Case Report
Mol Imaging Radionucl Ther 2023;32:90-93 DOI:10.4274/mirt.galenos.2021.30922

^{18}F-FDG PET/CT Findings Overlapping Lymphoma in a Patient with Systemic Juvenile Idiopathic Arthritis

Sistemik Jüvenil İdiyopatik Artritli Bir Hastada Lenfoma ile Örtüşen ^{18}F-FDG PET/BT Bulguları

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Abstract

Systemic juvenile idiopathic arthritis (sJIA) is an important autoinflammatory disease whose first symptom is usually fever, and life-threatening conditions such as macrophage activation syndrome can develop when diagnosis and treatment is delayed. sJIA is an exclusion diagnosis, and there is no specific test that distinguishes it from other febrile diseases. We report the positron emission tomography/computed tomography (PET/CT) findings of sJIA in a 12-year-old girl who presented with fever, rash, and arthralgia. ^{18}F-fluorodeoxyglucose (FDG) uptake was observed in the spleen, bone marrow, and lymph nodes in ^{18}F-FDG PET/CT performed to investigate the etiology of fever of unknown origin. The result of excisional biopsy performed with the suspicion of lymphoma from the left cervical lymph node with intense ^{18}F-FDG uptake was reported as reactive hyperplasia. PET/CT is an alternative diagnostic method for patients with fever of unknown origin. In this case report, we emphasize that in patients with sJIA, there may be intense fluorodeoxyglucose-avid lymph nodes that may lead to the consideration of lymphoproliferative disease, and PET/CT findings along with spleen and bone marrow involvement may overlap with lymphoma.

Keywords: ^{18}F-FDG, PET/CT, juvenile idiopathic arthritis, fever of unknown origin

Öz

Sistemik juvenil idiyopatik artrit (sJIA), ilk semptomu genellikle ateş olan önemli bir otoenflamatuvar hastalık olup tanı ve tedavi geciktiğinde makrofaj aktivasyon sendromu gibi hayatı tehdit eden durumlar gelişebilir. sJIA, diğer ateşli hastalıklardan ayıran spesifik testi olmayan bir dışlama tanısıdır. Ateş, döküntü, artralji ile başvuran 12 yaşındaki bir kız çocuğunda sJIA'nın pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) bulgularını sunuyoruz. Nedeni bilinmeyen ateş etiyolojisini araştırmak için yapılan ^{18}F-florodeoksiglukoz (FDG)-PET/BT'de dalak, kemik iliği ve lenf düğümlerinde ^{18}F-FDG tutulumu gözlendi. Yoğun ^{18}F-FDG tutulumu olan sol servikal lenf düğümünden lenfoma şüphesiyle yapılan eksizyonel biyopsi sonucu reaktif hiperplazi olarak rapor edildi. PET/BT, nedeni bilinmeyen ateşi olan hastalar için alternatif bir tanı yöntemidir. Bu olgu sunumunda, sJIA'lı hastalarda, lenfoproliferatif hastalık düşünülmesine yol açabilecek yoğun florodeoksiglukoz tutan lenf nodları olabileceğini, dalak ve kemik iliği tutulumu nedeniyle PET/BT bulgularının lenfoma ile örtüşebileceğini vurgulamaktayız.

Anahtar kelimeler: ^{18}F-FDG, PET/BT, jüvenil idiyopatik artrit, nedeni bilinmeyen ateş

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Received: 29.01.2021 **Accepted:** 17.03.2021

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease that constitutes 10%-15% of children with JIA and has different pathogenesis and clinical features from other JIA subtypes. sJIA manifests itself with quotidian fever and arthritis. The evanescent rash, serositis, hepatosplenomegaly, and lymphadenopathy may be accompany (1,2). The diagnosis of sJIA is an exclusion diagnosis, and no specific test distinguishes it from other febrile diseases. Other causes of fever, such as infection, malignancy, systemic lupus erythematosus, and Kawasaki disease, should be ruled out. Arthritis may not be present at the beginning and may develop later. This complicates the diagnosis and identification may be difficult even for experienced physicians (2). ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) can detect the underlying cause in about half of all children with fever of unknown origin (FUO) (3). Here, we report an adolescent patient with sJIA who presented with FUO, whose findings were compatible with lymphoproliferative disease in ^{18}F-FDG PET/CT, but lymphoma was ruled out histopathologically.

