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Vascular Behcet's Disease Preceded by Fever of Unknown Origin: Usefulness of Ultrasonography for the Detection of Large-Vessel Vasculitis

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Behcet's disease is a systemic vasculitis characterized by oral and genital ulcers, erythema nodosum, and ocular involvement. Fever of unknown origin is a relatively rare event in Behcet's disease. We present the case of a 17-year-old male patient who suffered from prolonged fever for two months. The patient tested positive for HLA-B52 and levels of acute phase reactants were elevated. He complained of sore throat and neck pain that were evaluated by cervical ultrasonography, which revealed thickening of the carotid arterial wall and narrowing of the vessel lumen. The patient was diagnosed with vascular Behcet's disease and treated with glucocorticoid, which improved the clinical symptoms and thickening of the carotid arterial wall as detected by color duplex ultrasonography. Since vascular Behcet's disease may lead to morbidity and mortality, we suggest the early use of ultrasonography to help detect medium/large-vessel vasculitis. Prolonged fever in patients with Behcet's disease should be promptly evaluated for vascular involvement.

Keywords: color duplex ultrasonography; fever of unknown origin; vascular Behcet's Disease
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Introduction

Behcet's disease (BD) is a chronic multisystem disorder characterized by oral and genital aphthae, cutaneous lesions, and ophthalmic and rheumatic manifestations. Other inflammatory symptoms that may be seen in patients with BD include arthritis, colitis (intestinal BD), central nervous system inflammation (neurologic BD), and various forms of vasculitis (vascular BD) (Sakane et al. 1999; Hamdan et al. 2006). Vascular BD is rare and affects approximately 8% of Japanese patients with BD (Kirino et al. 2016). Although ophthalmic or cutaneous manifestations are the common initial symptoms of BD, fever may also accompany acute manifestations of BD (Niamane et al. 2005). However, fever is rarely the sole manifestation (Saltoglu et al. 2004; Niamane et al. 2005). Therefore, vascular BD should be considered in the differential diagnosis for fever of unknown origin (FUO) (Tascilar et al. 2014). In this report, we present the case of a 17-year-old male Japanese patient who presented with FUO and was later diagnosed with vascular BD.

Case Presentation

A 17-year-old male Japanese patient was referred to our hospital for in-depth examination of FUO. He had no significant medical history. The patient reported that two months prior to admission in our hospital he developed a new-onset dry cough that was not relieved by cough medicine. Thereafter, he gradually developed a fever of 38℃. He was admitted to a community hospital where they ruled out respiratory disease as the cause of the fever. Computed tomography (CT) showed a slight left pleural effusion but otherwise revealed no abnormal findings. Blood tests showed a high C-reactive protein (CRP) level of 14 mg/dL. The patient was admitted and observed for a week to rule out transient viral infection. During this period, he reported a sore throat and left neck pain with redness, pain, and itching in the glans. The patient reported no history of sexual

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Table 1. Laboratory findings on admission.

