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CASE REPORT
Other

Recurrent myocarditis in the context of Behçet's disease: a case report

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Background Behçet's syndrome is a multisystemic vasculitis of unknown aetiology. Cardiac involvement is rare, with described prevalence between 1% and 46%, with pericarditis, valvular insufficiency, intracardiac thrombosis, and eventually sinus of Valsalva aneurysms being the most common findings. Although previously reported, myocarditis is a very rare complication of Behçet's syndrome.

Case summary A 26-year-old man, smoker but otherwise healthy, was admitted to the emergency department with atypical chest pain, with no radiation, relation to efforts, position or deep inspiration, and dyspnoea, since the day before. His physical examination was unremarkable, including no fever, tachycardia, or pericardial friction rub. Electrocardiogram (ECG) revealed an early repolarization pattern, with no changes noted in subsequent exams. He had elevation of inflammatory parameters and an increased high-sensitivity troponin level of 3300 ng/L. Transthoracic echocardiography (TTE) was unremarkable. Coronary angiography showed no coronary stenosis. A presumed diagnosis of non-complicated viral myocarditis was established. The patient's condition improved with acetylsalicylic acid as needed and colchicine and he was discharged after 3 days. Cardiac magnetic resonance was performed, showing late epicardial enhancement in the apical segment of the lateral wall, supporting the diagnosis of myocarditis. Four months later, the patient returned with recurrence of chest pain. Additionally, he also complained of fever, odynophagia, and otalgia since the previous week. Oropharyngeal examination revealed tonsillar pillars aphthosis. The ECG was similar to the previous and TTE was normal. Bloodwork revealed once again elevation of inflammatory parameters and elevation of troponin. Recurrent myocarditis was diagnosed. Treatment with ibuprofen, colchicine, and antibiotic therapy was started with no significant improvement. After a more thorough physical examination, an ulcerated scrotal lesion, a left buttock folliculitis, and an axillary hidradenitis were found, which, according to the patient, were recurrent in the last year. Accordingly, the diagnosis of Behçet's syndrome with mucocutaneous and cardiac involvement was established. The patient was kept on colchicine and was also started on immunosuppressive therapy with corticosteroids and azathioprine, with resolution of the symptoms in the following day. A positron emission tomography (PET) was performed 2 days after discharge and showed a higher myocardial uptake in the left ventricular basal segments and both papillary muscles. Prednisolone tapering was started after 2 months, while maintaining azathioprine. At 1-year follow-up, the patient remained asymptomatic. A re-evaluation PET was performed, showing no images suggestive of metabolically active disease in the myocardium.

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Discussion This case highlights the importance of awareness of this rare but potentially serious entity and reinforces the significance of aetiology investigation in cases of recurrent myocarditis. It also shows the success of immunosuppressive therapy in a context where the optimal management is still considerably uncertain.

Keywords Myocarditis • Behçet disease • Auto immune disease • Case report

Learning points

Our case:

- Emphasizes the importance of aetiology investigation in cases of recurrent myocarditis.
- Raises awareness for Behçet's syndrome as a possible rare aetiology underlying myocarditis.
- Demonstrates the relevance of aggressive immunosuppressive therapy with high-dose glucocorticoids and azathioprine in a field where the optimal therapy scheme is unknown.

Introduction

Behçet's syndrome is a multisystemic vasculitis of unknown aetiology.[1] Cardiac involvement is rare, with described prevalence between 1% and 46%.[2–4] Cardiac abnormalities reported in the literature include pericarditis, myocarditis, endocarditis, intracardiac thrombosis, endomyocardial fibrosis, coronary arteritis with or without myocardial infarction, and coronary arteries or sinus of Valsalva aneurysms.[4]

