CASE REPORT

A rare case of Behçet disease with generalised myositis, cardiomyositis and necrotising fasciitis

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Accepted 15 December 2015

SUMMARY

Behçet disease (BD) is a rare relapsing, multisystem vasculitis characterised by recurrent oral and genital ulcers, and uveitis. As an autoimmune small vessel vasculitis, BD can involve other organs including the skin, joints, nervous system, kidney and the gastrointestinal tract. This report describes a 40-year-old woman who presented with an uncommon feature of BD, namely myositis, and who went on to develop myocarditis and polymicrobial necrotising fasciitis. To the best of our knowledge, this is the first reported case of an immunocompromised-associated infection occurring in BD without concurrent immunosuppressive therapy.

BACKGROUND

Behçet disease (BD) is a rare ailment and the complications that our patient encountered were extremely unusual.¹ Only 14 cases of non-ocular myositis and 5 cases of dilated cardiomyopathy (DCM) have been previously reported. To the best of our knowledge, this is also the first reported case of an immunocompromised-associated infection (ie, polymicrobial necrotising fasciitis, NF) occurring in BD without concurrent immunosuppressive therapy. NF typically occurs in immunosuppressed individuals due to diabetes or immunosuppressants. This suggests that the underlying immune dysregulation of BD can predispose to an immunosuppressed state.

CASE PRESENTATION

A 40-year-old woman presented to hospital, with a 6-day history of malaise, anorexia and generalised proximal myalgia. She was of Spanish and Turkish ethnic background. Her medical history included transfusion-related hepatitis C virus (HCV) infection, lower limb deep vein thrombosis with heterozygous factor V Leiden (FVL) mutation and depression. She denied infective symptoms, recent trauma or strenuous exercise, and had neither rash nor arthralgia. Physical examination was unremarkable except for proximal generalised myalgia without weakness. Initial laboratory investigations revealed a normal erythrocyte sedimentation rate and C reactive protein (CRP), and an elevated serum creatine kinase (CK) of 3550 U/L (reference range (RR)<145).

Over the next 72 h, she developed an acute bilateral polyarthropathy of the wrist and metacarpophalangeal joints. Multiple cutaneous manifestations were observed. These included a rapidly evolving erythema nodosum-like rash over the legs ([figure 1](#)), which progressed to a purpuric

non-blanching rash with fluctuant subcutaneous oedema, as well as multiple oral aptheous ulcers and perioral acneiform papular nodules. Further laboratory studies showed mildly raised inflammatory markers (CRP of 19.1 mg/L) and a normalising CK of 428 U/L. Other haematological, biochemical and serological tests were within normal limits ([table 1](#)). Multiple skin biopsies were taken and showed changes consistent with neutrophilic dermatosis without evidence of vasculitis. Aptheous ulcer swabs and serological studies excluded infective causes including herpes simplex virus, cytomegalovirus, varicella zoster and syphilis infection.

On day 6, the patient was systemically well but developed a mildly tender natal cleft excoriation which became pustular over the next 2 days. The CRP increased to >380 mg/L and renal function deteriorated from a previously normal level (plasma creatinine rose from 90 to 359 µmol/L). A wound swab grew methicillin-sensitive *Staphylococcus aureus*, and oral flucloxacillin and metronidazole were started. MRI showed enhanced T2 signals in the presacral fascia correlating to the sacral wound. A biopsy of the natal cleft wound again showed a neutrophilic dermatosis reaction.

Figure 1 Multiple cutaneous manifestations included rapidly evolving erythema nodosum rash on the legs.

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To cite: Ng F, Chiong FJK, Buchanan R, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211983