Peripheral blood		Erythrocyte sedimentation rate	52 mm/hr (< 15)
Red blood cells	477 × $10^4/\mu$L	sIL-2R	833 U/ml (121-613)
Hemoglobin	12.9 g/dL	IgG	1,963 mg/dL (861-1,747)
Hematocrit	40.9%	IgA	510 mg/dL (93-393)
Platelets	56.9 × $10^4/\mu$L	IgM	194 mg/dL (50-269)
White blood cells	12,800/μL	Complement 3	206 mg/dL (73-138)
Neutrophil	77%	Complement 4	42 mg/dL (11-31)
Eosinophil	0%	ANA	< 80 (0-159)
Monocytes	9%	Anti-ds-DNA Ab	(−) (< 9.9)
Lymphocytes	13%	Anti-SSA Ab	< 0.5 U/mL (−) (< 6.9)
Basophil	1%	Anti-SSB Ab	(−) (< 6.9)
Blood chemistry		PR3-ANCA	(−) (< 2.0 U/mL)
Total protein	8.6 g/dL	MPO-ANCA	(−) (< 3.5 U/mL)
Total bilirubin	0.7 mg/dL	Serum amyloid A	802.5 μg/mL(0-8)
Albumin	3.5 g/dL	Human Leukocyte Anigen	A23, A33, B07, B52
Asparate aminotransferase	37 IU/L (13-30)	Microbiologocal tests	
Alanine aminotransferase	72 IU/L (10-42)	HBs Ag	(−)
Lactate dehydrogenase	155 IU/L (124-222)	Anti-HCV Ab	(−)
Alkaline phosphatase	858 IU/L (106-322)	HIV-Ab	(−)
Creatine Kinase	64 IU/L (41-153)	Nontreponemal test	(−)
Blood urea nitrogen	13 mg/dL	β-D glucan	< 6.0 (0-11.0)
Creatinine	0.79 mg/dL	Tuberclosis specifix interferon γ	(−)
Ferritin	319 ng/mL	Blood culture	(−)
Sodium	138 mEq/L	Anti-streptolysin O	102 IU/mL (0-240)
Potassium	4.8 mEq/L	Anti-streptkinase	640 (0-1,280)
Chloride	98 mEq/L	Urinalysis	
Blood sugar related tests		Blood	(3+)
Postprandial plasma glucose	99 mg/dL	Protein	(±)
Coagulation tests		Sugar	(−)
D-dimer	1.2 μg/mL	Dysmorphic red blood cell	(+)
Immunoserological tests		Erythrocyte column	1-4/whole field
C-reactive protein	18.94 mg/dL (< 0.30)	Epithelical column	1-4/whole field

ANA, anti-nuclear antibody; Anti-ds-DNA Ab, anti-double stranded DNA antibody; Anti-HCV Ab, anti-hepatitis C virus antibody; HBsAg; hepatitis B virus surface antigen; HIV-Ab, human immunodeficiency virus antibody; IgA, immunoglobulin A; IgG, immunogolobulin G; IgM, immunoglobulin M; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; sIL-2R, soluble interleukin-2 receptor.
Reference values are shown in parentheses.

intercourse and tests for sexually transmitted diseases, including human immunodeficiency virus and other viral infections, were negative. Results of contrast-enhanced CT (CECT) of the trunk were not informative. Tests for human leukocyte antigens (HLA) A26 and B51 were negative.

The patient presented to our hospital with prolonged fever and elevated markers of inflammation. At the time of admission, his body temperature was 39.5℃, heart rate was 118 beats/min, and blood pressure was 111/65 mmHg. A physical examination revealed redness in the glans and erythema with infiltration in the lower extremities. Laboratory results showed elevation of erythrocyte sedimentation rate (52 mm/h), CRP (18.94 mg/dL), and serum amyloid A (802.5 μg/mL) (Table 1). Urinalysis showed 3+ hematuria, and a kidney biopsy revealed immunoglobulin A nephropathy. Tests of autoantibodies for collagen diseases were negative. Culture and specimen of blood, sputum, urine, and glans fluid were negative. A chest X-ray showed pulmonary artery dilation (Fig. 1 A).

The patient's sore throat and neck pain prompted a carotid artery echocardiography to rule out large-vessel vasculitis syndrome or other vasculitis. Results showed maximum wall thickening of three millimeters and intramural blood flow from the left common carotid artery to the carotid sinus (Fig. 2). Another CECT showed wall thickening of the ascending aorta to the cervical aorta and to the branch arteries of the neck (i.e., the brachiocephalic, left common carotid, and left subclavian arteries) and dilation of the main trunk of the pulmonary artery. A skin biopsy of the erythema nodosum in the lower extremities revealed

