CASE REPORT

DOI: 10.5336/caserep.2021-85044

Positron Emission Tomography/Computed Tomography as a New Diagnostic Tool in Incomplete Behçet's Disease Manifesting with Inflammatory Vascular Thrombosis

Zeynep Canan ÖZDEMİR[a], Aslı KAVAZ TUFAN[b], İlknur AK SİVRİKOZ[c], Ersin TÖRET[a], Özcan BÖR[a]

[a]Division of Pediatric Hematology/Oncology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[b]Division of Pediatric Nephrology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[c]Department of Nuclear Medicine, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye

ABSTRACT Behçet's disease (BD) is a multisystemic inflammatory disease. Diagnosis is difficult in patients who do not fully meet the diagnostic criteria. A 9-year-old male patient presented with right common and deep femoral vein thrombosis. Low-molecular-weight heparin (LMWH) was administered due to deep venous thrombosis. The patient developed pulmonary embolism on the 9th day of treatment. LMWH was discontinued, and unfractionated heparin (UFH) with tissue plasminogen activator (tPA) combination was given for 5 days. After discontinuation of tPA treatment, UFH was continued. On the 20th day of treatment, the patient developed another thrombosis in the left iliac vein and embolism in the anteromedial-basal segmental branches of the left pulmonary artery. tPA was re-administered. The positron emission tomography/computed tomography (PET/CT) findings supported vascular inflammation in the inferior vena cava and popliteal vein. The patient was diagnosed with incomplete BD due to uveitis and thromboses coexisting with vascular inflammation. PET/CT can be used as a tool to examine for vascular inflammation that would support BD in patients with anticoagulant and thrombolytic therapy-refractory thrombosis.

Keywords: Behçet's disease; child; vascular thrombosis; positron emission tomography/computed tomography

Behçet's disease (BD) is a chronic and multisystemic inflammatory disease of unknown etiology and causes significant morbidity. Five cross-sectional studies showed that the prevalence of BS was between 20-421/100,000 in adolescent/adult population in Turkey.[1] Children constitute approximately 2.5-4.5% of the patients with BD.[2,3] BD is characterized by recurrent oral and/or genital aphthous ulcers along with inflammatory lesions on the skin, in the eyes, joints, gastrointestinal tract, and central nervous system.[3] Systemic vasculitis is considered the main pathology in BD, wherein an important characteristic of the disease is that it can cause any kind and extent of vascular involvement. Therefore, BD is classified as a variable vessel vasculitis.[3] Blood vessels in the venous system are more frequently involved in BD. Patients with BD exhibit thrombotic tendency that cannot be explained by thrombophilic factors.[4,5]

Deep vein thrombosis is a medical condition that occurs when a blood clot forms in a deep vein. These clots usually develop in the lower leg, thigh, or pelvis, but they can also occur in the arm. Symptoms can include pain, swelling, redness, and enlarged veins in the affected area. Pulmonary embolism is the most common complication of deep vein thrombosis and can be life threatening.

^{18}F fluorodeoxyglucose (^{18}F FDG) positron emission tomography/computed tomography (PET/CT) is

Correspondence: Zeynep Canan ÖZDEMİR
Division of Pediatric Hematology/Oncology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
E-mail: efecanan@yahoo.com

Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 18 Jun 2021 ***Received in revised form:*** 22 Oct 2021 ***Accepted:*** 02 Dec 2021 ***Available online:*** 06 Dec 2021

a functional imaging method that has mainly been used in oncology as well as for inflammatory diseases.[6] It is used to diagnose large vessel vasculitis, assess disease activity, and monitor the treatment efficacy.[7]