Table 1 Initial haematological, biochemical and serological investigations

		Reference range
ESR	18	7–18
Rheumatoid factor	36	<20
CRP	4	<8
LD	300	98–192
Complement levels (C3/C4)	1.15/0.20	0.79–1.52/0.16–0.38
ANA	Negative	
Extractable nuclear antigens	Negative	
Myositis antibody	Negative	
<i>(Includes Anti-Mi-2/Ku/PM-SCI100/PM-Sci75/Jo-1/SRP/PL-12/EJ/OJ)</i>		
Antineutrophil cytoplasmic antibody	Negative	
Cardiolipin antibody, lupus anticoagulant	Negative	
β 1 glycoprotein antibody	Negative	
Antiplatelet antibody	Negative	
HCV PCR	Detected	
HCV load	<615 IU/mL	
Liver function test	Normal	
<i>(Includes ALT/AST/GGT/ALP/bilirubin level)</i>		
Serum albumin	40 g/L	36–48
Coagulation profile (INR/APTT)	Normal	
Cryoglobulins	0.15	<0.1
Cryofibrinogen	0.46	<0.5
Serum electrophoresis	Negative	
ACE	60	16–85
HIV	Negative	
(IgG/IgA/IgM)		
ASO titre	Insignificant	
Anti-DNase	Insignificant	
Hepatitis B virus antigen, antibody	Negative	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; APTT, activated partial thromboplastin time; ASO, antistreptolysin O; AST, aspartate aminotransferase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GGT, γ -glutamyl transferase; HCV, hepatitis C virus; INR, international normalised ratio; LD, Lactate dehydrogenase.

Around this time, pustular vesicles appeared simultaneously at multiple previous intravenous cannula and biopsy sites. Given that this occurred in the context of antibiotic therapy for the sacral wound, it was presumed to indicate a positive pathergy test ([figure 2](#)). Further clinical history revealed a 5-year history of recurrent oral (up to 4 episodes/year) and genital (yearly) ulceration. A clinical diagnosis of BD was made. Subsequent human leucocyte antigen (HLA)-B51 testing was negative and ophthalmological examination was normal.

Figure 2 Pustular formation at previous intravenous cannula sites. **Figure 3** CT of the pelvis revealing numerous sacral subcutaneous gas locules and fluid.

On day 10, the patient acutely deteriorated with hypotension and hypoxia. CT pulmonary angiography revealed bilateral pneumonia without evidence of pulmonary embolism. Serum white cell count and CK had increased substantially from $11.0 \times 10^9/L$ to $37.2 \times 10^9/L$ (RR 4.0–11.0) and 233 U/L to 3715 U/L, respectively, in 4 days. The patient was intubated and started on broad-spectrum antibiotics (vancomycin/ceftriaxone/metronidazole/azithromycin) with systemic glucocorticoid and inotropic support. A pelvic CT showed numerous sacral subcutaneous gas locules and fluid ([figure 3](#)). Multiple debridement procedures achieved drainage of a large amount of pus and excision of the necrotic tissue ([figure 4](#)). Sacral necrotising myofasciitis was confirmed on histological examination of the debulked specimen with evidence of extensive necrosis and infiltration of mixed Gram-positive and Gram-negative bacteria within subcutis, fascia and skeletal muscle ([figure 5](#)). Microbiological studies on surgical specimens were non-diagnostic as the patient was already being treated with systemic broad-spectrum antibiotics at the time.

Postoperatively, cardiac troponin I level was elevated at $51.33 \mu g/L$ (RR<0.04) and an ECG showed precordial ST segment depression and biphasic T wave changes. A transthoracic echocardiogram (TTE) showed a dyskinetic septum, and inferior and anterior wall with a reduced left ventricular (LV) ejection fraction (EF) of 25%. An angiogram showed normal coronary anatomy without flow-limiting lesions. Apical

Figure 4 Postdebridement packed sacral wound.

Figure 5 Sacral necrotising myofasciitis confirmed on a frozen section specimen showing extensive necrosis within subcutis, fascia and skeletal muscle with numerous mixed bacteria.

ballooning was not seen on the LV ventriculogram. The patient was discharged to the ward from the intensive care unit after 20 days. Her progress was further complicated by a ventricular fibrillation cardiac arrest on day 36. She made a slow but steady recovery and the remainder of her acute admission was uneventful. The oral ulcers, myalgia and cutaneous rashes resolved with systemic glucocorticoids and azathioprine. She was discharged on prednisolone 50 mg daily and azathioprine 100 mg daily. Prednisolone was gradually weaned over a 1 year period while she remained on long-term azathioprine 100 mg daily. An automatic implantable cardioverter defibrillator was inserted 4 weeks after her cardiac arrest when a repeat TTE demonstrated persistent moderately severe segmental systolic and diastolic dysfunction with features of DCM. Cardiac function remained impaired with an EF of 24% at 4-year follow-up.