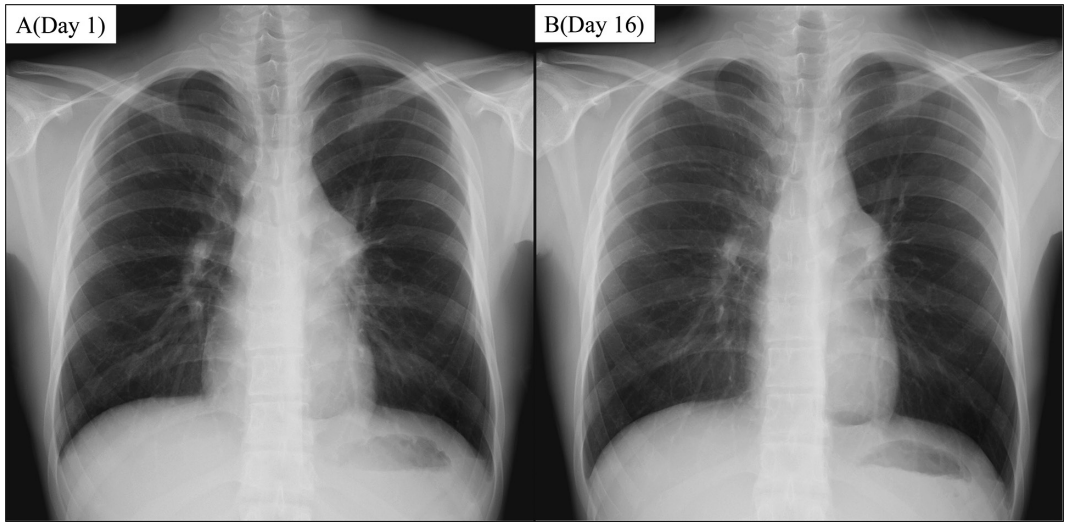

Fig. 1. Chest X-ray before and after treatment.
(A) Chest X-ray on the first day of admission showed protrusion of the left second arch (pulmonary artery) and enlargement of the cardiac shadow. (B) Chest X-ray on the sixteen days after admission showed improvement of abnormal shadows in the mediastinum and heart.

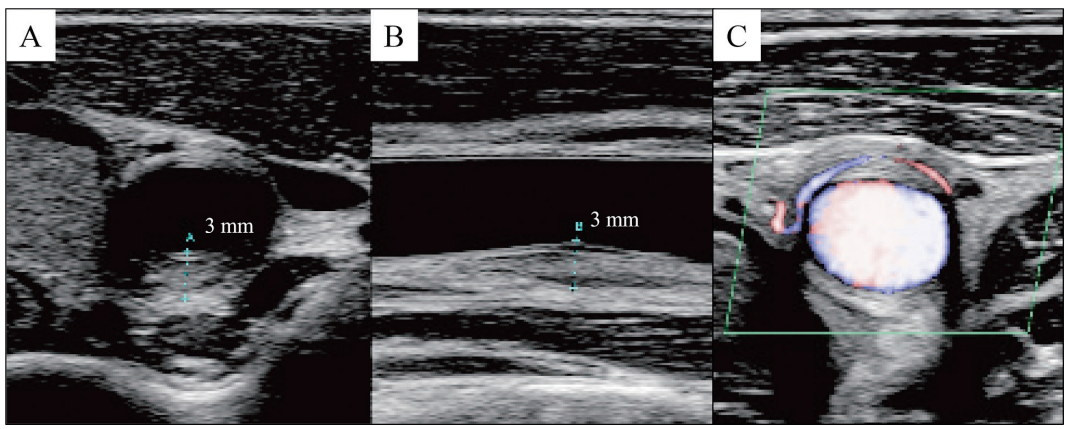

Fig. 2. Color duplex ultrasonography (CDU) features of left common carotid artery before glucocorticoid therapy.
(A, B) Ultrasonography (B-mode) showed the vessel-wall-thickening (the maximum thickness of arterial wall was 3 mm); transverse (A) and longitudinal (B) view. (C) CDU showed blood flow signals in the vessel wall suggestive of inflammation.

thrombophlebitis (Fig. 3). Fundus examination showed no obvious active inflammation; however, posterior iridocorneal adhesions and suprachoroidal pigmentation were observed. The patient fulfilled the diagnostic criteria of the International Study Group for Behcet's Disease (International Team for the Revision of the International Criteria for Behcet's Disease 2014): recurrent genital aphthosis, skin lesions, and vascular manifestations. The clinical course is summarized in Fig. 4.

The patient received pulse therapy with corticosteroids [methylprednisolone, 1,000 mg/day IV for three consecutive days (day 9, 10 and 11)], followed by 60 mg of oral prednisolone. After completion of therapy, we observed improvement in fever, cough, sore throat, neck pain, redness in the glans, and erythema of the lower extremities. Glucocorticoid therapy was tapered and discontinued. Levels of inflammatory markers decreased, and a repeat chest X-ray showed reduction of the pulmonary artery shadow (Fig. 1 B). Seven weeks after glucocorticoid treatment, vascular wall thickness decreased to 1.3 mm, and left carotid artery intramural blood flow improved (Fig. 5).

