# Diagnostic challenge

# Oral ulcers, uveitis and thrombosis are looking for a diagnosis…

E. Forkosh[1], Y. Ishay[1], A. Schwartz[1], A. Talmon[2], E. Ben-Chetrit[3]

*With this issue of Behçet's disease and other autoinflammatory conditions, we are introducing a new section entitled* ***Diagnostic Challenge****.*

*To attract the attention of our readers to the differential diagnosis of autoinflammatory conditions/diseases, which can admittedly be quite challenging to all of us, we aim to present a detailed account of a particularly intriguing and a difficult case you might wish to share with your colleagues.*

*This case report should start with a patient description (history, physical examination, laboratory blood tests and imaging), followed by the differential diagnosis, a discussion and the final diagnosis.*

*We like to think that this new section will be of particular interest to colleagues actively practicing clinical rheumatology.*

*E. Ben-Chetrit*
*H. Yazici*

[1]*Department of Medicine A,*
[2]*Allergy Unit,* [3]*Rheumatology Unit,*
*Hadassah Hebrew University Medical Centre, Jerusalem, Israel.*

*Ester Forkosh, MD*
*Yuval Ishay, MD*
*Asaf Schwartz, MD*
*Aviv Talmon, MD*
*Eldad Ben-Chetrit, MD*

*Please address correspondence to:*
*Eldad Ben-Chetrit,*
*Rheumatology Unit,*
*Hadassah-Hebrew University Medical Centre,*
*POB: 12000, Jerusalem 91120, Israel.*
*E-mail: eldad@hadassah.org.il*

*Received on July 10, 2022; accepted on July 21, 2022.*

*Clin Exp Rheumatol 2022; 40: 1593-1597.*



**Key words:** Rickettsia, Behçet's disease, uveitis, thrombosis, arthritis

*Competing interests: none declared.*

**Case presentation**

*Chief symptoms*

A forty-year-old man came to the Emergency Department (ED) of our Medical Centre, because of fever, headache and weakness of two weeks duration.

*History of present illness*

Two weeks before admission, the patient complained of fever (up to 39°C), headache, blurred vision, and diffuse muscle and joints pain. He also suffered from urinary urgency, dysuria and meatal redness without discharge.

The patient denied consuming unpasteurised dairy products or raw meat, nor travelling outside of Israel. The patient did not recall having direct contact with animals, except having stray dogs around his house. He also denied recent insect bites.

He was seen by his family physician who suspected a viral infection, but due to the urinary symptoms he prescribed cefuroxime 1 gr per day for possible urinary tract infection. Since he did not improve, he came to the ED.

*Medical, social and family history*

The patient's medical history was unremarkable. At the time of the current admission, he was under treatment of cefuroxime, as mentioned above.

The patient was a carpenter of Palestinian Arab origin, married, with 5 children. He denied any new sexual partners. He smoked one pack of cigarettes per day and used marijuana occasionally. There was no history of a similar disease among his family members.

*Review of systems*

The patient had ophthalmic symptoms including blurred vision and mild photophobia. He suffered from muscle and joints pain with a normal range of motion, he did not suffer from respiratory or gastrointestinal symptoms. Despite his complaint of urinary symptoms, there was no flank pain or back pain or gross haematuria.

*Physical examination*

On examination the patient was febrile (38°C). His blood pressure was 105/60 mmHg, pulse rate was 97 beats per minute and oxygen saturation 100% at room air. He appeared pale and weak but was alert and oriented. He did not have nuchal rigidity. Oral examination disclosed small mucosal ulcers on the posterior wall of the oropharynx (Fig. 1). The lungs were clear on auscultation. The heart sounds were normal with no murmurs. The abdomen was soft, non-tender and without organomegaly. No cervical, axillary or femoral lymphadenopathy was noted. Nevertheless, moderate tenderness and swelling on both ankles were evident. Erythematous circular blanching macules with some raised papules were