Timeline

Time	Events
1 Year prior to presentation	Recurrent buttock folliculitis and axillary hidradenitis
Day 0	Admission to the emergency department with chest pain and dyspnoea since the previous day
Day 1	Coronary angiography showed no coronary stenosis or aneurysms. Diagnosis of presumed myocarditis. Treatment with aspirin as needed and colchicine
Day 3	Discharged from hospital
1 month after initial presentation	Cardiac magnetic resonance imaging showed late epicardial enhancement in the apical segment of the lateral wall, consistent with the diagnosis of myocarditis
4 months after initial presentation	Return to the emergency department with recurrence of persistent chest pain with no pleuritic characteristics, fever, sore throat, odynophagia, and otalgia with a week of duration. Oropharyngeal examination revealed tonsillar pillars aphthosis with exudate. Recurrent myocarditis with possible bacterial tonsillitis was diagnosed, and the patient was hospitalized. Ibuprofen, colchicine, and antibiotic therapy was started
4 months and 2 days after initial presentation	Persistence of fever, chest pain, and elevation of inflammatory markers despite treatment. Thorough physical exam noting an ulcerated scrotal lesion, left buttock folliculitis, and axillary hidradenitis. Diagnosis of Behçet's syndrome with mucocutaneous and cardiac involvement was established. The patient was kept on colchicine and was also started on immunosuppressive therapy with corticosteroids and azathioprine
4 months and 13 days after initial presentation	Discharge from hospital
4 months and 15 days after initial presentation	A positron emission tomography (PET) with fludeoxyglucose (FDG) showed a more intense myocardial uptake in the left ventricular basal segments, as well as in both papillary muscles

Continued

Case presentation

A 26-year-old man, smoker but otherwise healthy, was admitted to the emergency department with atypical chest pain with no radiation and no relation to efforts, position or deep inspiration; associated with dyspnoea, since the day before. There was no history of previous flu-like symptoms, fever, or gastrointestinal symptoms. On examination, the patient was haemodynamically stable, afebrile, and eupnoeic; no pericardial friction rub and no cardiac murmurs were noted. Electrocardiogram (ECG) revealed an early repolarization pattern with no changes noted in subsequent exams (*Figure 1A*). His blood test results showed neutrophilic leucocytosis (white blood cell

Continued

Time	Events
6 months after presentation (2 months after initiation of immunosuppressant therapy)	Weaned from steroids
1 year after presentation (6 months after initiation of immunosuppressant therapy)	Follow-up PET-FDG showed no images suggestive of metabolically active disease. The distribution of FDG in the myocardium presented as a diffuse pattern, without individualization of hypermetabolic foci

Table 1 Cases of cardiac involvement in Behçet disease—review of the literature (1990–2019)