Informed consent was obtained from the patient. Because of a case report of single patient, ethical approval was waived for institutional review board in Fukushima Medical University.

Discussion

BD is an autoinflammatory disease characterized by recurrent oral and genital ulcers with chronic relapsing uveitis and skin lesions and the highest reported prevalence of BD is in the Japanese population (Ishido et al. 2017). Vascular BD may present with musculoskeletal, neurologi-

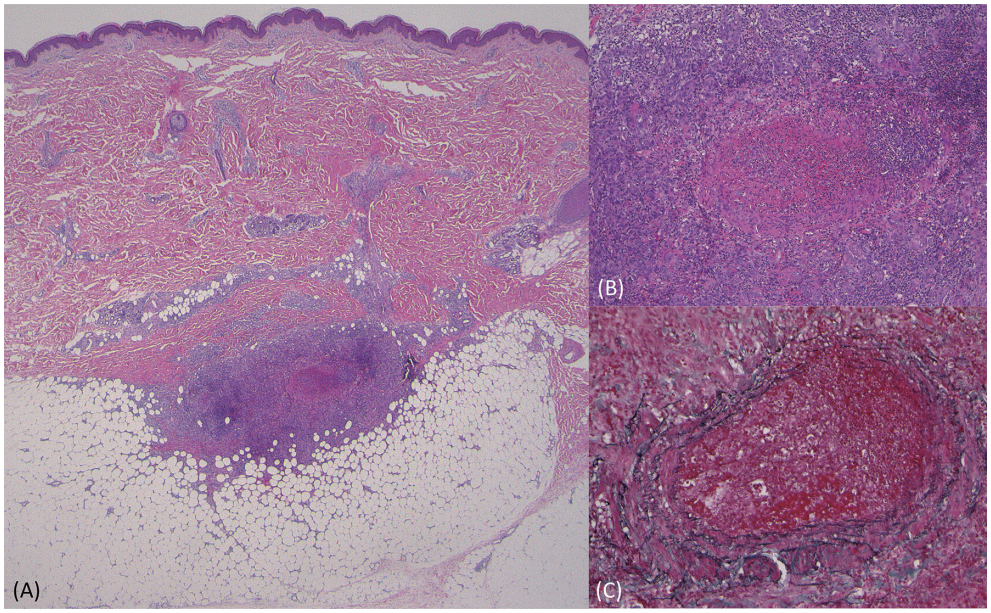

Fig. 3. Histological features showed thrombus in the lumen of blood vessels in lower dermis and subcutaneous tissue.
(A, B) Inflammatory cells, mainly neutrophils, histiocytes and lymphocytes, infiltrated within the damaged vessel walls (hematoxylin-eosin stain, original magnification: A; × 12.5, B; × 200). (C) Immunohistochemistry revealed that the affected blood vessels were veins because the elastic fiber were rich in the vessel wall. (elastica-masson stain, original magnification: C; × 200).

