Brucellosis-induced Leukocytoclastic Vasculitis

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Abstract

Brucellosis is a zoonotic bacterial infectious disease caused by Brucella spp. It is transmitted to humans through contact with animal products and body fluids. The resulting disease is multisystemic with skin being rarely involved at presentation or during the disease course. We reported a 36-year-old female, who presented with a history of intermittent fever, polyarthralgia, and painful non-pruritic round erythematous scaly plaques with raised borders on her extremities of 1-month duration. Laboratory findings showed positive serology for brucellosis and skin biopsy showed leukocytoclastic vasculitis. She was successfully treated with a combination therapy of prednisolone and antibiotics (Doxycycline and Rifampicin) with complete resolution of all symptoms.

Introduction

Brucellosis is one of the most common zoonotic infectious diseases worldwide. It is caused by intracellular Gram-negative coccoid or rod-like aerobic bacteria from the genus Brucella. The disease is transmitted to humans via direct or indirect contact with infected animals, or through the consumption of infected animal products like raw meat or dairy products.[1,2] It is mostly encountered in the Middle East, Central Asia, China, India, sub-Saharan Africa, and parts of Mexico and Central and South America.[1] So far, 4 Brucella species have been identified to cause human disease. B. melitensis (found in goats, sheep, and camels) is the most common cause of brucellosis in humans, Others include B. abortus (isolated from cattle), B. suis (isolated from swine), and B. canis (isolated from dogs).[1] Brucellosis is a multisystemic infection. It can affect different organ systems like osteoarticular, genitourinary, central nervous system, cardiovascular system, respiratory system, and ocular system.[3]It can present with a wide spectrum of clinical manifestations that are non-specific and can therefore lead to misdiagnosis and delay of the proper treatment.[2] Patients may present with intermittent fever, weight loss, depression, hepatomegaly, splenomegaly, and joint pain.[3] Fever (87%), tiredness (63%), arthralgia (62%), and muscular discomfort (56%) are the primary clinical characteristics of this disease.[4,5] Skin involvement is less common, and it was observed in less than 10% of the cases.[1]

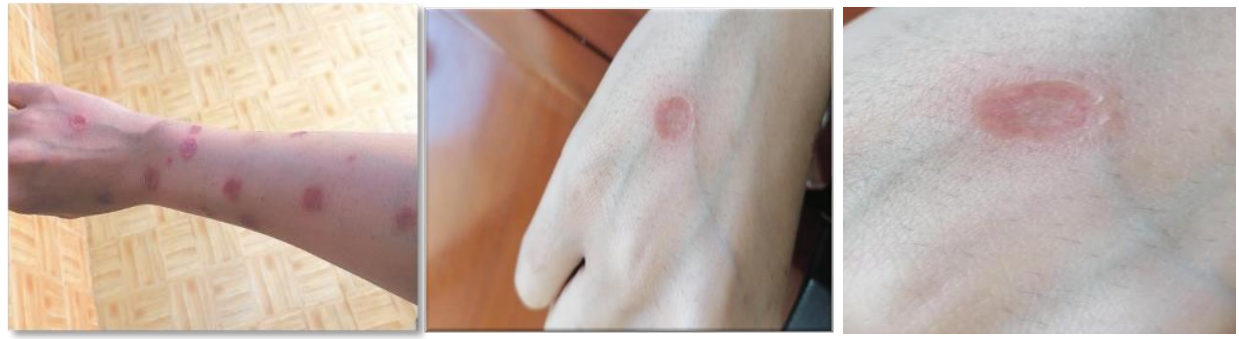
Leukocytoclastic vasculitis is one of the rarest cutaneous manifestations of brucella infection, and it is seldom reported in the literature. Here we reported a novel case of a young female who had systemic manifestations, underwent a comprehensive workup by a multidisciplinary team, and was finally diagnosed as a case of Brucella induced leukocytoclastic vasculitis.

Case Report

A 36-year-old female who was previously healthy, presented with a 1-month history of painful erythematous scaly plaques over both upper and lower limbs. It was initially started in the dorsum of the right hand. Then, it spreaded to both forearms and left lower limb anteriorly. The eruption was non-itchy and was associated with a burning sensation. This rash was preceded and accompanied by recurrent episodic fever occurring 3-4 times a month, polyarthralgia, muscular pain, and recurrent episodes of vertigo. The vertigo initially started 2 years back, remained for 2 months, and was accompanied by episodes of sudden loss of vision for minutes, followed by blurred vision, which remained for days then disappeared. She had MRI brain done after the first episode of vertigo and impaired vision, which showed normal brain parenchyma with a small 3.6 mm pituitary lesion suggestive of a calcified small hemorrhagic focus within the gland. A second follow-up MRI done 2 months later showed a normal study.