First author, year	Type of cardiac involvement	Treatment	Outcome
Marzban *et al.*, 2008[1]	Severe aortic insufficiency	Corticosteroids; surgery	Complete remission
Kusuyama *et al.*, 2002[2]	Aortic insufficiency and aneurysm of sinus of Valsalva	Surgery	Complete remission
Vanhaleweyk *et al.*, 1998[3]	Intracardiac thrombosis (right atrium and ventricle and left ventricle)	Anticoagulant, corticosteroids, cyclophosphamide	Complete remission
Basaran *et al.*, 2000[4]	Intracardiac thrombosis	Anticoagulant; corticosteroids; surgery	Relapse (surgical excision)
Yakut *et al.*, 2007[5]		Anticoagulant, corticosteroids, cyclophosphamide	Complete remission
Baykan *et al.*, 2001[6]		Anticoagulant, corticosteroids, cyclophosphamide	Complete remission
Cevik *et al.*, 2009[7]		Anticoagulant	Complete remission
Noureddine *et al.*, 2004[8]		Corticosteroids	Complete remission
Kirali *et al.*, 1998[9]		Surgery	Complete remission
Chiari *et al.*, 2008[10]		Anticoagulant; corticosteroids; immunosuppressants	Complete remission
Dogan *et al.*, 2007[11]		Anticoagulant; corticosteroids; immunosuppressants	Complete remission
Darie *et al.*, 2005[12]	Right ventricular thrombus and endo-myocardial fibrosis	Surgery	Complete remission
Soulami *et al.*, 1996[13]		—	Death
Kosar *et al.*, 2005[14]	Acute myocardial infarction	Colchicine	Partial remission
Beyranvand *et al.*, 2009[15]		Corticosteroids	Partial remission
Rolland *et al.*, 1993[16]	Left ventricular and coronary artery aneurysms	Surgery	Complete remission
Marashi *et al.*, 2005[17]	Left ventricular pseudoaneurysm	Surgery	Complete remission
Nakata *et al.*, 1995[18]	Right atrial vegetation	Corticosteroids	Complete remission
Kwon *et al.*, 2006[19]	Pericarditis and cardiac tamponade, coronary arteritis	Colchicine; corticosteroids; surgery	Complete remission
Jagadeesh *et al.*, 2014[20]	Pericarditis	Corticosteroids; methotrexate; pericardiocentesis. Patient intolerant to azathioprine, 6-mercaptopurine, mycophenolate, thalidomide	Complete remission
Lewis *et al.*, 1964[21]	Myopericarditis	Aspirin	Complete remission
Satoshi *et al*, 2014[22]	Giant-cell myocarditis	—	Death
Felix *et al*, 2016[23]	Myocarditis and dilated cardiomyopathy	Corticosteroids; azathioprine; ICD	Partial remission
Jagadeesh *et al.*, 2014[20]	Dilated cardiomyopathy	Colchicine, AINE's; corticosteroids; azathioprine Beta-blocker, IECA and diuretics; CRT-D	Partial remission
Scheuble *et al.*, 2003[24]		—	—
Mustafa *et al.*, 2010[25]		Corticosteroids	Partial remission
Kaatz *et al.*, 1998[26]		Corticosteroids; azathioprine	Complete remission

References provided in the Supplementary material online.