CASE REPORT

A 9-year-old male patient presented with swelling and pain in the right limb that started 1 week ago. Tenderness and swelling on the upper portion of the right limb were observed. Erythrocyte sedimentation rate (45 mm/h), C-reactive protein level (9.7 mg/dL), and D-dimer level (15.2 mg/L) were high. Doppler ultrasound showed thrombus in the right common and deep femoral veins. The patient was initiated on low-molecular-weight heparin (LMWH). The patient developed chest pain and respiratory distress on the 9th day of treatment. A spiral CT of the thorax revealed partial embolism and filling defects in the lower lobar and segmental branches of the right and left pulmonary arteries. LMWH was discontinued, and the patient was initiated on unfractionated heparin (UFH) in combination with tissue plasminogen activator (tPA). After discontinuation of tPA treatment, intravenous UFH was continued. Doppler ultrasound performed on the 13th day of treatment showed the absence of recanalized flow in the femoral vein despite the treatment and that the thrombosis has extended from the distal aspect of the right femoral vein to the popliteal vein. Protein C, S, antithrombin III, homocysteine, lipoprotein (a), and C3 and C4 levels were normal. In addition, the following results were obtained: lupus anticoagulant was positive; rheumatoid factor, antinuclear antibody, anti-dsDNA, anti-cardiolipin antibodies immunoglobulin G and immunoglobulin M were negative. Heterozygous gene mutation was detected in MHTFR C677T and MTHFR A1298C. Factor V Leiden or prothrombin G20210A mutation was not revealed. The patient complained of severe pain in the left inguinal region on the 20th day of hospitalization. Doppler ultrasound showed thrombosis in the left iliac vein. Simultaneous spiral CT of the thorax showed a newly developed embolism in the anteromedial basal segmental branches of the left pulmonary artery. Therefore, tPA was re-administered. The ophthalmologic examination showed signs of a previous uveitis event. The patient was considered to have BD due to the presence of oral aphthous ulcers recurring every 2 years, findings of ophthalmic examination and thromboses affecting the arteries and veins. Pathergy test (PT) and HLA-B5 results were negative. ^{18}F FDG PET/CT showed diffuse, slightly increased activity in an area extending from the right femoral vein to the popliteal vein and inferior vena cava (Figure 1 and Figure 2). Increased FDG activity in the veins was considered as vessel wall involvement. The patient was treated with methylprednisolone followed by prednisolone, colchicine tablet and cyclophosphamide. Tumor necrosis factor-α inhibitor was added to therapy for resistant and recurring thromboses. The patient did not develop thrombosis following immunosuppressive therapy.

Informed consent was obtained from the patient's parents. They also agreed to the publication of this case.

DISCUSSION

Clinical signs in BD vary based on patients' age, sex, ethnicity and country of residence. However, there is no laboratory or imaging method tailored to BD. The pediatric BD (PEDBD) criteria based on a large PEDBD cohort was first developed in 2015.[8] According to these diagnostic criteria, each symptom is scored 1 point and a score of ≥3 is required to confirm a diagnosis. The symptoms consist of recurrent oral aphthous ulcers (≥3 attacks, per year), genital aphthous ulcers, skin involvement, ocular involvement, and vascular involvement. Oral aphthous lesion is not a mandatory criterion. A positive PT is not included within the criteria. Our patient experienced oral aphthous ulcers every 2 years. Therefore, oral aphthous ulcers were not included in scoring. Of the other symptoms, our patient experienced uveitis (1 point) and arterial-venous thrombosis (1 point). Accordingly, our patient was determined to have a score of 2, as per the PEDBD criteria, and was diagnosed with incomplete BD.

The pathology of venous disease typically involves thrombus formation on the inflamed vessel wall.[4,9,10] On the other hand, arterial involvement en-

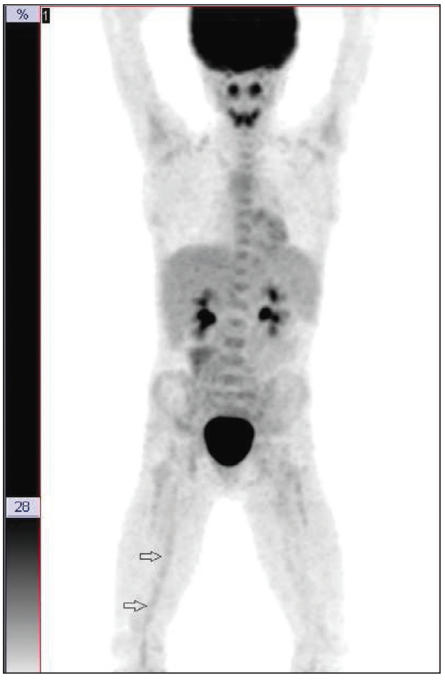

FIGURE 1: Maximum intensity projection positron emission tomography images show the vascular 18F fluorodeoxyglucose uptake in the right femoral area (arrows). The severity of fluorodeoxyglucose uptake is visually graded as Grade 2.