There was no history of similar episodes of rashes in the past. Patient had no history of taking raw caw or camel milk. There was no history of contact with animals or pets. And no family history of connective tissue diseases.

On examination, there were multiple tender and well-demarcated tender annular erythematous and scaly plaques with raised borders on both upper limbs and left lower limb mainly on extensor aspects. Some of these plaques were eroded and semi-ulcerated [Figure 1]. In addition, there was one small erythematous plaque on the tip of her nose. There was no petechial or purpuric rash, no mucosal or genital involvement and no malar rash. Hair, nails and systemic examinations were unremarkable.



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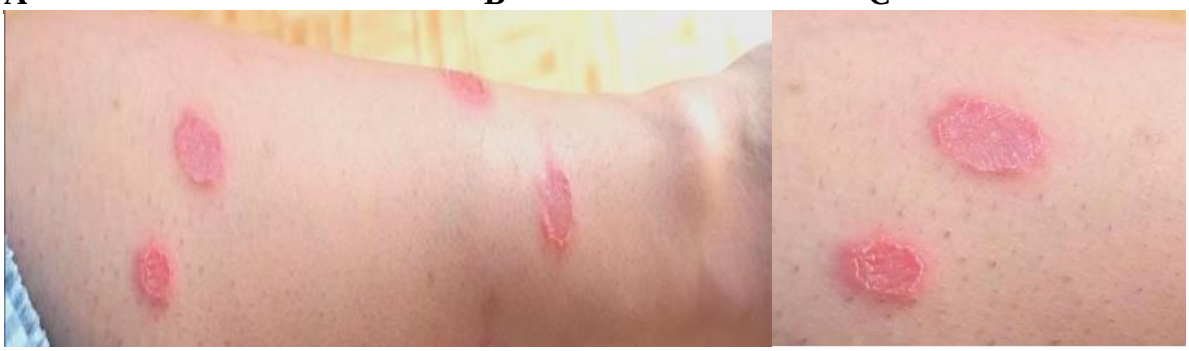

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Figure 1: (a) Scattered annular erythematous and scaly plaques over the right upper limb. **(b)** Eythematous plaque with central erosion on the dorsum of the patient's right hand. **(c)** On high magnification for the skin lesion in figure 1B, it showed eroded and some ulceration ring like plaque on dorsum of right hand. **(d)** Multiple well-demarcated erythematous and scaly plaques with raised borders on the patient's left upper limb. **(e)** On high magnification, annular erythematous plaques.

A differential diagnosis list was formulated, and it included superficial and deep fungal infections, nummular dermatitis, vasculitis, sporotrichosis spread like rashes, behcet disease, sweet syndrome, and disseminated granuloma annulare. Wood's lamb showed no fluorescence. The burning sensation along with the tenderness were against fungal infections so fungal scraping was not done and we preferred to go directly to skin biopsy which will also show the fungal elements and the other possible pathologies. Routine blood investigations were grossly normal except for mild neutrophilia (5.48 10*3/uL [1-4.8]). Skin punch biopsy was taken from right upper limb lesion showed irregular

acanthosis, epidermis covered with thick parakeratotic crust showing aggregates of neutrophils and plasma cells. There was intraepidermal neutrophilic bullae and subepidermal blister formation with neutrophil infiltrate. Dermis showed marked edema, fibrin, red blood cells extravasation and infiltrate composed of neutrophils, mononuclear cells, and histiocytes. There were focal crushing artifacts and few preserved vessels showed swelling of endothelial cells, smudged walls, and fibrin deposits around and within vessel walls. A small amount of nuclear dust was also present. Special PAS stain showed dermatophyte spores within hair follicles [Figure 2]. Gram stain was negative, and features were in favor of pustular dermatoses with leukocytoclastic vasculitis and dermatophyte spores with no hyphae seen.