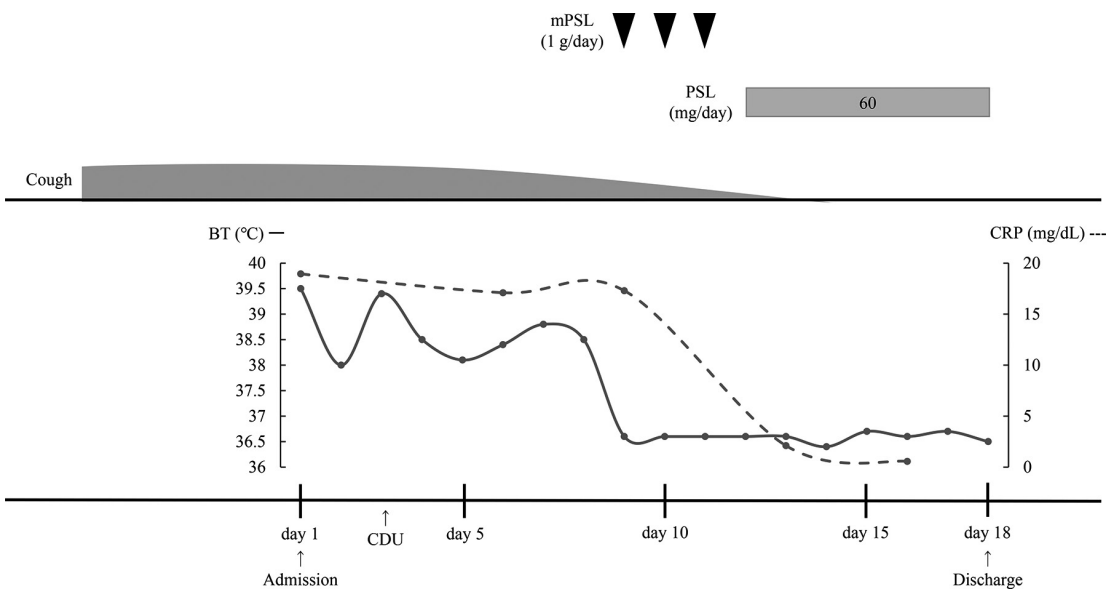

Fig. 4. Clinical course.
After the examination, the patient received pulse therapy with corticosteroids [methylprednisolone, 1,000 mg/day IV for three consecutive days (day 9, 10 and 11)], followed by 60 mg of oral prednisolone. After completion of therapy, we observed improvement in fever. Glucocorticoid therapy was tapered and discontinued. Levels of inflammatory markers decreased.
BT, body temperature; CRP, C-reactive protein; mPSL, methylprednisolone; PSL, prednisolone; CDU, color duplex ultrasonography.

cal, and gastrointestinal involvement, and it may involve veins and arteries of all sizes (Lie 1992). Presentations with recurrent ulcers and uveitis are common; however, vascular involvement may precede these findings (Sarica-Kucukoglu et al. 2006; Melikoglu et al. 2008). BD may be associated with life-threating complications such as occlusion/stenosis or aneurysm of large vessels (Baki et al. 2006; So and Yip 2014). Therefore, these serious consequences should be diagnosed promptly and treated precisely.