OUTCOME AND FOLLOW-UP

At 7-year follow-up, the patient has had no further flares or acute complications from BD, but has suffered a cardioembolic stroke secondary to DCM. She resides in a supported accommodation and requires assistance with domestic duties.

DISCUSSION

BD is a rare multiorgan chronic inflammatory disorder of unknown aetiology. It has increased prevalence in countries along the ancient 'Silk Road', which extends from Japan to the Middle East. Turkey has the highest prevalence with 421/10⁵ populations, while Australia has a prevalence of <1/10⁵ population.¹ The peak age of onset of BD is between 20 and 40 years, with similar rates in male and female adults. The aetiology of BD is thought to be a proinflammatory process secondary to Th1-based/Th17-based hyperactivation, with complex genetic and environmental interplay as the principal pathogenic mechanism.² Genetic factors that have been implicated include HLA-B51 and the more recently described major histocompatibility complex (MHC) class I amino acid residue, GIMAP (GTPases of immunity-associated protein), complement copy variation and microRNA polymorphism. Proposed environmental factors include exposure to bacteria (most extensively studied in *Streptococcus sanguinis*) and viral molecules such as heat shock protein.²

BD was first named by a Turkish dermatologist in 1937,¹ and, nearly 80 years later, remains a challenging condition to diagnosis. There is no pathognomonic test for BD and the diagnosis is

based on evaluation based on clinical criteria. The International Study Group (ISG) criteria, developed in 1990, requires recurrent oral ulcers plus two additional features from the following: genital ulcers, characteristic skin lesions (eg, erythema nodosum, cuneiform papulopustular lesions), characteristic ocular lesions (uveitis, retinal vasculitis) or a positive pathergy test.³ The more recent International Criteria for Behçet Disease (ICBD) further incorporates the increasingly recognised clinical features of neurological, vascular and gastrointestinal manifestations into the diagnostic criteria.⁴

Myositis

The presenting symptom in our case was generalised myositis, which is an uncommon feature of BD. Only 14 cases of myositis have been reported.^{5–7} Most cases had localised myositis and presented as recurrent focal tenderness in the lower limbs without a rise in CK. A minority of cases presented with generalised myositis with progressive myalgia and weakness accompanied by an elevated CK. The diagnosis of myositis can be made by muscle biopsy or MRI. Histological studies of BD myositis suggest an initial neutrophil-mediated vasculitis and a subsequent lymphomonocytic infiltration as the main underlying pathological process.⁷

Cardiac manifestation

Cardiac involvement is another uncommon but well-recognised manifestation of BD. Abnormalities include pericarditis, valvular insufficiency, intracardiac thrombosis, endomyocardial fibrosis, coronary arteritis with myocardial infarction, coronary aneurysm, myocarditis and cardiomyopathy. In a series of 807 patients with BD, there was cardiac involvement in 6% of BD flares, with pericarditis being the most frequent manifestation. Cardiac involvement worsens the prognosis of BD, with mortality rates of up to 15.4% over 3 years compared to 5.4% in the absence of cardiac disease.⁸ In our case, myocarditis and DCM were both present. These are very rare manifestations of BD and only five cases of DCM have been previously reported.⁹ Although a myocardial biopsy was not taken, the diagnosis of myocarditis was made on the biochemical, ECG and ultrasonographic results in the context of normal coronary arteries. Takotsubo cardiomyopathy is an alternative diagnosis, but is less likely given the absence of characteristic apical ballooning on angiogram and the persistence of cardiac dysfunction. In contrast to our patient, the near-complete resolution within days to weeks is a recognised mandatory diagnostic feature of Takotsubo cardiomyopathy agreed on in its international diagnostic criteria.¹⁰

Necrotising fasciitis

This case was also complicated by type 1 polymicrobial NF, a rare but life-threatening condition with a high mortality rate (approximately 30%).¹¹ This occurred despite none of the traditional risk factors for NF such as immunosuppression, diabetes, liver cirrhosis or chronic kidney disease, being present.^{11 12} Immunosuppression is the mainstay of therapy in BD and used in 59% of patients.¹³ Glucocorticoids, with or without colchicine and cyclosporine, often lead to dramatic resolution of symptoms. Other approaches include monoclonal antibodies such as the tumour necrosis factor α antagonist. In our case, NF occurred before the diagnosis of BD had been made, and steroids had not yet been started.