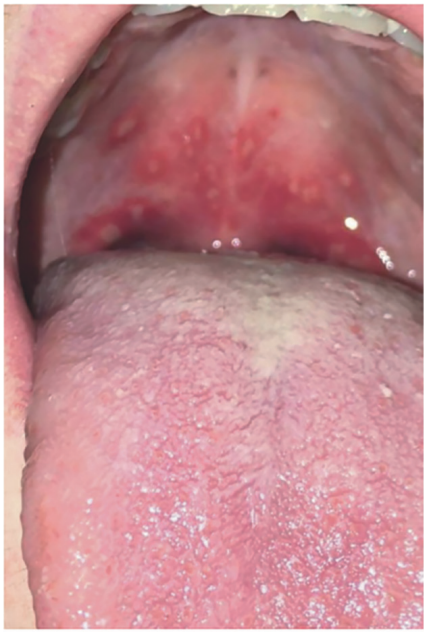

**Fig. 1.** Oropharyngeal ulcers of the patient seen on his admission.

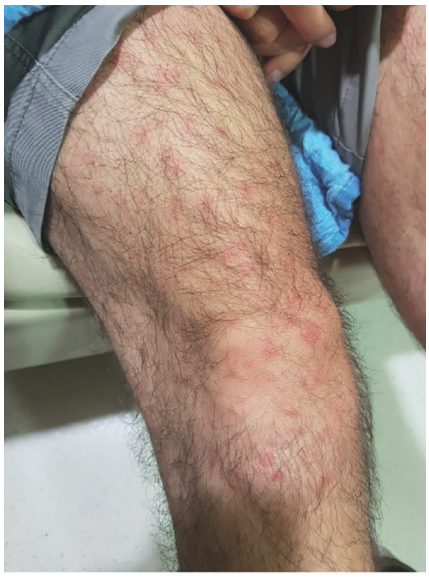

**Fig. 2.** Maculopapular rash involving the patient's lower extremity.

seen on his legs, sparing the soles (Fig. 2). There were no genital ulcers, meatal redness or penile discharge. Neurological examination was normal.

## Clinical course

On admission ceftriaxone was empirically prescribed instead of cefuroxime. On the second day of hospitalisation, the patient complained of worsening blurred vision with ocular pain and worsening photophobia. An ophthalmologist examination revealed bilateral anterior uveitis.

Following three days of antibiotic treatment, no clinical improvement was observed. The patient's fever persisted (38°C-39°C), the rash spread to the arms, thorax and back and transformed to a petechial pattern sparing the palms and soles. A diagnosis of vasculitis was raised, and skin biopsy was obtained. Due to evolution of the rash, ceftriaxone was replaced by doxycycline for possible zoonotic infections such as Rickettsia. Two further days of treatment with doxycycline yielded no improvement. Moreover, the patient started complaining of pain and swelling in his left calf, which appeared swollen and tender on physical examination. A Doppler ultrasound demonstrated a thrombus in the lesser saphenous vein, extending into the popliteal vein. It should be stressed that the patient was actively mobile during his hospitalisation. The lack of adequate response to antibiotics made a non-infectious inflammatory disease more considerable and a course of hydrocortisone 100mg IV TID was prescribed in addition to enoxaparin and doxycycline.

*Laboratory evaluation*

Complete blood counts showed 4,000 white cells per cubic millimetre with 84% neutrophils and 11% lymphocytes, anaemia and mild thrombocytopenia (Table I). Biochemistry showed mild hyponatremia, normal renal function and mildly elevated liver enzymes without bilirubinemia. ESR and CRP were elevated. Chest radiogram and brain CT were normal. Urinalysis revealed normal colour urine with a pH of 6.0, specific gravity of 1.010, and traces of protein with no red blood cells, leukocytes or nitrites. Urine culture was sterile. Serologies for *Brucella*, *Leptospira*, *Coxiella burnetii* (Q fever) were negative. ELISA test for HIV was negative. A urethral swab Nucleic-Acid Amplification Tests (NAAT) for *Chlamydia trachomatis* and for *Neisseria gonorrhoeae* were negative. Syphilis serologies were negative. Serum antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. C3 and C4 serum levels were normal. Tests for HLA-B51 and HLA-B27 were negative. Pathergy test was negative. Serology and immunofluorescent assay for Rickettsiosis were pending.