Case Report

A 12-year-old girl presented to the pediatric emergency department with fever and joint pain. Her physical examination revealed fever that reached 40.5°C, an erythematous rash on her body, and tenderness in the right knee joint. There was no redness or temperature increase in the joint, and her other systemic examinations were normal. Her hemoglobin was 12.7 g/dL, the leukocyte count was 14100/µL, platelet count was 281.000/µL, erythrocyte sedimentation rate was 57 mm/hr, C-reactive protein was 81 mg/L, and ferritin was 5964 ng/mL. The microbiologic examinations (blood, urine, throat culture) of the patient were not diagnostic. Infective endocarditis and uveitis were excluded with echocardiography and ophthalmic examinations, respectively. A tuberculin skin test, thorax and abdominal CT, and immunologic tests were normal. No findings were found in the bone marrow aspiration biopsy. ^{18}F-FDG PET/CT was performed after obtaining written consent from the family to determine the etiology of the fever in the patient whose biochemical parameters and fever did not regress despite broad-spectrum antibiotherapy. Conglomerated lymphadenopathies were observed in the bilateral cervical chain, more intensely on the left, on ^{18}F-FDG PET/CT [maximum standardized uptake value (SUV_{max}): 31.80]. Additionally, there were several lymph nodes in the bilateral axillar and abdominal regions that showed increased metabolic activity. Diffuse hypermetabolism was observed in the bone marrow and spleen. No ^{18}F-FDG uptake suggestive of arthritis was detected (Figure 1). A histopathologic examination was recommended from the cervical lymph nodes to exclude lymphoproliferative disease according to PET/CT findings. The result of excisional biopsy from the left cervical lymph node was reported as reactive hyperplasia.

sJIA was considered with the presenting findings of fever, rash, arthralgia, no response to antibiotic therapy, increased acut-phase reactants, hyperferritinemia, and the exclusion of other diagnoses such as infections, malignancy, and hematologic disorders. The patient's symptoms resolved completely with appropriate therapy (steroid and methotrexate).

Literature Review and Discussion

sJIA is an important childhood disease that remains difficult to diagnose even for experienced physicians (2). The disease can manifest with quotidian fever, evanescent rash, serositis, hepatosplenomegaly, and lymphadenopathy. It

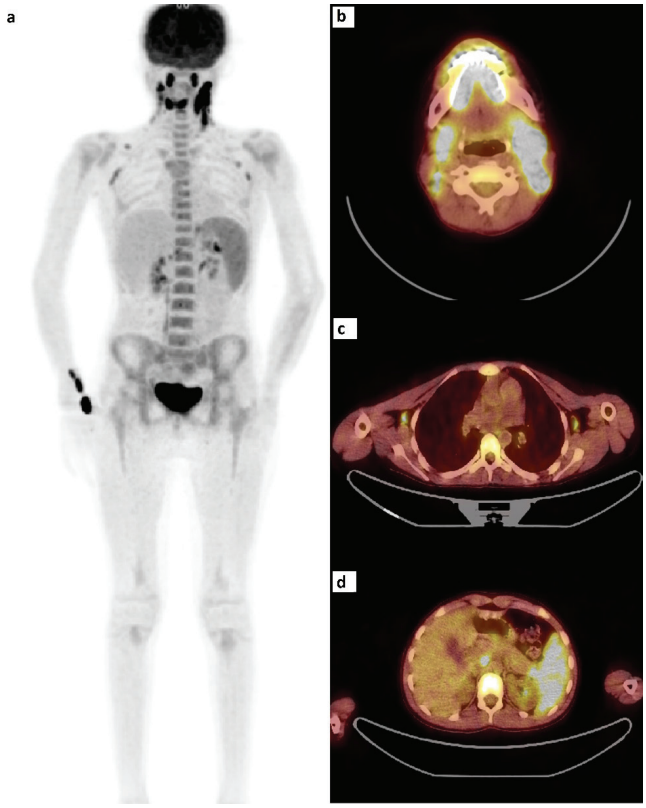

Figure 1. Increased ^{18}F-fluorodeoxyglucose (FDG) uptake in the cervical, axillary lymph nodes, spleen, and bone marrow in the patient on maximum intensity projection positron emission tomography/computed tomography image (a); bilateral cervical and axillary lymph nodes with increased ^{18}F-FDG uptake (b, c); intraabdominal lymph node with increased ^{18}F-FDG uptake and intense ^{18}F-FDG uptake in the spleen (d)