compasses focal aneurysmal dilatations and fibrous thickening in all layers of the vessel wall.[10] The pathogenesis of thrombosis remains unknown, with the underlying mechanisms in BD being unclear. It is considered that the underlying mechanisms are endothelial damage and endothelial dysfunction rather than hypercoagulability.[4,9,10] Other proposed mechanisms consist of decreased nitric oxide, impaired protein C pathway, and increased platelet-derived microparticles.[11]

The frequency of vascular involvement is reportedly 3.6-9.6% in studies conducted with pediatric patients with BD in Turkey.[12] The most common vascular events in adult patients with BD are lower extremity venous thrombosis, which constitute 70% of all vascular events.[13] Other common sites of venous involvement include the inferior or superior vena cava, hepatic veins, cerebral venous sinuses, and right side of the heart.[13,14] Although pulmonary arteries are frequently involved owing to their nature being similar to the venous structures, both aortic and peripheral artery involvement is less common.[14] Our patient showed thrombosis in large blood vessels, such as the popliteal vein, deep femoral vein, inferior vena cava, and pulmonary artery branches. The patient showed the absence of the large and medium artery involvement. FDG PET/CT showed vascular inflammation in addition to thromboses. Therefore, the thromboses were considered to be associated with vasculitis.

Vasculitis can be classified as large, medium, small, and variable vessel vasculitis. Large vessel vasculitis involves the aorta and aortic branches. Medium vessel vasculitis mainly involves the main visceral arteries and their branches, known as the

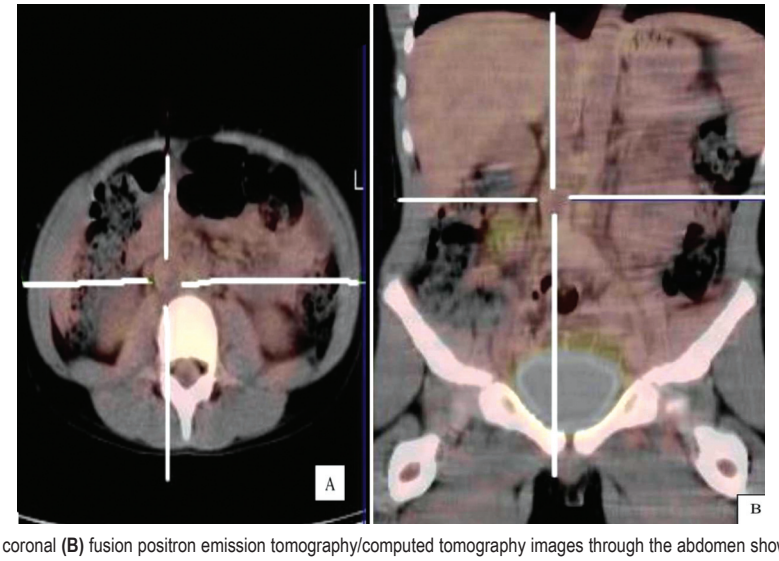

FIGURE 2: A, B) Axial **(A)** and coronal **(B)** fusion positron emission tomography/computed tomography images through the abdomen shows fluorodeoxyglucose activity distributed in the vena cava inferior. The severity of fluorodeoxyglucose uptake is visually graded as Grade 2, similar to liver uptake (SUVmax 3.2).

medium-sized arteries. Small vessel vasculitis predominantly affects the small intraparenchymal arteries, arterioles, capillaries, and venules, known as the small vessels. Variable vessel vasculitis affects blood vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries). Moreover, BD is classified as a variable vessel vasculitis.[4,5] The vascular involvement in our patient was consistent with variable vessel vasculitis.

PET/CT is used to diagnose large vessel vasculitis, assess disease activity, and monitor treatment efficacy. Furthermore, there is evidence showing that it can be useful in detecting small vessel vasculitis.[7] The use of PET/CT for vasculitis is based on the ability to detect increased glucose uptake due to the high glycolytic activity of inflammatory cells on inflamed artery walls.[7] Our patient showed the absence of large artery involvement. There was slightly increased FDG uptake in the inferior vena cava and popliteal veins, indicating that PET/CT is useful in revealing venous involvement, besides large artery involvement.