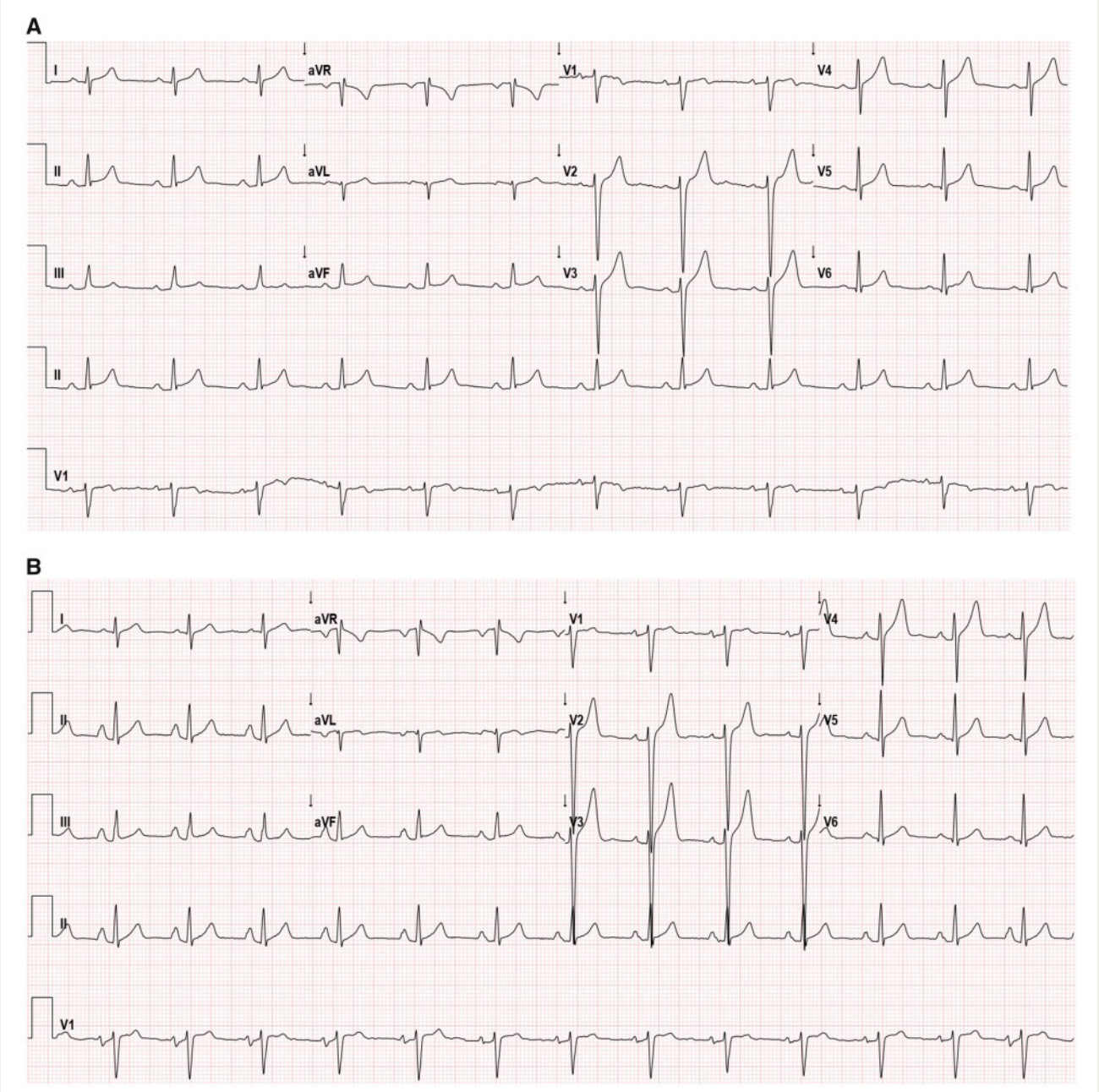

Figure 1 (*A*) Twelve-lead electrocardiogram at initial presentation with early repolarization pattern. (*B*) Twelve-lead electrocardiogram at the second hospital admission with no evolution noted when compared to the previous electrocardiogram.

count of 13.3 × 10^9/L—normal range 4–10.0 × 10^9/L), a normal C-reactive protein (0.68 mg/dL—normal value < 0.05 mg/dL), mild elevation of erythrocyte sedimentation rate (ESR) of 20 mm/h (normal value < 14 mm/h), and an increased initial high-sensitivity troponin level of 3300 ng/L (normal value < 34.2 ng/L). Transthoracic echocardiography (TTE) was unremarkable, with no pericardial effusion. Invasive coronary angiography showed no coronary stenosis or aneurysms (*Figure 2*). A presumed diagnosis of non-complicated viral myocarditis was established. The patient's condition improved with aspirin as needed and colchicine, and he was discharged after a 3-day in-hospital stay with complete resolution of his symptoms. Cardiac magnetic resonance (*Figure 3*) was performed 1 month after presentation, with identification of an area of late epicardial enhancement, located in the apical segment of the lateral wall, supporting the diagnosis of myocarditis. Four months later, the patient returned to the emergency department with recurrence of chest pain. Additionally, he also complained of fever, sore throat, odynophagia, and otalgia since the previous week. Oropharyngeal examination revealed the tonsillar pillars aphthosis with exudate, while his otoscopy was normal. The ECG was similar to the one of the previous hospitalization

