exotoxins, fimbriae, and the ability to suppress apoptosis. It is believed that S-LPS contributes to the blockade of innate immunity in the early stages of the infectious process and the bactericidal activity of the immune system. *Brucella* impedes the recognition by TLRs and complement, which also results in an inadequate antimicrobial effect of immunity in brucellosis [4,5,6].

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The main pathogenic factors of *Brucella* include the aggressive enzyme hyaluronidase and low molecular weight proteins that inhibit phagosome-lysosome fusion. After infection, most *Brucella* are quickly eliminated through phagocytosis. However, this phagocytosis is incomplete, and some *Brucella* remain viable within macrophages after penetration. The bacteria can survive and multiply in the endoplasmic reticulum and remain unrecognized within the reticuloendothelial system. Via the lymphatic route, the pathogens are carried to regional lymph nodes, where they accumulate. This phase of the infection is called the lymphogenic phase and corresponds to the incubation period of the disease. The duration of this phase can vary and depends on the balance between the activity of the pathogens (infectious dose) and the body's defensive forces. With the prolonged presence of *Brucella* in the lymph nodes, immunological reorganization occurs (antibodies accumulate), and an allergic transformation develops (the Bourne skin allergy test becomes positive), yet clinical manifestations do not emerge. This phase of the infectious process should be regarded as primary latency [17,18,19,20,21].

The entry of *Brucella* into the bloodstream (the hematogenous phase or primary generalization) coincides with the onset of clinical manifestations. Some of the *Brucella* that enter the bloodstream die, releasing antigens from various structures

of the bacteria, which stimulate both nonspecific and specific protective factors (activation of T and B lymphocytes, increased levels of interleukins, interferons, etc.). Inhibition of tumor necrosis factor-alpha (TNF-α) synthesis by the bacteria leads to impaired bactericidal activity of NK cells and macrophages. The production of protective antibodies by B lymphocytes is of lesser importance in forming the immune response. One of the key virulence factors determining the survival of *Brucella* in phagocytic cells is the development of delayed-type hypersensitivity (Type IV hypersensitivity). Against the backdrop of bacteremia, a process of *Brucella* dissemination occurs in various organs, leading to the formation of metastatic foci [14,15,16].

The primary targets for *Brucella* are organs rich in reticuloendothelial system (RES) cells: the liver, bone marrow, spleen, and lymph nodes. However, *Brucella* dissemination can occur in nearly all organs and tissues, resulting in multi-organ symptoms even in the early stages of the disease. In the areas where *Brucella* penetrate, inflammatory and necrotic foci form, and later granulomas develop due to the proliferation and transformation of phagocytic cells. Granulomatous inflammation is especially characteristic of infections caused by *B. abortus*. The formation of granulomas is a kind of result of the ongoing confrontation between the pathogen and the human body. On one hand, granulomas limit the replication of *Brucella*, but due to hypersensitivity reactions, macrophages survive, and the bactericidal effect is insufficient to eliminate the bacteria. The extent of local changes determines the characteristics of clinical manifestations. Protective antibodies, specifically agglutinins, appear in the blood relatively early, already during the first week. However, their role, like that of other antibodies, in clearing the infection from the body is minimal, as they can only eliminate extracellular *Brucella* [10,12,13].

Various mediators of inflammation-such as interferon, interleukin-1, interleukin-12, and tumor necrosis factor-act as inducers of phagocytosis. *Brucella* can persist in phagocytic cells for an indefinitely long time. With high macrophage activity, the process may lead to complete clearance of the organism within the first weeks of the disease (acute brucellosis). The acute process may subside, but any factor that reduces the body’s defenses-such as stress or a concurrent illness (especially an infectious one)-can trigger a recurrence of symptoms. In this case, another generalization of the process occurs, but the main active agents will no longer be *Brucella*; rather, they will be allergic reactions, the intensity of which will increase the longer the *Brucella* persist in the body and the more frequent the exacerbations occur. Subsequent episodes of pathogen entry into the bloodstream maintain bacteremia and endotoxemia, giving the disease a wave-like character. These mechanisms develop during the phase of subacute brucellosis, although in some cases, focal lesions form early, even during the acute phase of the brucellosis process. Allergic reactions are most pronounced in areas where

Brucella selectively localize (foci), leading to more distinct focal changes that determine the degree of dysfunction in various organs and systems and clinical symptoms with clear focal manifestations. The most significant changes occur in connective tissue, blood vessels, the nervous system, and the lymphatic system. It should be noted that in individuals suffering from various allergic diseases, such focal changes may be distinctly observed even in the acute phase of the illness. The disease tends to have a prolonged course and can transition into a chronic state [7,8,9].

Characteristic of brucellosis are fibrositis (histologically, collections of histiocytic cells), which present as small, dense nodules that most often localize around the joints, leading to pain syndrome and the appearance of limited or diffuse infiltration. The size of these fibrositis (cellulitis) can range from 5-10 mm to 3-4 cm. Initially, they can be palpated as soft, oval formations that are painful upon examination (sometimes patients themselves notice their appearance). Over time, they may decrease in size, completely resolve, or become sclerosed, remaining for extended periods as small, firm formations that are still painful to the touch. During exacerbations, new fibrositis may develop [4,5,6].

Thus, musculoskeletal lesions in brucellosis are characterized by their systemic nature, with inflammation affecting soft tissues (muscles, ligamentous structures), cartilage, and bone in various combinations. To prevent irreversible destructive processes and deformation of the skeletal and articular system, it is important to accurately assess complaints, correlate them with clinical manifestations and radiological findings, and prescribe appropriate therapy [1,2,3].

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