**Table I.** Laboratory results.

| | Normal values | at admission | at discharge |
|---|---|---|---|
| WBC count ($10^9$/L) | 4-10 | 4.0 | 8.2 |
| Haemoglobin (GR%) | 14- 18 (MALE) | 11.2 | 10.4 |
| Platelet count ($10^9$/L) | 140- 400 | 72 | 471 |
| Sodium (MMOL/L) | 135-145 | 127 | 139 |
| Creatinine (MMOL/L) | 58- 110 | 57 | 46 |
| UREA (MMOL/L) | 0-8.3 | 3.6 | 3.8 |
| Albumin (GR/L) | 35-50 | 28 | 32 |
| ALT (U/L) | 0-40 | 187 | 117 |
| AST (U/L) | 0-35 | 116 | 38 |
| ALK (U/L) | 40- 130 | 86 | 73 |
| GGT (U/L) | 8- 61 | 88 | 74 |
| Bilirubin (MMOL/L) | 0-17 | 5 | 4 |
| CPK (U/L) | 39- 308 | 199 | ND* |
| LDH (U/L) | 240- 480 | 617 | 398 |
| CRP (MG%) | <0.5 | 21.9 | 1.5 |
| ESR mm/1hour | <20 | 54 | 40 |

*ND: no data.

*Case summary*

A forty-year-old patient presented with fever, malaise, headache and dysuria of two weeks duration. Physical examination disclosed oropharyngeal ulcers, bilateral ankles arthritis, skin rash sparing the palms and soles and meatal redness. On the second day of hospitalisation bilateral anterior uveitis was diagnosed and two days later left calf pains evolved to saphenous and popliteal vein thrombosis. The rash spread

to the arms, thorax and back and transformed to a petechial pattern yet sparing the palms and soles.

*Differential diagnosis*

The defining features of this patient were fever, headache, arthritis, skin rash, oral ulcers, uveitis and venous thrombosis. This complex of symptoms and findings suggests that the strongest considerations in the differential diagnosis include various infections, Behçet's syndrome and reactive arthritis. However, lupus, sarcoidosis and ANCA associated vasculitis should also be discussed.

*Viral infection*

Fever, headache and blurred vision may represent primary viral infection involving the CNS such as meningitis. The additional clinical findings; skin rash, oral ulcers and general weakness may indicate possible infections caused by Coxsackie virus, Varicella zoster virus (VZV), EBV, CMV, or primary HIV infection. Uveitis may complicate CMV infection in HIV infected population (1). Since the patient lacked nuchal rigidity or changes in mental status, acute meningitis or meningoencephalitis appeared unlikely. The patient's rash spared the palms and soles making a diagnosis of infection caused by Coxsackie virus less plausible. In addition, the rash was not vesicular as typically seen in VZV infection.

*Rickettsiosis*

Rickettsiosis is a family of diseases caused by various rickettsia distributed in various geographic areas (2). Fever, thrombocytopenia, hyponatremia and elevated liver enzymes combined with the presence of skin rash and arthralgia are common features of this disease.

Moreover, the maculopapular rash which later evolved to petechial rash is also typical for Rickettsia (3). Thromboembolic disease may also complicate Rickettsial disease (4). However, in the present case the patient denied having contact with animals and did not recall any insect bite. Furthermore, oral ulcers have not been reported in rickettsiosis and bilateral uveitis and arthritis are rare in this infection.

