Clinical note

Autoimmune lymphoproliferative syndrome and non-Hodgkin lymphoma: What 18F-fluorodeoxyglucose positron emission tomography/computed tomography can do in the management of these patients? Suggestions from a case report

A. Cistaro a,c,1, F. Paze b, S. Durando b, M. Cogoni c, R. Faletti d, S. Vesco e, S. Vallero f, N. Quartuccio g, G. Treglia h, U. Ramenghi f

aPositron Emission Tomography Centre, IRMET S.p.A., Euromedic Inc., Turin, Italy
bDepartment of Radiology, San Luigi Gonzaga Hospital, Turin, Italy
cDepartment of Neuroradiology, CTO Hospital, Turin, Italy
dDepartment of Radiology, San Giovanni Battista Hospital, Turin, Italy
eDepartment of Physical Medicine and Rehabilitation, Martini Hospital, Turin, Italy
fPediatric Department, University of Turin, Turin, Italy
gDepartment of Radiological Sciences, Nuclear Medicine Unit, University of Messina, Messina, Italy
hDepartment of Nuclear Medicine and PET/CT Centre, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

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ABSTRACT

A young patient with undefined autoimmune lymphoproliferative syndrome (ALPS-U) and low back pain underwent a CT and MRI study that showed enhanced vertebral lesions, some pulmonary nodules and diffuse latero-cervical lymphadenopathy. A 18F-FDG-PET/CT scan showed many areas of intense 18F-FDG uptake in multiple vertebrae, in some ribs, in the sacrum, in the liver, in both lungs, in multiple lymph nodes spread in the cervical, thoracic and abdominal chains. A bone marrow biopsy showed a “lymphomatoid granulomatosis”, a rare variant of B-cell non-Hodgkin lymphoma (NHL). After the treatment, the 18F-FDG-PET/CT scan showed a complete metabolic response.

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Síndrome linfoproliferativo autoinmune indefinido y linfoma no-Hodgkin. ¿Qué puede aportar la exploración 18F-FDG-PET/CT al tratamiento de estos pacientes? Sugerencias a partir de un caso

RÉSUMÉ

Un patiente joven con síndrome linfoproliferativo autoinmune indefinido (ALPS-U) y dolor lumbar se sometió a una tomografía computarizada y a una resonancia magnética, estudos que mostraron varias lesiones vertebrales, algunos nódulos pulmonares y adenopatías laterocervicales difusas. Una exploración 18F-FDG-PET/TC reveló áreas de captación intensa de 18F-FDG en múltiples vértebras, algunas costillas, sacro, hígado, ambos pulmones y en varios ganglios linfáticos repartidos en las cadenas cervicales, torácica y abdominal. La biopsia de médula ósea diagnosticó una “granulomatosis linfomatoid”, una variante poco frecuente de Linfoma no-Hodgkin de células B (LNH). Tras el tratamiento, la exploración 18F-FDG-PET/TC demostró una respuesta metabólica completa.

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Introduction

The autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic disorder involving the Fas apoptotic pathway in lymphocytes. Fas (also called Apo-1 and CD95) is a death receptor belonging to the tumor necrosis factor receptor (TNFR) super-family that induces cell death, when triggered by Fas ligand (Fasl or CD95L).1 Fas pathway maintains the lymphocyte homeostasis and is involved in switching-off the immune response, limiting clonal expansion of lymphocytes, favoring peripheral tolerance. Fas is highly expressed by cytotoxic T cells and NK cells and plays an important role in preventing cancer.2 Thus, patients with Fas mutations show chronic lymphoproliferation, hepatosplenomegaly and even autoimmune manifestations. Furthermore subjects with ALPS have propensity to develop Hodgkin and non-Hodgkin lymphoma with a risk of 51 and 14 times greater than expected, respectively.3,4 We report a case of a young patient affected by ALPS, who developed a “lymphomatoid granulomatosis”, a rare variant of B-cell non-Hodgkin lymphoma. In this case fluorine-18-fluorodeoxyglucose positron emission

1 Corresponding author.
E-mail address: acistaro@irmet.com (A. Cistaro).
1 Coordinator of Italian PET-Pediatric Study Group.
tomography/computed tomography (18F-FDG-PET/CT) has been useful in staging the disease and in evaluating the treatment response.

Case report

A 27-year-old man was referred to our center for low back pain and legs paresthesia for about one month. The patient had a history of lymphoid hyperplasia and autoimmune thrombocytopenia. Splenectomy was performed at the age of 15. Thrombocytopenia disappeared at the age of 21. Since he displayed defective Fas function and expansion of double-negative (CD4−/CD8−) T cells (2–4% of total lymphocytes), a Canale-Smith syndrome was diagnosed. He never displayed signs of Epstein-Barr virus (EBV) infection. No mutation was found on Fas, Caspase 10 and Fas-L genes.