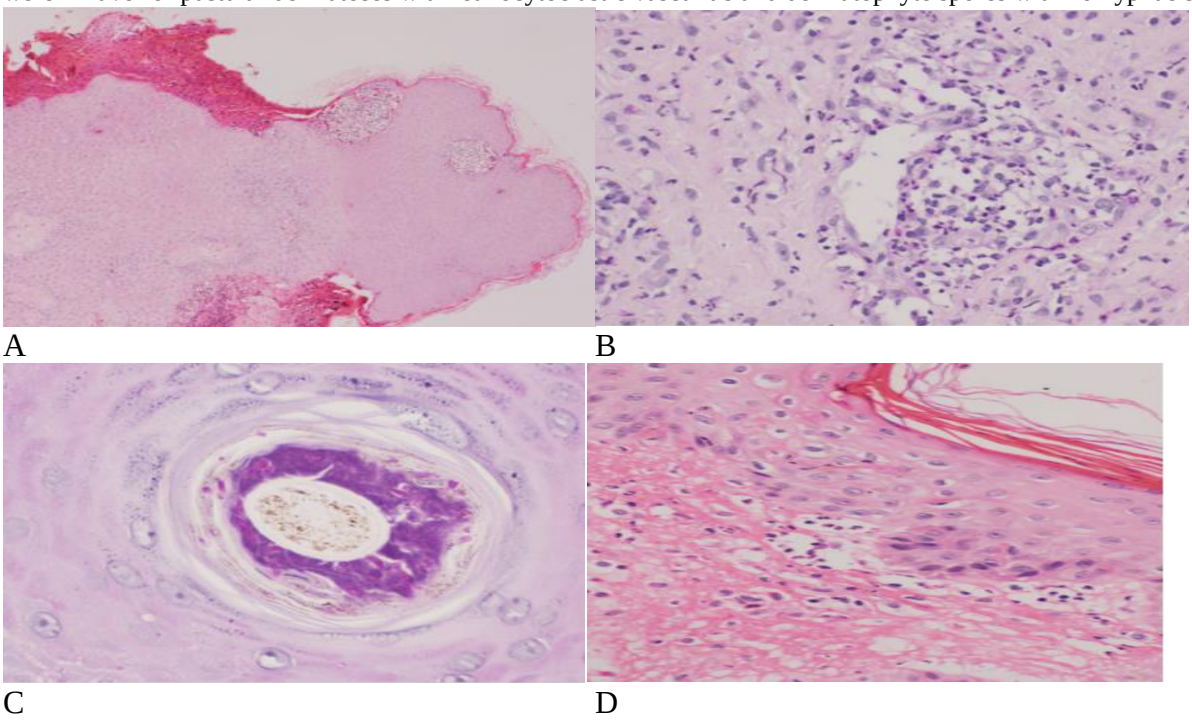

Figure 2: **(a)** H&E magnification: X10. A canthotic epidermis, covered with thick parakeratotic crust, containing aggregates of neutrophils and plasma cells. Intraepidermal neutrophilic vesicles are also seen. **(b)** H&E magnification: X40. Blood vessel showing prominent endothelial cells, smudged walls, neutrophils within and around vessel wall. **(c)** PAS magnification: X40. Dermatophytes spores and hypha within hair follicle. **(d)** H&E magnification: X20. Subepidermal blood vessel dilation with prominent fibrin and neutrophilic infiltrate.

With the above biopsy result of leukocytoclastic vasculitis along with her chronic recurrent fever; she was labeled as a case of pyrexia of unknown origin and underwent a comprehensive workup. The following tests were done including antinuclear antibody (ANA), cytoplasmic antineutrophil cytoplasmic autoantibody (C-ANCA), creatinine kinase (CK), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), complements C3 and C4, antistreptolysin (ASO) titer, human immunodeficiency virus (HIV), hepatitis profiles, rheumatoid factor (RA) factor, brucella antibodies and interferon-Gamma release assays (IGRA). Add to that, imaging studies were also performed including chest X-ray and abdominal ultrasound. All of them were normal except brucella melitensis and brucella abortus antibodies titer was reported to be positive with results of 1:20 and 1:160 respectively.Incidentlly, she was also found to be a hepatitis B carrier. Direct Immunofluorescence was not done as we found no clues toward bullous disorders or SLE from history and investigations.

From the above history, clinical examination, and investigation results, a most likely rare diagnosis of leukocytoclastic vasculitis due to brucellosis was suggested. Although there were dermatophytes spores present, the rash distribution, the clinical (presence of tenderness rather than itching), and the histopathological pictures were not suggestive of pathogenic fungal elements at all, and the fungal spores were considered as a coincidental finding. Add to the above, the presence of leukocytoclastic vasculitis in skin biopsy is not related to tinea and extremely rare.

The patient was treated cautiously with oral prednisolone 20 mg OD tapered every 3 days till reaching 5 mg then the last dose continued for 14 days along with Rifampicin 600 mg once daily and Doxycycline 100 mg twice daily both for six weeks. No topical antifungal was given as for the above explained reasons. Following treatment, she had

a full and complete recovery from the previous skin eruption as well as fever and other symptoms in 3 weeks after starting the treatment. In the subsequent follow-ups months later, the patient reported no new lesions or symptoms suggestive of brucellosis and no vasculitis rashes but only post-inflammatory hyperpigmentation over the previous skin lesions which were fading gradually with time.