has also been thought for some time that sJIA is a polygenic autoinflammatory disease comprising several diseases of different clinical characteristics that have a common endpoint resulting in marked activation of the natural immune system. In nearly half of all cases, the disease is characterized by relapses following periods of remission; the arthritis usually resolves when systemic symptoms are controlled. As for the other half of the patients, the disease continues incessantly and chronic arthritis remains a life-restricting problem when systemic symptoms are eventually resolved. Moreover, there is a group of patients who show all other possible clinical systemic features in sJIA, but never develop arthritis (4,5).

In some articles published recently, the International League of Associations for Rheumatology (ILAR) classification criteria for JIA have been criticized as being inadequate, especially in the diagnosis of sJIA (5,6). Early and effective treatment of sJIA is important for preventing macrophage activation syndrome. It is especially important to make an accurate diagnosis before starting steroid therapy because it can temporarily mask malignancy (2). However, arthritis of at least of 6 weeks, as defined in the ILAR criteria is unrealistic and can cause a delay in diagnosis. It was determined that up to 50% of patients diagnosed with sJIA in Germany did not meet the ILAR criteria due to the absence of chronic arthritis (6).

The Pediatric Rheumatology International Trials Organization (PRINTO) criteria (2019) revising the ILAR classification criteria, removed the necessity for arthritis in the diagnosis of sJIA. The PRINTO criteria emerged because of the process initiated to distinguish the diseases seen only in children from diseases seen both in children and adults by identifying homogeneous disease groups found under the JIA umbrella term. Although the PRINTO criteria have yet to be validated, they were created with an international consensus (5). Our patient did not meet the ILAR criteria due to the absence of arthritis, but she could be defined as having sJIA according to the PRINTO criteria.

When the cause of fever of at least 8 days in a child cannot be explained with a cautious and detailed history, physical examination, and preliminary laboratory tests, it is defined as FUO (7). ^{18}F-FDG PET/CT is a valuable tool in the diagnosis of underlying causes in adult patients with FUO (8). As for children with FUO, most ^{18}F-FDG PET/CT data are limited, and a comprehensive study from 2020 provided the most detailed information. Pijl et al. (3) could identify the underlying true cause of fever with ^{18}F-FDG PET/CT in almost half (53 patients- 48%) of 110 pediatric patients with FUO. In this study, sJIA was the second most frequently diagnosed disease, with inflammatory bowel diseases following endocarditis. The diagnosis was established based on ^{18}F-FDG PET/CT findings in three of five patients with sJIA (3).

Clinical practice guidance for JIA proposed ^{18}F-FDG PET as an imaging method for the diagnosis of sJIA in 2018 (9). It is important to recognize the ^{18}F-FDG PET findings of sJIA, one of the major causes of FUO, and remains a clinical exclusion diagnosis. However, to our knowledge, there is only one study in the literature investigating characteristic ^{18}F-FDG PET findings in sJIA (10). Kanetaka et al. (10) evaluated the ^{18}F-FDG PET findings of 59 patients with sJIA and they suggested that their evidence might be used as effective diagnostic tools in patients who do not receive a firm diagnosis. These researchers identified two different characteristic ^{18}F-FDG uptake patterns on ^{18}F-FDG PET in patients with sJIA. In the group defined as type 1, pathologic ^{18}F-FDG uptake in the spleen and bone marrow (especially red bone marrow reflecting systemic inflammation) was observed, and no pathologic uptake was detected in joint synovia. It is note worthy that the type 1 involvement pattern findings were similar to those of PET in adult-onset Still's disease, whose characteristic ^{18}F-FDG involvement has been defined in the bone marrow, spleen, and lymph nodes. Additionally, it was stated that findings similar to the type 1 involvement pattern in sepsis and bone marrow involvement in leukemia could be seen, so the diagnosis should be supported through serologic tests. As for patients in the group defined as type 2, characteristic ^{18}F-FDG uptake was observed, suggesting synovitis in inflamed joints, similar to patients with polyarticular JIA or rheumatoid arthritis. Pathologic ^{18}F-FDG uptake in the bone marrow and spleen has not been described previously.