Clinical manifestations in this case were remarkable

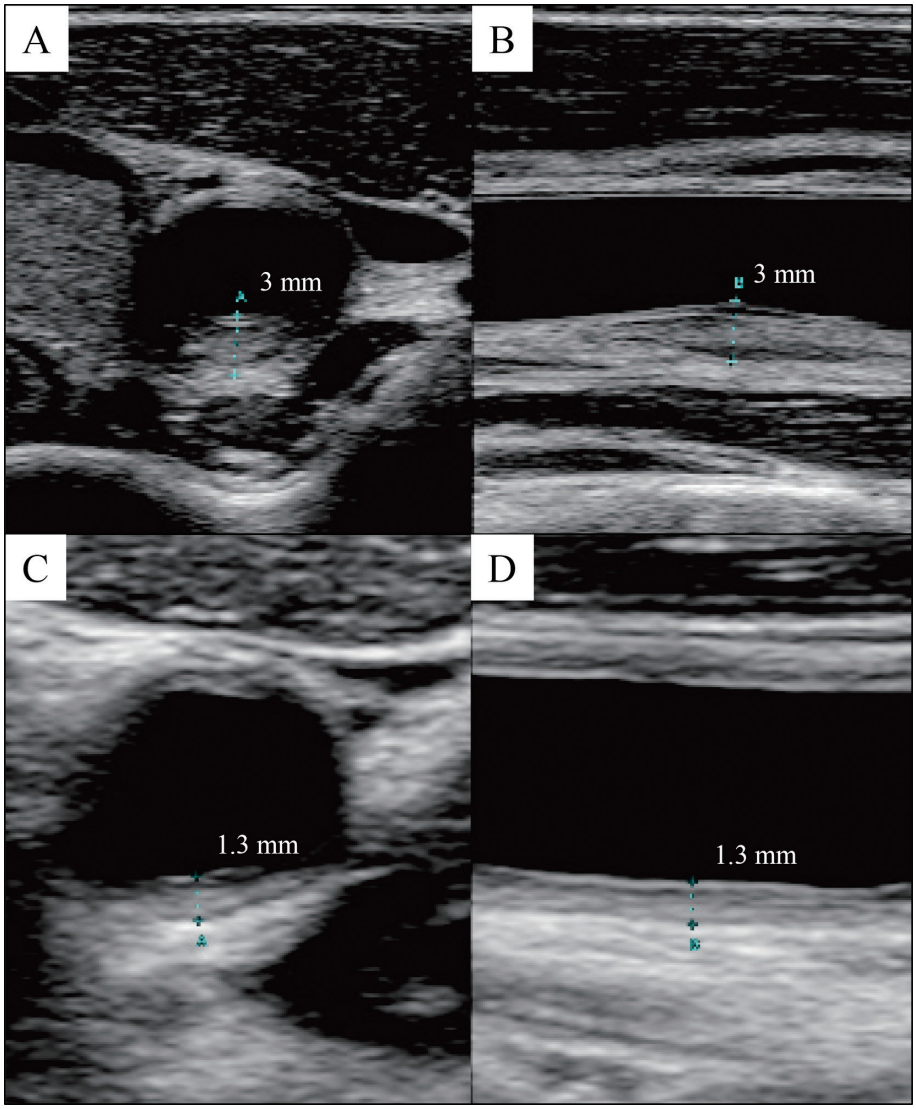

Fig. 5. Color duplex ultrasonography (CDU) features of left common carotid artery after glucocorticoid therapy.
(A, B) Before treatment, CDU features of left common carotid artery before glucocorticoid therapy showed the vessel-wall-thickening (The maximum thickness of arterial wall was max 3 mm); transverse (A) and longitudinal (B) view. (C, D) Post treatment, CDU features of left common carotid artery showed reduction of vessel-wall-thickening (the maximum thickness of arterial wall was 1.3 mm); transverse (C) and longitudinal (D) view.

because they involved large-vessel vasculitis that extended to the carotid and pulmonary arteries despite a lack of vascular symptoms. Corresponding with previous case reports (Sarica-Kucukoglu et al. 2006; Melikoglu et al. 2008), our patient presented with unexplained fever, which could be an important initial sign of vascular BD. Patients presenting with FUO are typically younger and have more severe inflammatory responses than those with other common signs and symptoms (Yazici et al. 1984). Vision loss or other signs of central nervous system ischemia that is consistent with other large-vessel vasculitis involving the carotid arteries may be observed in vascular BD (Reynolds 2008; Mendes et al. 2009; Ksiaa et al. 2019). However, a diagnosis may be delayed because overt vascular symptoms are not present in most patients (Cinar et al. 2017).

Vascular inflammation resulting in thickening of the arterial wall and narrowing lumen is a common finding in medium/large-vessel vasculitis (Isobe et al. 2020). Magnetic resonance imaging (Akpolat et al. 2000), positron emission tomography (Furuya et al. 2019), and CECT are currently recommended for diagnosis of BD, but there is no diagnostic standard (Ishibashi 2018). It should be noted that CT or conventional angiography requires special expertise, and there is a risk of iodine allergy and arterial injury (Tavakol et al. 2012).

Ultrasound has been proposed as a safe and valuable routine screening tool for large-vessel vasculitis, with evidence in diseases such as Takayasu arteritis (Brkic et al. 2019) and giant cell arteritis (Monti et al. 2018). Therefore, it may be useful in vascular BD with cervical or subclavian

arterial involvement. The presence of unexplained fever, such as the one in the present case, may benefit from diagnostic imaging to detect signs of vascular wall swelling and lumen stenosis/occlusions. The guidelines given by the European League Against Rheumatism do not recommend any single method, but defer imaging decisions to the resources and expertise of the local clinical site (Hatemi et al. 2018). The diagnostic algorithm for vascular BD depends on the clinical presentation and the available imaging method. The use of ultrasound is not well established in vascular BD, but the procedure can detect early vasculitis and may be useful for monitoring disease progression and therapeutic response. Therefore, we recommend compression ultrasound for the initial diagnosis work-up of supra-aortic arteries in cases of unexplained fever, because it is accessible, inexpensive, repeatable, and does not require radiation.

In conclusion, vascular BD should be kept in mind as a differential diagnosis for FUO, even in young patients. Clinical and imaging assessment of large-vessel vasculitis is important in the diagnosis of vascular BD. The use of ultrasound in patients with vascular BD may be valuable, because it is accessible and does not require radiation or contrast media.

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Conflict of Interest

The authors declare no conflict of interest.

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