*Leptospirosis*

Leptospirosis can cause high fever, headache, thrombocytopenia, disturbed liver function tests, and a petechial rash. Furthermore, Leptospira is endemic in the Middle East. However, the typical eye finding in Leptospirosis is conjunctival suffusion rather than uveitis. Moreover, patients with this disease present with jaundice (hyperbilirubinemia), abdominal pain, vomiting and diarrhoea. In severe cases they may have pulmonary haemorrhage, and even renal failure (5). In the current case the patient did not have any of these features and serology for Leptospira was negative.

*Systemic lupus erythematosus*

Fever with anaemia and thrombocytopenia may be consistent with systemic lupus erythematosus (SLE). Joint involvement and neurologic symptoms (headache), oral ulcers, venous thromboembolism and skin rash may further support this diagnosis (6). However, the type and spread of the rash (sparing the face), the involvement of large joints (ankles) and the presence of bilateral uveitis are not typical in SLE.

*Sarcoidosis*

Sarcoidosis may present with cutaneous and ocular involvement, as well as nonspecific constitutional symptoms (7). The most commonly affected organs in sarcoidosis are the lungs and intrathoracic lymph nodes (over 90% of patients). Common symptoms include cough, dyspnoea, and chest tightness. Cutaneous sarcoidosis usually includes skin lesions with noncaseating granuloma or erythema nodosum, none of which the patient had. Thus, it seems that sarcoidosis is also an unlikely diagnosis.

*ANCA associated vasculitis*

Fever, headache, oropharyngeal ulceration, arthritis, uveitis and wide spread petechial rash could very well fit with an ANCA associated vasculitis. The fact that the patient's ANCA test was negative does not exclude the diagnosis since not all cases have positive ANCA testing (8). However, the patient did not display many typical features of the disease including: necrotising or granulomatous lesions affecting the ears, nose or throat (ENT), causing symptoms of chronic rhinitis, sinusitis or laryngitis. He neither had lung involvement, presenting with shortness of breath, cough or haemoptysis due to pulmonary haemorrhage. He did not have kidney involvement which usually presents as rapidly-progressive glomerulonephritis with haematuria, proteinuria and hypertension. His chest x-rays did not show cavitating lung nodules. Thus, ANCA vasculitis is another less likely diagnosis.

*Reactive arthritis*

The musculoskeletal features of reactive arthritis include four major manifestations: asymmetric peripheral oligoarthritis, often affecting the lower extremities, enthesitis, dactylitis, and back pain (9). Extraarticular involvement in reactive arthritis may include ocular symptoms, such as conjunctivitis, and less frequently, anterior uveitis. In addition, genitourinary tract symptoms may present as dysuria, pelvic pain, urethritis, or cystitis. Oral lesions include painless mucosal ulcers and cutaneous eruptions include skin changes, such as keratoderma blennorrhagica resembling psoriasis. Although many of the patient's symptoms were consistent with reactive arthritis, the presence of maculopapular and later petechial rash, relative leukopenia, thrombocytopenia and elevated liver enzymes did not support this diagnosis.

*Behçet's disease*

Most patients with Behçet's disease (BD) present initially with recurrent painful oral aphthous ulcerations which tend to be extensive and often multiple. The skin manifestations of BD vary and may include acneiform lesions, papulovesiculo-pustular eruptions, pseudofolliculitis, erythema nodosum, and pyoderma gangrenosum (10). Uveitis is another dominant feature of BD. It is typically bilateral and episodic, often involves the entire uveal tract (pan uveitis), and may not resolve completely between episodes. Neurologic disease occurs in less than 15% of patients with BD. In general, it is classified as parenchymal or non-parenchymal brain involvement and its clinical manifesta-

tions may include headache, papilledema, sixth nerve palsy and mental disturbances. Regarding the vascular system, BD may involve veins and arteries of all sizes. Venous disease resulting in venous thrombosis is more common than arterial involvement, and is often an early feature of the disease (11).