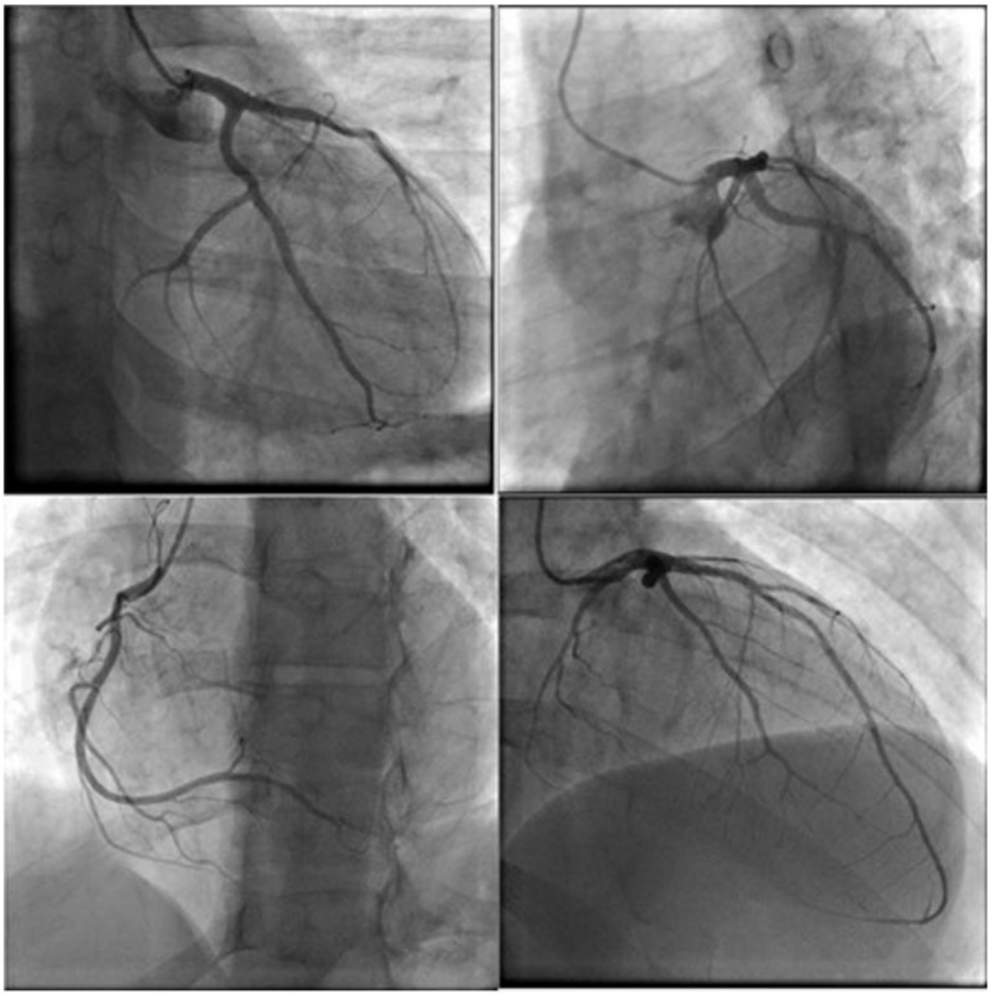

Figure 2 Invasive coronary angiography showing no coronary stenosis.