According to the 2018 recommendations of the European League Against Rheumatism, anticoagulant therapy had the lowest recommendation strength (C) based on the lowest level of evidence (III) for venous thrombosis in BD. It is recommended to administer immunosuppressive therapy instead of anticoagulants in these patients.[15]

In conclusion, BD should be considered in children with inflammatory thrombosis refractory to anticoagulant and thrombolytic therapy and each patient should be individually evaluated. PET/CT can be used in order to properly treat the vascular involvement of BD.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zeynep Canan Özdemir, Aslı Kavaz Tufan;* ***Design:*** *Zeynep Canan Özdemir, Aslı Kavaz Tufan;* ***Control/Supervision:*** *Özcan Bör;* ***Data Collection and/or Processing:*** *İlknur Ak Sivrikoz, Ersin Töret;* ***Analysis and/or Interpretation:*** *İlknur Ak Sivrikoz, Ersin Töret;* ***Literature Review:*** *Zeynep Canan Özdemir;* ***Writing the Article:*** *Zeynep Canan Özdemir;* ***Critical Review:*** *Özcan Bör;* ***References and Fundings:*** *Zeynep Canan Özdemir;* ***Materials:*** *İlknur Ak Sivrikoz, Ersin Töret.*

REFERENCES

1. Yurdakul S, Yazıcı Y. Epidemiology of Behçet's syndrome and regional differences in disease expression. In: Yazıcı Y, Yazıcı H, eds. Behçet's Syndrome. 1st ed. New York: Springer; 2010. p.35-52. [Crossref]
2. Atmaca L, Boyvat A, Yalçındağ FN, Atmaca-Sonmez P, Gurler A. Behçet disease in children. Ocul Immunol Inflamm. 2011;19(2):103-7. [Crossref] [PubMed]
3. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11. [PubMed]
4. Koné-Paut I. Behçet's disease in children, an overview. Pediatr Rheumatol Online J. 2016;14(1):10. [Crossref] [PubMed] [PMC]
5. Seyahi E, Yurdakul S. Behçet's syndrome and thrombosis. Mediterr J Hematol Infect Dis. 2011;3(1):e2011026. [Crossref] [PubMed] [PMC]
6. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med. 1992;33(11):1972-80. [PubMed]
7. Slart RHJA; Writing group; Reviewer group; Members of EANM Cardiovascular; Members of EANM Infection & Inflammation; Members of Committees, SNMMI Cardiovascular; Members of Council, PET Interest Group; Members of ASNC; EANM Committee Coordinator. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. Eur J Nucl Med Mol Imaging. 2018;45(7):1250-69. [Crossref] [PubMed] [PMC]
8. Koné-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, et al; PEDBD group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis. 2016;75(6):958-64. [Crossref] [PubMed]
9. Demirkesen C, Öz B, Göksel S. Behçet's disease: Pathology. In: Yazıcı Y, Yazıcı H, eds. Behçet's Syndrome. 1th ed. New York: Springer; 2010. p.215-41. [Link]

10. Calamia KT, Schirmer M, Melikoglu M. Major vessel involvement in Behçet's disease: an update. Curr Opin Rheumatol. 2011;23(1):24-31. [Crossref] [PubMed]
11. Springer J, Villa-Forte A. Thrombosis in vasculitis. Curr Opin Rheumatol. 2013;25(1):19-25. [Crossref] [PubMed]
12. Batu ED. Diagnostic/classification criteria in pediatric Behçet's disease. Rheumatol Int. 2019;39(1):37-46. [Crossref] [PubMed]
13. Seyahi E. Behçet's disease: How to diagnose and treat vascular involvement. Best Pract Res Clin Rheumatol. 2016;30(2):279-95. [Crossref] [PubMed]
14. Tascilar K, Melikoglu M, Ugurlu S, Sut N, Caglar E, Yazici H. Vascular involvement in Behçet's syndrome: a retrospective analysis of associations and the time course. Rheumatology (Oxford). 2014;53(11):2018-22. [Crossref] [PubMed]
15. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018;77(6):808-18. [Crossref] [PubMed]