Introduction

Human brucellosis is considered to be a typical Mediterranean zoonosis. That fact is confirmed by many synonyms for this illness: Malta fever, Cyprus fever, Gibraltar fever, Mediterranean fever, Neapolitan fever, Undulant fever, Bang’s disease, Bruce’s septicaemia. The first description by J.A. Marston dates from the late 19th century about the illness among British Army physicians serving on Malta [1]. Sir David Bruce in 1887 noted the discovery of a microorganism in Malta fever [2]. In 1897, B.Bang published further information on the etiology, i.e. Brucella abortus, of this zoonotic infection [3]. In the 1950s, brucellosis was proposed as one of the first “causes” of the “chronic fatigue syndrome” (CFS).

Nowadays, brucellosis is re-emerging as a worldwide veterinarian, public health and human medicine problem. The disease is widespread in many countries of the Mediterranean basin, as well in the Republic of Macedonia in the last c. 30 years.

Cutaneous manifestations or complications have
rarely been reported (3.8% - 17%) in different published studies [4-7]. A large variety of skin manifestations are associated with brucellosis. The same or similar skin lesion patterns are associated with numerous dermatological entities other than brucellosis. The unspecificity of etiologic factor/s causing the same type of skin lesion, confirm the historical statement that “Brucellosis is a Great Imitator”[4, 7]. The list of differential diagnoses is practically endless [8-10]. Thus brucellosis has to be associated with other, well known "Imitators in Dermatology": Cutaneous Drug Reactions, Tuberculosis cutis, Lues secundaria / resolutiva [6, 7, 10-12]. It is well known that different microbiological agents such as Treponema pallidum, Mycobacterium tuberculosis, Borrelia burgdorferi, and many different drugs can trigger and provoke the same or very similar cutaneous reactions / skin lesions and histopathologic processes in dermo-epidermal structures.

**Brucella** is a Gram-negative coccobacillary organisms. There are three different species most important for human pathology: *Brucella suis* (swine), *B. melitensis* (sheep and goats) and *B. abortus* (cattle) – Bang’s disease. *B. melitensis* is the most common human pathogen [13]. The most risky professions (occupational exposure to *Brucella*) are: farmers, butchers, veterinarians and workers in slaughterhouses. A possible way of infection is direct contact with a sick animal / inoculation (mucosal or percutaneous exposure), ingestion of milk (about 10% from raw milk) and milk products and, rarely, by inhalation. After 1-3 weeks of *Brucella* entry, the patient develops a low grade fever with cyclic pattern / undulant fever and malaise [5].

**Complications** include spondylitis, sacroiliitis, osteomyelitis, meningitis, and orchitis. The main cause of mortality, however, is endocarditis. Early diagnosis and timely initiation of proper treatment are of main importance to prevent the later complications of the disease. Clinical recognition and laboratory verification of brucellosis is an important public health problem.

Additionally, the use of microbial pathogens as potential or actual weapons of terrorism and warfare dates from antiquity. The Working Group for Civilian Biodefense has compiled a list of characteristics of biologic agents that can be used as bioweapons [9]. The ease of dissemination and potential virulence of several organisms makes them suitable for intentional spread as biological weapons [9]. According to CDC (U.S. Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases) brucellosis (*Brucella spp*) is included in category B (A, B and C categories) of potential biologic agents used as bioweapons [8].

**Cutaneous manifestations / literature review**

We looked through a few basic (classic) textbooks and atlases of dermatology [5, 8-10] and internal medicine [4], the 10-year study of Bosilkovski et al. [14-19], and some recent case reports of cutaneous brucellosis and reviews of the relevant literature.