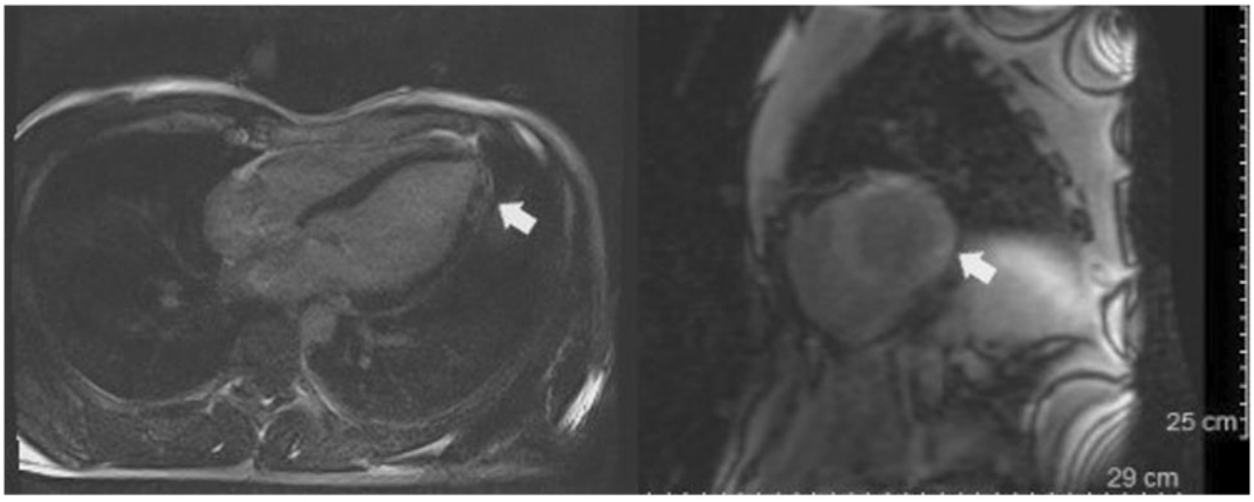

Figure 3 Cardiac magnetic resonance with identification of an area of late epicardial enhancement, located in the apical segment of the lateral wall, reinforcing the diagnosis of myocarditis.

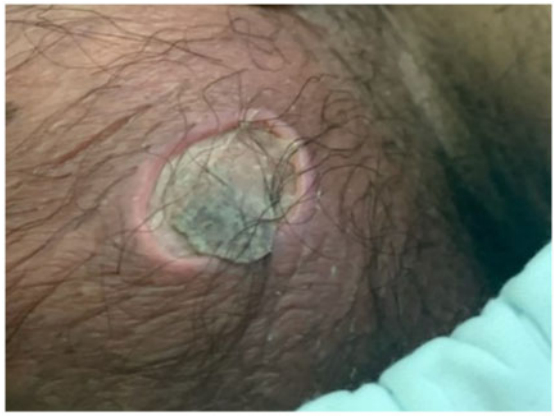

Figure 4 Ulcerated scrotal lesion.

(*Figure 1B*) and TTE was again normal. Bloodwork revealed once more elevation of inflammatory markers (white blood cell count of 14.0×10^9/L, C-reactive protein of 4.02 mg/dL, and ESR of 140 mm/h) and elevation of troponin (2828 ng/L). There was a normal platelet count (338×10^9/L—normal range 150–400 $\times 10^9$/L) and coagulation parameters (INR: 1.07—normal range 0.88–1.12). Recurrent myocarditis was diagnosed, and the patient was hospitalized. Treatment with ibuprofen and colchicine was started and, given the possibility of concomitant bacterial tonsillitis, he was also initiated on antibiotic therapy. Despite treatment, there was no significant improvement, with persistence of fever and elevation of inflammatory markers. After a more thorough physical examination, an ulcerated scrotal lesion (*Figure 4*), a left buttock folliculitis, and axillary hidradenitis were found, which, according to the patient, were recurrent for the last year. Accordingly, the diagnosis of Behçet's syndrome with mucocutaneous and cardiac involvement was established. The patient was kept on colchicine 1 mg per day, and was also started on

