CLINICAL AND IMMUNOLOGICAL FEATURES OF BRUCELLOSIS IN DIFFERENT CLINICAL FORMS

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Abstract

Brucellosis is a zoonotic bacterial infection caused by microorganisms of the genus Brucella. The disease is characterized by considerable clinical heterogeneity, ranging from an acute febrile illness to prolonged and relapsing forms with involvement of the osteoarticular, hepatobiliary, cardiovascular, genitourinary, and nervous systems. The variability of clinical manifestations is closely associated with the ability of Brucella spp. to survive and replicate within host cells, particularly macrophages, and to modulate both innate and adaptive immune responses. Cellular immunity, especially the Th1-mediated response, plays a central role in controlling intracellular Brucella infection. Interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12) contribute to macrophage activation and bacterial clearance, whereas regulatory mechanisms involving interleukin-10 (IL-10) may limit excessive inflammation but, under certain conditions, facilitate persistence of the pathogen.

Keywords: brucellosis, Brucella, acute brucellosis, chronic brucellosis, cellular immunity, Th1 response, IFN-γ, TNF-α, IL-10, cytokines.

Introduction

Brucellosis remains an important zoonotic infection in many regions where animal husbandry and consumption of unpasteurized animal products are common. Human infection is most frequently associated with *Brucella melitensis*, *B. abortus*, *B. suis*, and, less commonly, *B. canis*. Transmission may occur through direct contact with infected animals or their tissues, occupational exposure, or ingestion of contaminated dairy products. Because the incubation period can be prolonged and the initial clinical manifestations are often nonspecific, diagnosis may be challenging, particularly in patients with atypical or chronic disease [1].

The clinical spectrum of brucellosis is broad. Fever, fatigue, headache, sweating, arthralgia, myalgia, anorexia, and weight loss are among the most frequently reported manifestations. Depending on the duration and severity of infection, patients may develop focal complications involving the joints, spine, liver, spleen, heart, genitourinary system, or central nervous system [1,2]. The disease may therefore be classified according to its clinical course into acute, subacute, and chronic forms, although the precise definitions and duration criteria vary among clinical studies.

The pathogenesis of brucellosis is largely determined by the intracellular lifestyle of *Brucella*. Following phagocytosis, the pathogen can survive within macrophages and interfere with several host-cell mechanisms, including phagosome maturation, antigen presentation, cytokine production, and apoptosis. Consequently, the interaction between the microorganism and the host immune system is a major determinant of whether infection is rapidly controlled or becomes persistent [3,4].

The objective of this review is to summarize the clinical manifestations and major immunological characteristics of different clinical forms of human brucellosis and to emphasize the relationship between immune response and disease persistence.

Clinical Characteristics of Brucellosis

Acute brucellosis. Acute brucellosis usually develops after an incubation period that may extend over several weeks. The onset can be gradual or relatively abrupt. Fever is one of the most characteristic clinical findings and may have an undulating pattern. Patients frequently complain of weakness, excessive sweating, headache, myalgia, arthralgia, and reduced appetite. General intoxication and fatigue may persist even when the body temperature fluctuates or temporarily returns to normal.

Musculoskeletal manifestations are particularly common. Arthralgia may occur during the early stages of infection, while arthritis and spondylitis are more characteristic of focal disease. Hepatomegaly, splenomegaly, and lymphadenopathy may also occur. The clinical presentation, however, varies considerably between individual patients, and no single symptom is sufficiently specific for establishing the diagnosis [1,2].

Laboratory abnormalities may include changes in leukocyte counts, inflammatory markers, liver enzymes, and hematological parameters. Nevertheless, routine laboratory findings are not pathognomonic. Therefore, the epidemiological history and specific laboratory investigations remain essential components of diagnostic evaluation.

Subacute and relapsing disease

In some patients, the initial manifestations persist for an extended period or recur after a temporary improvement. Relapsing disease may be characterized by recurrent fever, weakness, sweating, arthralgia, and focal inflammatory manifestations.