**Table 1: Cutaneous manifestations (CM) of brucellosis.**

<table>
<thead>
<tr>
<th>Most frequent cutaneous manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Papul-nodular eruptions and</td>
</tr>
<tr>
<td>- Erythema nodosum (EN)/ Erythema nodosum-like (EN-like) lesions</td>
</tr>
<tr>
<td>s. Erythema nodosum syndrome (25%)</td>
</tr>
<tr>
<td>- Exanthemas / maculopapular rashess s. Exanthema infectiousum (EI) (25%)</td>
</tr>
<tr>
<td>- Pustuliforment (12.5%) and Ecroneatous lesions (12.5%)</td>
</tr>
<tr>
<td>- Urticaria / -like lesions</td>
</tr>
<tr>
<td>- Petechiae, Purpura, Disseminated violet erythematous lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sporadic cases of cutaneous manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Abscesses</td>
</tr>
<tr>
<td>- Suppurative lymphangitis</td>
</tr>
<tr>
<td>- Panniculitis</td>
</tr>
<tr>
<td>- Livedo reticularis pattern</td>
</tr>
<tr>
<td>- Erythema palmaris</td>
</tr>
<tr>
<td>- Malar erythema</td>
</tr>
<tr>
<td>- Cellulitis</td>
</tr>
<tr>
<td>- Cutaneous ulcers</td>
</tr>
</tbody>
</table>

Cutaneous changes are uncommon, uncharacteristic and infrequent – 5.71% (3.8% -17%) [6, 7, 13, 20]. The most frequent and rare / sporadic cases of cutaneous manifestations (CMs) of brucellosis are presented in Table 1.

The data from analysed reports in our study are summarized in Table 2. Bosilkovski et al. found arthralgias in 438 (79.6%), fever in 419 (76.2%) and sweating in 394 (71.6%). Elevated C-reactive protein, found in 389 (79.4%) patients, was the dominant laboratory characteristic [16-18]. Dermatological manifestations are not described / noted in that study. Oral communication with the author of the study led to the conclusion that some cases with exanthemas (skin eruptions) were probably misinterpreted as cutaneous drug reactions.

**Erythema nodosum/ Erythema nodosum-like lesions.** Erythema nodosum syndrome (Fig. 1) is an important acute inflammatory / immunologic reaction pattern of the subcutaneous fat characterized by the appearance of red “contusiforme”, indurated, very ten-
der inflammatory nodules mostly in the pretibial region, palpated as deep-seated nodules. Erythema nodosum (EN) should be differentiated from all other forms of panniculitis, panarteritis nodosa, nodular vasculitis, pretibial myxedema, nonulcerated gumma and lymphoma [8]. EN is caused by multiple and diverse aetiologies: bacterial, fungal, viral, parasitic infections, drugs, malignancies and other diseases such as sarcoidosis, Behcet’s disease, ulcerative colitis and Chron’s disease [8]. According to CMs of human brucellosis, EN is reported in 25% of all concomitant skin manifestations.

**Exanthemas / maculopapular rashes s. Exanthema infectiosum (IEs) (Fig. 2.)** is a generalised cutaneous eruption of erthematous macules and papules associated with a primary acute systemic infection; it is often accompanied by oral mucosal lesions, i.e. an enanthema. IEs are most commonly caused by viral agents but can also be associated with bacterial, rickettsial, and parasitic infections. Only certain IEs have a fairly characteristic morphology. Historic factors may be helpful, including season, disease contacts, immunisations, previous exanthematous illnesses, and associated prodromal symptoms. The eruption must be differentiated from an exanthematous, morbilliform, drug eruption [8]. Often mentioned differential diagnoses are: drug eruption, systemic lupus erythematosus, Kawasaki’s syndrome in children.

**Other CMs of brucellosis** such as petechiae and
purpura, disseminated violet-erythematous lesions, urticaria-like lesions (Fig. 3), psoriasiform and eccematosus lesions, abscesses, erythema palmarie, malar erythema, cutaneous ulcers, and suppurrative lymphangitis, livedo reticularis pattern, panniculitis, are the skin lesions referred to in the context of brucellosis [8, 9, 21-24]. Cutaneous ulcers, abscesses, and suppurrative lymphangitis appear to be more common with Brucella suis. Occasionally, epistaxis, gingivorrhea, haematuria, and cutaneous purpura occur in association with severe thrombocytopenia, which has been ascribed to hypersplenism, bone marrow haemaphagocytosis, and/or anti-platelet antibodies [25].