It is clear that opportunistic infections do occur in patients with BD on immunosuppressive therapy at a rate comparable to other diseases requiring immunosuppressive therapy.¹³ It is also

likely that the autoinflammatory dermatological involvement of BD, a heightened risk of thrombosis in BD leading to skin integrity compromise and local vascular insufficiency, and the systemic activity of BD leading to acute hepatorenal dysfunction, would predispose to NF. However, the development of a severe immunocompromised-associated infection without immunosuppressive therapy nonetheless raises the question of whether the underlying immune dysregulation of BD may lead to immunosuppression. Regardless of whether this is a rare coincidence or the first described case of primary immunosuppression in BD, our case highlights the need for physicians to be highly vigilant of serious infections in BD, given that immunosuppressive therapy—which itself poses an iatrogenic risk of infection—is the accepted standard of care for BD.

Differential diagnosis and contributing pathology

Differential diagnoses in this case include HCV-induced cryoglobulinaemic vasculitis (CryoVas). CryoVas is a multiorgan small-vessel vasculitis with dermatological, rheumatological, neurological and renal manifestations. The histopathological hallmark is a leucocytoclastic vasculitis on biopsy in the setting of cryoglobulinaemia.¹⁴ Accompanying serological changes in CryoVas include low complement levels (70–90%), elevated rheumatoid factor (66%), monoclonal proteinemia, presence of antinuclear antibody (17–41%), anticardiolipin (20–27%) and antismooth muscle cell antibody (9–40%).¹⁵ In our patient, there was no histological evidence of vasculitis on multiple biopsy samples. Instead, there was consistent demonstration of a neutrophilic dermatosis reaction, a characteristic histological features in Behçet's disease.^{16 17} Furthermore, except for an elevated rheumatic factor, our patients did not have any associated serological abnormalities of CryoVas. These findings suggest HCV-induced CryoVas is unlikely to be the primary pathology.

Another potential contributing pathology in this patient is thrombophilia in the setting of heterozygous FVL mutation and active BD. Thrombosis is prevalent in BD (up to 30% of patients) and tends to be multiple and venous, and associated with disease activity.¹⁸ The pathogenesis for thrombosis in BD is unclear. Recently, a meta-analysis reported FVL as a genetic risk factor for thrombosis in patients with BD of Turkish origin.¹⁹ In

our patient, BD/FVL-associated thrombophilia may have predisposed to superficial thrombophlebitis causing tissue vascular compromise leading to NF, multiple distal pulmonary embolism leading to bilateral pneumonia and arterial thrombosis leading to ischaemic cerebral infarction.

CONCLUSION

In conclusion, this case illustrates an uncommon presentation of BD and highlights the challenges in its diagnosis. It illustrates the need to think of BD as a differential diagnosis particularly when, as in this case, there is multisystem involvement (ie, muscle, joints, skin, heart). Physicians also need to be highly vigilant of serious infections in BD given that skin integrity is often compromised, and that immunosuppressive therapy is the mainstay of treatment.

Contributors FN and FJKC carried out the literature review on Behçet's disease. RB was the rheumatologist involved in the care of the patient described in the case. He provided his expert opinion on the case. LMB was the general physician who cared for the patient. She reviewed and edited the article. She also provided her expert opinion for the article.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Behçet's disease is a rare autoimmune condition that is most prevalent in people of Turkish background.
- The diagnosis of Behçet's disease remains a clinical one.
- Behçet's disease is a systemic disease with the predominant symptoms of oral ulcers, genital ulcers and uveitis. Other systemic involvement includes the skin and joints, and there can be neurological and gastrointestinal manifestations. Less common but well described is muscle and cardiac involvement.
- Clinicians should be aware of the risk of infections in BD given that skin integrity can be compromised, and immunosuppressive therapy is the mainstay of treatment. Disease-related immunosuppression has not been described previously but is possible.

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