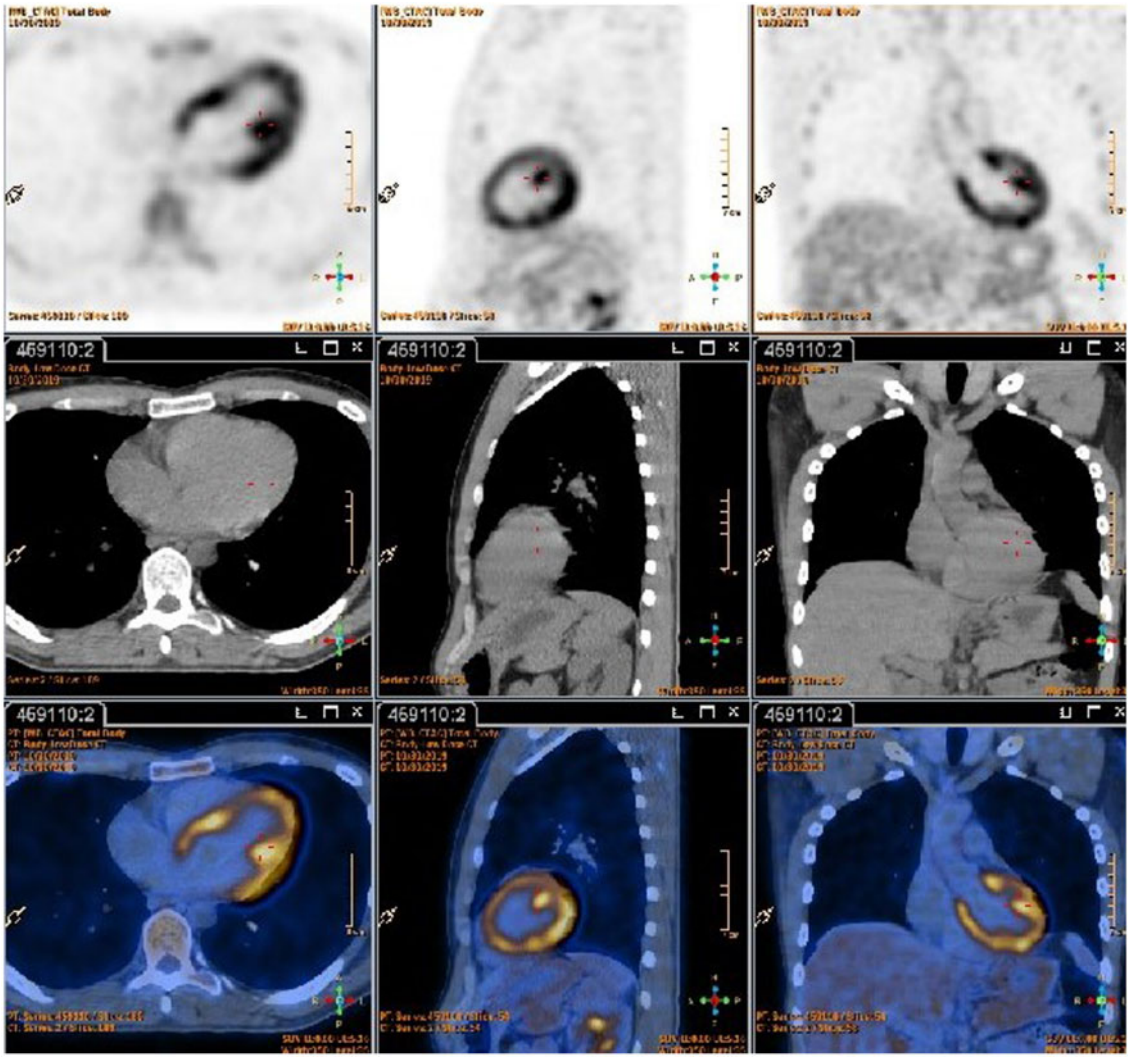

Figure 5 A positron emission tomography with fludeoxyglucose performed 2 days after discharge of the second hospitalization. It shows a more intense myocardial uptake at the left ventricular basal segments, and in both papillary muscles, corresponding to the locations with active inflammation.

immunosuppressive therapy with corticosteroids (initial 1 g 3-day pulse of methylprednisolone followed by prednisolone 1 mg/kg daily) and azathioprine (2.5 mg/kg daily) with resolution of the symptoms on the following day. A positron emission tomography (PET) with fludeoxyglucose (FDG) was performed 2 days after discharge (*Figure 5*) and showed a higher myocardial uptake in the left ventricular basal segments, as well as in both papillary muscles with no other foci of abnormal uptake. Prednisolone tapering was started after 2 months, while remaining on long-term azathioprine (100 mg daily) and colchicine (1 mg daily) therapy. At 1-year follow-up, the patient remained asymptomatic, with complete resolution of ulcerated and aphthous lesions and with no recurrence of chest pain. A re-evaluation PET was performed at that time, showing a uniform capture of FDG in the myocardium, with no images suggestive of metabolically active disease.