Discussion

Brucellosis is a multisystemic bacterial infection of a zoonotic origin. Cutaneous manifestations observed in brucellosis are very rare and nonspecific with only 1-14% of the patients affected with it.[6] It was first described in 1940.[7,8] The organism induces skin rashes by direct invasion of the skin, deposition of immune complexes, direct inoculation, or via the hematogenous route of spread.[6] This probably explains the diversity of rashes reported. Ariza et al. reported 6% of 436 patients with brucellosis had cutaneous manifestations with the mostly observed ones being disseminated violet erythematous papulonodular eruption, and erythema nodosum-like lesions.[3] Other rashes described were erythema, papules, petechiae, urticaria, impetigo-like, eczematous, chronic ulceration, and subcutaneous abscess [Tables 1 and 2].[1,3,9]

Table 1: Cutaneous rashes associated with brucellosis in general.[6,8.]

Most frequent skin lesions associated with brucellosis.
Papulonodular lesions
Erythema nodosum-like lesions
Maculopapular eruptions
Petechiae, purpura
Contact urticaria
Rare skin lesions associated with brucellosis
Vasculitis lesions
Subcutaneous abscesses
Chronic ulcerations
Liquefactive panniculitis
Recurrent epidermal cyst
Livedo reticularis

Table 2: The commonest rashes reported with brucellosis.[8]

Cutaneous lesion	**Percentage (%)**
Maculopapular eruptions	25%
Erythema nodosum-like lesion	25%
Psoriasiform lesion	12.5%
Palmar erythema	12.5%
Malar eruption	12.5%
Palmar eczema	12.5%

Our case had erythematous tender scaly red plaques with raised margins. Brucellosis-related vascular involvement was less often described in the literature. Leukocytoclastic vasculitis (LCV), also called hypersensitivity vasculitis, is a type of necrotizing, immune complex-mediated vasculitis that affects small vessels, mainly dermal capillaries, and venules. The etiology of it is unknown in nearly half of the cases but it can be triggered by viral, bacterial infections, autoimmune rheumatological conditions, medications, and even malignancies [Table 3].[3,10]

Table 3: Causes of Small Vessels Vasculitis.[10,11]

Causes Of Small Vessels Vasculitis

Association	Incidence	Agent/Disease		
		Common	**Uncommon**	**Rare**
Idiopathic	50%			
Infection	15–20%	**Bacterial**		
		Beta-hemolytic streptococci, especially group A Mycobacterium leprae	Neisseria meningococcus (in chronic meningococcemia) Mycobacterium tuberculosis, atypical mycobacteria	Mycoplasma pneumonia, Chlamydophila pneumonia, Chlamydia, trachomatis, **Brucella** Bartonella henselae, Salmonella, Campylobacter Yersinia, enterocolitica, Treponema pallidum
		Septic vasculitis*		
		Infective endocarditis	Neisseria meningitidis (acute), Neisseria gonorrhea, Staphylococcus aureus Rickettsia, Gram-negative rods, Escherichia coli, Klebsiella, Pseudomonas Disseminated fungal infections (immunocompromised hosts) Candida, Aspergillus, Fusarium, Mucor.	Francisella tularensis
		Viral		
		Upper respiratory tract infection Hepatitis C > B ≫ A, including vaccines	HIV Parvovirus B19	Cytomegalovirus, Varicella zoster virus, Influenza virus including vaccine
Inflammatory Disorders	15–20%	Autoimmune connective tissue diseases − Rheumatoid arthritis − SLE − Sjögren syndrome	Inflammatory bowel disease, Behçet disease Hypergammaglobulinemic purpura of Waldenström, Seronegative spondyloarthropathies	Sarcoidosis, Cystic fibrosis, Primary biliary cirrhosis, Bowel-associated dermatosis–arthritis syndrome, Gluten enteropathy
Drug Exposure†	10–15%	**Antibiotics, esp. β-lactams** Penicillin, Cephalosporin, Sulfonamides, Minocycline Quinolones, Macrolides **Cardiovascular** Thiazides Hydralazine, Quinidine **Other** Allopurinol, Bortezomib penicillamine, G-CSF, NSAIDs Propylthiouracil Streptokinase	**Antimicrobials** Quinine, Vancomycin **Cardiovascular** ACE inhibitors, Beta-blockers Furosemide, Other Cocaine, adulterated with levamisole, COX-2 inhibitors, Interferons Leukotriene inhibitors, Methotrexate, Oral contraceptives ,Phenytoin ,Retinoids , Sulfonylureas ,TNF-α inhibitors ,Warfarin	**Antimicrobials** Mefloquine, **Cardiovascular** Amiodarone, **Neuropsychiatric** Atypical antipsychotics, Gabapentin, Phenothiazine SSRIs, **Other** Insulin, Metformin Methamphetamine, Rituximab, **Miscellaneous** Radiographic contrast media Food/drug additives, Vitamins
Neoplasms	2–5%	Plasma cell dyscrasias Monoclonal gammopathies Multiple myeloma Myelodysplasia Myeloproliferative disorders Lymphoproliferative disorders Hairy cell leukemia	Solid organ carcinomas (IgA vasculitis in adults ≫ other forms of CSVV)	
Genetic disorders	Rare	Alpha-1 antitrypsin deficiency		Immunodeficiency syndromes Familial Mediterranean fever and other periodic fever syndromes