Nagore E. et al. stress that all the CMs mentioned above may cause the patient to seek medical attention as well as contribute to the diagnosis [26]

Pathogenesis of cutaneous manifestations

Skin lesions may be produced by the direct effect of microbial replication in infected cells, the host response to the microbe, or the interaction of these two phenomena [8]. Haematogeneous spread of the microorganism Brucella melitensis is the most important pathogenic mechanism of cutaneous lesions. Direct invasion by the organism reaching the skin haematogenously and secretion of endotoxins partially explain acute effects [5]. Brucella demonstrates affinity for the RES and can survive for long periods of time in macrophages, lymph nodes, and the spleen. If they evade the initial neutrophilic response they cause persistent problems. Hypersensitivity phenomena, deposition of immune complexes and granuloma formation are also employed [7, 12].

Histopathology of cutaneous manifestations

Histopathology of CMs reveals dermal inflammatoty infiltrate of lymphocytes and histiocytes in a perivascular and perianxenal arrangement, with a focally granulomatous appearance including giant cells, and occasional extension to subcutaneous fat [7].

Laboratory confirmation / investigations: As a gold standard, culture of tissue fluids, blood or biopsy material is valuable for isolation of the organism. To optimize the result, the cultures have to be held for several weeks if necessary [27]. ELISA titre is useful in following the response to therapy and for epidemiological studies. PCR confirmation is necessary in cases that are culture negative / serologically positive without significant titres [27].

Course and prognosis: Duration of the symptoms for less than 2 months is defined as acute brucellosis; 2-12 months – subacute brucellosis, and more than 12 months – chronic brucellosis [6]. If treated, the outlook is good. Not treated, brucellosis can evolve into a chronic (>12 months) disabling disease. Often misdiagnosed for long periods of time (2-12 months) subacute brucellosis is the so-called “Chronic fatigue syndrome” [6].

Therapy: currently recommended regimes include: Doxycycline 200 mg/day and Rifampicin 600-900 mg/day for at least 6 weeks. Streptomycin could be employed in severe or chronic cases. An additional recommendation could be safe and effective human vaccine (not yet available) [13, 28].

Discussion

Skin manifestations are infrequent, affecting less than 5% of patients with brucellosis, and have not been considered as a characteristic feature of brucellosis [11]. Complications of brucellosis can affect any organ, and, apart from abscess formation, can occur anywhere in the body. The clinician should be aware of the complex differential diagnosis and the variety of infective and not only infective agents, medicaments for example, which could be responsible for the CMs. The clinical challenge for the dermatologist is magnified by the luck of specific symptoms in the various forms of CMs of brucellosis and by the number of potential agents not routinely tested. Thus, an accurate assessment and effective treatment plan requires attention to details of the history and the accompanying clinical symptoms of CMs.