Although our patient had never experienced genital ulcers, the combination of oral ulcers, bilateral uveitis and arthritis, makes BD the most plausible diagnosis. Using the revised international criteria for BD (ICBD), the patient gained 4 points (oral ulcers and uveitis), sufficient for the diagnosis of BD (12). According to the ICBD score, the sudden appearance of vein thrombosis (DVT) granted the patient one more point, making the diagnosis of BD more definite. Nevertheless, the abrupt onset of all the features within 2-3 weeks is not typical and the nature of the skin rash was not characteristic of BD.

**Diagnosis**

Following the combined treatment with prednisone (40 mg daily), doxycycline and enoxaparin, the patient's condition improved clinically and his laboratory abnormalities normalised. However, after a week of hospitalisation, the petechial rash spread to his palms and soles. A biopsy from the skin rash showed perivascular mononuclear infiltrate with extravasation of erythrocytes with no evidence of vasculitis. The patient was discharge after 10 days feeling much better while on a tapering prednisone regimen and doxycycline for 4 more days.

Three weeks after his discharge, the patient came for a follow up visit in the clinic. He was completely healthy without any medication. Results of indirect immunofluorescence antibody assay for immunoglobulin M and G using Rickettsia antigens, supported the diagnosis of Rickettsia infection. Further species-specific Latex agglutination test, identified the infective agent as *Rickettsia conorii*.

Six months later, the patient was seen again in the clinic. He was healthy, free of any symptom or sign without any medication.

**Discussion**

This case demonstrates a diagnostic dilemma in which diseases of different nature share almost identical clinical features.

BD is a multisystem vasculitis of unknown aetiology. It has a unique geographic distribution along the ancient "Silk Road", which extends from eastern Asia to the Mediterranean basin (10, 11). However, the disease does occur in other parts of the world including the USA and Europe. The onset of BD is usually at the third decade of life. Susceptibility to BD is strongly associated with the presence of HLA-B51 allele, most commonly among patients who live in areas along the "Silk Road". BD is characterised by recurrent oral aphthae, genital ulcers, uveitis, variable skin lesions (acne, erythema nodosum, pyoderma gangrenosum etc.), arthritis and thrombophlebitis. Small-vessel vasculitis (endothelitis) is common and accounts for much of the pathologic process in BD. Superficial thrombophlebitis and deep venous thrombosis, are characteristic manifestations that can be used as additional diagnostic criteria for BD, according to the ICBD (12).

The diagnosis of BD is based on clinical findings; pathergy test is considered a pathognomonic sign but is present in only about 60% of patients. Carrying HLA-B51 may support the diagnosis, but it presents in only 40-60% of patients. In our patient both pathergy test and carriage of HLA-B51 were negative. The patient's age, origin and country of residence, meet the typical epidemiology of BD. The fact that he had no previous episodes of oral ulcerations, the most common manifestation of BD, does not preclude the diagnosis, as this may have been his first episode. Bilateral uveitis and venous thrombosis are also characteristic of BD, and together with oral ulcers award the patient a score of 5 points according to the revised ICBD criteria. However, according to the International Study Group (ISG) criteria which are more stringent, our patient had only oral ulcers and uveitis which are not sufficient for definite BD diagnosis (13). Furthermore, the relatively rapid course of the disease and the presence of thrombocytopenia, leukopenia, hyponatremia, elevated liver enzymes and maculopapular rash, further undermine the certainty of a BD diagnosis.

Rickettsia are obligately intracellular Gram negative (2). The species of the genus Rickettsia are divided into four groups or clades: a basal ancestral group, the spotted fever group (SFG), the typhus group, and the transitional group. The SFG and typhus group are the classic rickettsial clades causing human diseases. Currently, the SFG is comprised of the largest number of species, of which at least 15 cause disease. The names of diseases associated with an agent often reflect their region of discovery but often fail to encompass their full geographic range. For example, Rocky Mountain spotted fever (RMSF), though originally described in Idaho and attributed to ticks in Montana, is a disease of the entire Americas. Mediterranean spotted fever (MSF) is caused by *R. conorii* and may be found in Europe, Africa, and Asia too.