Discussion

Behçet's syndrome was first described in 1937 and it is classified as an inflammatory vascular systemic disease with an aetiopathogenesis that remains unknown.[1] As there is a lack of a universally recognized pathognomonic test, Behçet's syndrome diagnosis is primarily based on clinical criteria. Recurrent mucocutaneous lesions (oral aphthosis), skin lesions (papulopustular lesions, erythema nodosum, and skin ulcers), ocular findings (uveitis/retinitis/hypopyon-iritis), and reactivity to needle prick test are the most common clinical findings. Currently, the International Criteria for Behçet Disease (ICBD), reviewed in 2013,[5] are recommended as a guide for diagnosis, with a score ≥4 being supportive of Behçet's syndrome with estimated sensitivity of 93.9% and specificity of 92.1%. In this case, the patient had an ICBD score of 6.

The real prevalence of cardiac involvement in Behçet's syndrome remains unknown as it can be asymptomatic. The reports in the literature are very discrepant, with prevalence between 1% and 46%.[2,6] It is estimated to be the first manifestation of the disease in <2% of the cases.[2,3] The mean age at diagnosis in this specific group is 29.7 ± 9.9 years[7] and cardiac lesions are predominantly reported in men and in the first years of the disease's diagnosis, characteristics that are in conformity with our case.

In the largest review available, in 52 Behçet's syndrome patients with cardiac involvement,[7] pericarditis was the most common form (38.5%), followed by valvular insufficiency (26.9%), intracardiac thrombosis (19.2%), myocardial infarction (17.3%), and endomyocardial fibrosis (7.7%). In other series sinus of Valsalva aneurysms and aortitis were the most frequently reported cardiac complications.[8] Myocarditis related to Behçet's syndrome is very rare, with diagnosis in only 1.2% of the autopsies performed in a cohort of Japanese patients with Behçet's syndrome[9] and described in some series as isolated cases, with some developing heart failure in the context of dilated cardiomyopathy.[4,6,8,10–12]

Although veins are more frequently affected by vasculitis in Behçet's syndrome, arteries of any size can also be involved,[12] which seems to be the most prevalent underlying mechanism of cardiovascular manifestations. Necrotizing leucocytoclastic or polymorphonuclear, obliterative perivasculitis, and lymphocytic cell infiltration of capillaries, arteries, and vasa vasorum are the main pathologic features in affected tissues during acute phases. In advanced stages, a significant fibrosis and scarring may develop.[13]

Little is known about the optimal treatment for the patients with Behçet's syndrome. It is usually determined by the degree of systemic manifestations and involves a therapeutic combination of colchicine, corticosteroids, and/or other immunosuppressants.[13] The level of uncertainty increases in the context of Behçet's syndrome with myocarditis, with no guidelines established for this entity so far.[14] In the cases of reported Behçet's syndrome with cardiac involvement in a presumed context of vasculitis (*Table 1*) the majority of the authors report the use of a combination of colchicine,[3,14] corticosteroids,[2,3,14] and azathioprine.[12] Although there is no data in the literature about the recurrence rate of myocarditis in Behçet's syndrome, in the previously cited review article,[7] relapse of symptoms is documented in 35% of the patients with pericarditis.

In this case, anti-inflammatory therapy and colchicine only were clearly insufficient to control symptoms related to myocarditis, supporting an important role for stronger immunosuppressants in this kind of presentation.

Annual mortality in Behçet's syndrome varies between 2% and 4%. Studies show that overall survival in the patients with cardiac involvement is significantly worse than in those without, with a documented 5-year survival rate of 83.6% vs. 95.8% ($P = 0.03$), respectively.[3]

Conclusions

This case highlights the importance of awareness of this rare but potentially serious entity and emphasizes the significance of aetiology investigation in cases of recurrent myocarditis. It also shows the success of immunosuppressive therapy in a context where the optimal management is still considerably uncertain.

Lead author biography

Ana Moura, MD, is currently a third year resident in Hospital Distrital de Santarém, Portugal. She received an MD degree from Instituto Ciências Biomédicas Abel Salazar—University of Porto in 2016.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and

associated text has been obtained from the patient in line with COPE guidance.

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