Milionis et al. accentuate that in endemic areas, clinicians should always keep in mind that a skin rash could represent a rare manifestation of a relatively common infectious diseases [11]. Ariza et al. among 436 cases of brucellosis identified 27 patients (6%) with cutaneous lesions. A disseminated violet-erythematous, papulonodular eruption (20 cases) and erythema nodosum—like lesions (three cases) were the most frequent eruptions observed, appearing during the initial episode of the disease or in relapse. Histologic findings were a dermal inflammatory infiltrate of lymphocytes and histiocytes in a perivascular and perianxenal arrange-ment, with a focally granulomatous appearance, and occasional extension to subcutaneous fat. They point out that there are characteristic clinical and histologic
cutaneous findings in patients with brucellosis and that haematogenous spread of the microorganism can be the most important pathogenic mechanism of these lesions [7]. Young et al. describe 2 patients presenting with thrombocytopenic purpura, compared with (discussed in the context of) 41 additional cases from the literature [25]. As the largest organ of RES, the liver is probably always involved in brucellosis. If the thrombocytopenic purpura is complicated with haemorrhage into the central nervous system, then the prognostic value of skin manifestations and prompt recognition of this complication is essential for a good prognosis [25]. Omidi et al. present the case of a 32-year-old man with occurrence of pancytopenia and diffuse maculopapular rash during the course of *Brucella* infection [12]. The prospective study of Acali et al. determines the types and rates of cutaneous lesions in 140 patients with symptoms compatible with brucellosis in Turkey [6]. In the comprehensive review "Brucellosis in India", Mantur and Amarnath emphasize the problem of brucellosis as a common but often neglected disease in India, as in many developing countries [13]. As a result of unspecific symptomatology and low awareness of its existence among other than infectology specialists (clinicians), brucellosis is invariably under-diagnosed or easily misdiagnosed [13]. Karsen et al. published a very interesting case of brucellosis lymphadenitis mimicking scrofuloderma in a 20-years-old girl [29].

In Republic of Macedonia brucellosis has been an endemic problem for the last 30 years. Bosilkovski et al. are the most prominent clinicians dedicated to this human zoonosis in the previous 10 years [15-19]. During that 10-years period, Bosilkovski and colleagues from the University Infectious Diseases and Febrile Conditions Clinic in Skopje, Republic of Macedonia, assessed 550 patients for their demographic, epidemiological, clinical, laboratory characteristics and outcome. Brucellosis was diagnosed on the basis of clinical signs, and confirmed by the detection of specific antibodies at significant titres. Arthralgias (79.6%), fever (76.2%), sweating (71.6%) and hepatomegaly (49.6%) were the most frequent complaints. Elevated C-reactive protein was found in (79.4%) patients as the dominant laboratory characteristic. Focal brucellosis was reported in (65.8%) patients, and 299 (54.4%) of them had osteoarticular manifestations. Patients were followed up for 2-84 months (median 10 months) and 453 patients completed a follow-up period of at least 6 months. In that prospective study CMs were not identified / reported. Probably (we can speculate that) the most often manifested skin rashes / maculopapular exanthemas were misdiagnosed as exanthema iatrogenes / medicamentosum. The absence of pruritus, as the typical clinical symptom of drug hypersensitivity reaction, is valuable for differentiation or confirmation of infectious exanthema. So, we can conclude that the lack of sufficient cooperation and awareness of the existence of brucellosis in the differential-diagnostic spectrum among dermatologists in our country is the main explanation of under diagnosed CMs in that group of 550 patients with confirmed brucellosis. According to references mentioned in this review, we could calculate that cca 20-55 patients were misdiagnosed, or cutaneous clinical manifestations were not recognised in the context of brucellosis.

The most important contributor to complications and poor outcome of *Brucella* infection is probably a delay in instituting effective antibiotic treatment.

**Conclusion**

As a multisystemic infectious disease, human brucellosis should always be in the differential diagnosis of a patient with rash and fever. Cutaneous manifestations are generally not specific to brucellosis, but the findings may be useful in diagnosing the disease in persons who live in endemic regions suffering from chronic fever, malaise, and non-specific complaints (including musculoskeletal pain) or who have been exposed to sources of *Brucella* through travel to an endemic area, contact with animal tissues, consumption of unpasteurized dairy products, and/or work in a microbiology laboratory. With its nonspecific clinical manifestations and laboratory parameters, brucellosis has to be considered as one of the differential diagnoses of any patient with the symptoms mentioned above. The most important contributor to complications and poor outcome is probably a delay in diagnostic confirmation and instituting effective antibiotic treatment. Early diagnosis and timely initiation of proper treatment are of main importance to prevent the later complications of the disease. General practitioners and clinicians, especially dermatologists, have to be more aware and alert in clinical recognition and laboratory verification of brucellosis as an important public health problem.

**References**