*Rickettsia conorii*, is the most widespread rickettsia of the spotted fever group. The disease is normally transmitted by a tick bite, but may also be acquired through the skin or eye when the ticks are crushed (14). Mediterranean spotted fever is an endemic disease occurring during spring and summer. It varies in severity and seldom fatal. The incubation period is 5-7 days and the onset is sudden in about 50% of cases. The duration of disease is 7-14 days. The clinical signs and symptoms include fever (up to 40°C), headache, chills, myalgias, arthralgias, malaise, and anorexia. Maculopapular rash, involving also the palms and soles, is a hallmark of rickettsia infection, but usually follows systemic symptoms. Its absence should not rule out a possible rickettsia aetiology, especially during the first week of illness (2).

Although our patient presented with the typical triad of *Rickettsia* infection, fever, headache and skin rash, he also displayed unusual features for this infection including: oral ulcers, bilateral anterior uveitis, and deep vein thrombosis. Despite the fact that uveitis is an uncommon feature of MSF, Agahan *et al*.

claimed that in endemic areas, *Rickettsia conorii* infection should be part of the workup of uveitis (15). This statement is based on a series of 7 patients, living in endemic area for MSF presented with uveitis as the main manifestation of the disease without typical systemic manifestations (15).

A review of the literature suggests that approximately 9% of patients experience deep venous thrombosis (DVT) during the late acute and early convalescent phases of MSF [16]. Hypercoagulability associated with Rickettsial spotted fevers can be explained by endothelitis caused by *R. Conorii* infection. Moreover, Rickettsia may cause haemostatic and haematologic perturbations varying from mild thrombocytopenia to a severe hypercoagulable state (2, 16).

The patient presents a constellation of symptoms and signs that lend support for both diseases, BD and Rickettsial infection. Among his main clinical manifestations, oral ulcers, anterior uveitis and DVT are clearly atypical for Rickettsia infection and support a diagnosis of BD. Conversely, a relatively acute disease onset is more consistent with an infectious aetiology, as most BD patients present in a cumulative, gradual manner. The findings of thrombocytopenia, hyponatremia and elevated liver enzyme are also in favour of Rickettsia infection. The skin rash involving the palms and soles further support this diagnosis.

Immunofluorescence assay (IFA) is the serologic method of choice for the diagnosis of Rickettsia infection (17). The IgM isotype does not appear much earlier than IgG and is less specific. Therefore, IFA for the detection of IgG requires sera drawn during both the acute and convalescent stages of illness. Although a single high titre during illness may be suggestive of the diagnosis, confirmation requires seroconversion or a four-fold increase in titer from acute to convalescent-phase sera. Since group-specific antigens are cross reactive, serology is unable to offer a species-specific diagnosis. Detection of antibodies to specific Rickettsia can be done by latex agglutination test of the appropriate antigens.

In the current case the diagnosis of Rickettsiosis was based upon the triad of fever, headache and the typical skin rash which evolved later to petechial rash. The presence of leukopenia, thrombocytopenia and hyponatremia with liver functions disturbance further supports the diagnosis. The positive immunofluorescence assay for rickettsia followed by the positive species-specific latex agglutination test for *Rickettsia conori* nailed down this diagnosis.

In conclusion, the intriguing and acute presentation of this patient's disease, carried interesting features of both BD and Rickettsia infection. However, the weight of objective evidence accumulated in favour of *R. conorii* infection displaying atypical and rare features of this infection. This diagnostic conundrum brings to light noteworthy aspects of these two diseases.

## Final diagnosis

*Rickettsia conorii* infection.

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