Our case is compatible with the type 1 pattern due to the presence of bone marrow and spleen involvement and no joint involvement. However, our patient also had increased ^{18}F-FDG involvement in the lymph nodes in the cervical, axillary, and intraabdominal regions. The cervical lymph nodes in particular had very high SUV_{max} values (SUV_{max}: 31.80). We estimate that the reason for the absence of examples similar to our case in the article by Kanetaka et al. (10) was patients being included in the study according to the ILAR criteria. A case of sJIA has been reported previously with ^{18}F-FDG PET/CT findings mimicking lymphoma (11). Here, lymphadenopathies were more disseminated, but SUV_{max} values were more moderate (SUV_{max}: 4.5-10.7). There are also cases of lymphoma mimicking JIA in the literature (12,13).

Based on the findings in our case, we emphasize that there may be lymph nodes with increased metabolic activity that can reach high SUV_{max} values in ^{18}F-FDG PET findings of

sJIA, and a differential diagnosis with lymphoma should be made in such patients presenting with FUO.

Ethics

Informed Consent: Informed consent was obtained from the patient's family.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A., Ö.M.A., Concept: Ö.Ş., Design: Ö.Ş., Data Collection or Processing: Ö.Ş., Analysis or Interpretation: Ö.Ş., A.E.Ş., Literature Search: Ö.Ş., Writing: Ö.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, Ayala R, Groh B, Finkel TH, Cron RQ. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). J Rheumatol 2008;35:343-348.
2. Shenoi S, Wallace CA. Diagnosis and treatment of systemic juvenile idiopathic arthritis. J Pediatr 2016;177:19-26.
3. Pijl JP, Kwee TC, Legger GE, Peters HJH, Armbrust W, Schölvinck EH, Glaudemans AWJM. Role of FDG-PET/CT in children with fever of unknown origin. Eur J Nucl Med Mol Imaging 2020;47:1596-1604.
4. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis 2012;71:1437-1439.
5. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, Ilowite NT, Khubchandani R, Laxer RM, Lovell DJ, Petty RE, Wallace CA, Wulffraat NM, Pistorio A, Ruperto N; Pediatric Rheumatology International Trials Organization (PRINTO). Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol 2019;46:190-197.
6. Hinze CH, Holzinger D, Lainka E, Haas JP, Speth F, Kallinich T, Rieber N, Hufnagel M, Jansson AF, Hedrich C, Winowski H, Berger T, Foeldvari I, Ganser G, Hospach A, Huppertz HI, Mönkemöller K, Neudorf U, Weißbarth-Riedel E, Wittkowski H, Horneff G, Foell D; PRO-KIND SJIA project collaborators. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J 2018;16:17.
7. Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ. Feigin and Cherry's textbook of pediatric infectious diseases. 8th ed. Philadelphia, Elsevier 2019; 608-610.
8. Wang Q, Li YM, Li Y, Hua FC, Wang QS, Zhang XL, Cheng C, Wu H, Yao ZM, Zhang WF, Hou QY, Miao WB, Wang XM. 18F-FDG-PET/CT in fever of unknown origin and inflammation of unknown origin: a Chinese multi-center study. Eur J Nucl Med Mol Imaging 2019;46:159-165.
9. Okamoto N, Yokota S, Takei S, Okura Y, Kubota T, Shimizu M, Nozawa T, Iwata N, Umebayashi H, Kinjo N, Kunishima T, Yasumura J, Mori M. Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018. Mod Rheumatol 2019;29:41-59.
10. Kanetaka T, Mori M, Nishimura K, Nozawa T, Kikuchi M, Sakurai N, Hara R, Yamazaki K, Yokota S. Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis. Mod Rheumatol 2016;26:362-367.
11. Lord M, Allaoua M, Ratib O. Positron emission tomography findings in systemic juvenile idiopathic arthritis. Rheumatology (Oxford) 2011;50:1177.
12. Del Torto M, Breda L, Di Marzio D, De Sanctis S, La Barba G, Chiarelli F. Hodgkin's lymphoma mimicking juvenile arthritis. Clin Exp Rheumatol 2010;28:143.
13. Jesus AA, Jacob CM, Silva CA, Dorna M, Pastorino AC, Carneiro-Sampaio M. Common variable immuno deficiency associated with hepatosplenic T-cell lymphoma mimicking juvenile systemic lupus erythematosus. Clin Dev Immunol 2011;2011:428703.