The pathogenesis of the vasculitis in brucellosis is not fully understood.[12,13] However, the presumed hypersensitivity reaction in small blood vessels due to disease antigens is probably the cause.[12]

Fortunately, this disease-induced vasculitis can usually respond to antibiotic treatment.[6] Nagore et al. and Karaali et al. reported quick regression of the rashes within 48 hours after proper disease-oriented antibiotic treatment.[13] The same authors also reported spontaneous resolution as well.[13] In our case, a complete clinical response has been achieved in 3 weeks. The delay in response to treatment could be probably explained by the severity of the condition at presentation, the vasculitic nature of the rash, and the use of systemic steroid in an infectious process.

Conclusion

Brucellosis has a non-specific wide spectrum of clinical manifestations. Early diagnosis and intervention can prevent serious complications associated with this multisystemic dangerous disease. Brucellosis induced leukocytoclastic vasculitis is very rare, but it needs to be considered in the endemic areas like the Middle East especially when there is suggestive history, suspicious contact, and suggestive specific or nonspecific symptoms and signs.

References

1. Ekinci, Ö., Ebinç, S., Doğan, A., Aslan, M. and Demir, C.F. 2020. Acute brucellosis presenting as leukocytoclastic vasculitis. Available at .

2. Zheng R, Xie S, Lu X, Sun L, Zhou Y, Zhang Y, et al. A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. Biomed Res Int 2018 Apr;2018:5712920. .

3. Korkmaz P, Kıdır M, Namdar ND, Özmen A, Uyar C, Değer AN. A Case of Brucellosis with Recurrent Attacks of Vasculitis. Case Rep Infect Dis 2016;2016:5740589. .

4. Cheikh M, Kabli A, Sendi E, Almoallim H. P-ANCA Systemic Vasculitis Induced by Brucellosis in an Elderly Male Patient. Case Rep Rheumatol 2021 Nov;2021:6117671. .

5. Bouomrani S, Mrad H, Teber SB. 2021. Cutaneous Leuckocytoclastic Vasculitis Revealing Acute Brucellosis: A Case Report. Available at: http://pubs.sciepub.com/ajmcr/9/6/8/index.html.

6. Karaali Z, Baysal B, Poturoglu S, Kendir M. Cutaneous manifestations in brucellosis. Indian J Dermatol 2011 May;56(3):339-340. .

7. Milionis H, Christou L, Elisaf M. Cutaneous manifestations in brucellosis: case report and review of the literature. Infection 2000;28(2):124-126. .

8. Korkmaz P, Doyuk Kartal E. 2016. Skin Manifestations Associated with Brucellosis. *EMJ Dermatology*, pp. 119–125. Available at: .

9. Metin A, Akdeniz H, Buzgan T, Delice I. Cutaneous findings encountered in brucellosis and review of the literature. Int J Dermatol 2001 Jul;40(7):434-438. .

10. Al-Busafi SA, Al-Suleimani A, Al-Hamadani A, Rasool W. Tenofovir-induced Leukocytoclastic Vasculitis. Oman Med J 2017 Sep;32(5):429-431. .

11. Bolognia JL, Schaffer JV, Cerroni L. 2017. *Dermatology: 2-Volume Set*. Elsevier Health Sciences. 4th edition 2017. pp. 415-416.

12. Catakli T, Arikan FI, Acar B, Dallar Y. Cutaneous vasculitis in a patient with acute brucellosis. Clin Exp Dermatol 2009 Oct;34(7):e387-e388. .

13. Uçmak F, Uçmak D, Bestas R, Azizog Lu Anli R, Adanir H. (n.d.). Acute brucellosis associated with leukocytoclastic vasculitis and splenic infarct Available at: https://www.infezmed.it/media/journal/Vol_22_4_2014_11.pdf [Accessed 12 Mar.2023].