A longitudinal study of patients with brucellosis demonstrated that the disease may change clinically over time and that arthritis can be associated with subsequent progression toward chronic disease. The persistence of antibodies after clinical recovery also emphasizes that serological positivity should be interpreted in conjunction with the clinical picture and other diagnostic findings [2].

Chronic brucellosis

Chronic brucellosis represents a prolonged disease course and may develop when infection persists despite an apparently adequate clinical response. Chronic disease can manifest as prolonged weakness, fatigue, recurrent low-grade fever, sweating, arthralgia, chronic arthritis, and localized organ involvement.

The osteoarticular system is among the most frequently affected systems in complicated brucellosis. Sacroiliitis, spondylitis, peripheral arthritis, and osteomyelitis can substantially impair the patient's functional status. Neurological involvement may result in meningitis, meningoencephalitis, radiculopathy, or other neurological syndromes. Cardiovascular involvement, particularly endocarditis, is less common but represents one of the most serious complications of brucellosis [1].

Chronic infection is of particular interest from an immunological perspective because persistent intracellular survival of *Brucella* may be associated with inadequate or dysregulated cellular immunity. Studies have demonstrated alterations in Th1-associated responses and T-cell function in chronic disease [3,4].

Material and methods

The nonspecific nature of many clinical manifestations makes laboratory confirmation essential. Depending on the clinical situation and available resources, diagnostic evaluation may include bacterial culture, serological testing, molecular methods, and assessment of epidemiological exposure [1].

Culture remains an important method for microbiological confirmation but may have limited sensitivity, particularly after antimicrobial treatment or in focal and chronic disease. Serological tests can provide valuable evidence of exposure and infection, although antibody persistence may complicate interpretation after clinical recovery [2].

Molecular methods, including PCR-based assays, may be useful in selected clinical circumstances, particularly when rapid etiological confirmation is required. However, interpretation should take into account the clinical context and the characteristics of the diagnostic assay.

From an immunological perspective, assessment of cytokine profiles and cellular immune parameters remains primarily a research tool. IFN-γ, TNF-α, IL-12, IL-10, and T-cell subsets may help clarify disease mechanisms and potentially contribute to future prognostic models. Nevertheless, further prospective studies are required before such markers can be routinely recommended for individual patient management.

Results

Successful treatment of brucellosis requires adequate antimicrobial therapy because intracellular persistence increases the risk of relapse. Current clinical recommendations generally favor combination antibiotic regimens and an adequate treatment duration. For commonly encountered *Brucella* species, doxycycline combined with rifampin for at least six weeks is among the standard approaches, while treatment may need to be modified according to species, complications, contraindications, pregnancy, and local clinical guidance [1].

Patients with focal complications may require longer treatment and specialized management. Osteoarticular, neurological, and cardiovascular involvement should be actively investigated when clinically suspected.

The relationship between antimicrobial treatment and immune response is also important. Studies have shown that cytokine abnormalities observed during active brucellosis may decrease after successful antimicrobial therapy, supporting the concept that immune activation is partly related to the presence and activity of the pathogen [7].

Conclusion

Brucellosis is a clinically heterogeneous zoonotic infection in which the severity and persistence of disease are determined by a complex interaction between *Brucella* and the host immune system. Acute disease is commonly associated with systemic inflammatory manifestations and activation of Th1-mediated cellular immunity, with increased involvement of IFN-γ, TNF-α, and other pro-inflammatory mediators. In chronic and relapsing forms, persistent intracellular infection may be accompanied by impaired or dysregulated cellular immunity, altered antigen presentation, and T-cell exhaustion.

The clinical assessment of patients with suspected brucellosis should therefore include not only recognition of characteristic symptoms and epidemiological risk factors but also evaluation for focal organ involvement. Laboratory confirmation remains essential because clinical manifestations alone are insufficiently specific.

Further research into cytokine profiles, T-cell responses, macrophage function, and immune exhaustion may contribute to the identification of biomarkers capable of differentiating acute, chronic, and complicated forms of brucellosis. Such approaches may ultimately improve early recognition of persistent infection, prediction of complications, and individualized management.

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