Magnetic Resonance Imaging (MRI) of the lower trait of the dorsal spine and all lumbar vertebrae showed enhancing lesions involving L1 vertebra with heterogeneous low signal intensity on T1 and high signal intensity on T2-weighted images, with the involvement of correspondent nervous roots and extension of pathological tissue in the correspondent paravertebral space. The spinal canal was not invaded by pathological tissue (Fig. 1). Computed tomography (CT) revealed a focal and subtle cortical erosion of the vertebra adjacent to the paravertebral tissue, few pulmonary nodules and diffuse enlargement of lateral-cervical lymph nodes. Abdominal ultrasonography (US) showed hepatomegaly. Blood values showed increased fibrinogen (601 mg/dL), gamma glutamyl transpeptidase (γ-GT) (111 U/L), lactate dehydrogenase (LDH) (540 U/L) and C-reactive protein (CRP) (15.8 mg/L). A bone marrow biopsy, made on L1 vertebra, showed an increased population of granulocytes. A 18F-FDG-PET/CT scan was required in order to metabolically characterize the vertebral, lung lesions and the latero-cervical lymph nodes and to complete the staging.

PET/CT was acquired using an integrated PET/CT device (Discovery ST-E, General Electric Medical Systems, Milwaukee, WI, USA) with the patient fasting for 6h: at the time of the radiopharmaceutical injection, the patient presented glucose blood levels corresponding to 87 mg/dL. Images were acquired one hour after intravenous injection of 248 MBq of FDG according to the body mass index. The unenhanced CT scan was performed from the skull base to the inguinal region with a voltage of 120 KeV and tube current of 30 mA for the anatomic localization and the attenuation correction of PET data. PET scan was acquired in 3D mode (multiple bed positions, 3 min for each bed position), Iterative reconstruction and CT-based attenuation correction were used. Visual and semi-quantitative image analysis using standardized uptake value (SUV) was performed.

The analysis of PET images showed multiple areas of intense 18F-FDG uptake corresponding to multiple vertebrae, some ribs, the sacrum, the liver and both lungs. Further areas of increased 18F-FDG uptake were detected in multiple lymph nodes in the cervical, thoracic and abdominal stations (Fig. 2).

By using the PET/CT as a guide, a second bone marrow biopsy was performed on the left iliac bone, leading to the definitive diagnosis. The histopathological analysis showed a population of cells consistent with granulocytic hyperplasia. The immunological analysis showed a “lymphomatoid granulomatosis”, a rare variant of B-cell non-Hodgkin lymphoma, mostly associated with EBV infection and possibly secondary to immunological disorders. Using more recent diagnostic criteria, a diagnosis of undefined autoimmune lymphoproliferative disease (ALPS-U) can be made.4

In order to treat the B-cell non-Hodgkin lymphoma, the patient underwent six cycles of Rituximab resulting in a partial reduction of the multiple lesions. In addition, autologous EBV-specific cytotoxic T lymphocytes (EBV-CTL) were expanded, and at the end of the sixth Rituximab course the patient received two infusions of autologous EBV-CTL (2 × 10⁶ cells/kg body weight) 15 days apart, followed by a consolidation dose of 1 × 10⁶ cells/kg body weight, in order to obtain complete remission. He was put under treatment with Interferon. The following bone marrow biopsy of the iliac bone resulted negative. The subsequent MRI showed a significant reduction of the paravertebral mass lesion in L1 and a regression of the vertebral lumbar oedema except for a small remnant area of high signal intensity on T2-weighted images (Fig. 3). On the contrary, the 18F-FDG-PET/CT post-treatment scan showed a positive response to
the treatment, with a complete regression of all areas of 18F-FDG uptake (Fig. 4). Nine months later, in the follow-up, 18F-FDG-PET/CT scan confirmed the complete regression of disease.

Discussion

ALPS is a rare disorder characterized by splenomegaly, chronic massive lymphadenopathy and autoimmune manifestations which predominantly involve blood cells.1,2 Patients with ALPS-U need to be monitored over the years due to the risk for the development of lymphomas, requiring close surveillance and even repeated biopsies.3 FDG-PET/CT may play an important role in this setting.5

Diagnosis of lymphoma in ALPS is difficult because patients with ALPS experience lymphadenopathy that fluctuates over time. The main drawback of morphological imaging techniques, such as CT, is their reliance on size criteria to define disease, with consequent failure in detecting disease in small lymph nodes and in excluding disease in large, but treated, masses. In case of suspicious malignant transformation in patients with ALPS, FDG-PET/CT may help in the differential diagnosis of ALPS-associated lymphoma with benign lymphadenopathy suggesting the most appropriate site for the biopsy on the basis of the greatest degree of FDG uptake.6 ALPS patients have usually normal nodal FDG uptake and no reliable SUV threshold to distinguish between benign lymphadenopathy with malignant lesions has been identified yet.7 Rao et al.9 reported that the 18F-FDG avidity of benign lymph nodes in ALPS can be high and overlapping the SUVmax values described in some patients with low-grade lymphomas.6 The few data present in literature document high and variable SUVmax values in benign lymph nodes of patients affected by ALPS, ranging from 4.7 to 8.3.5,7 On the contrary higher grade lymphomas usually show greater FDG uptake than ALPS without transformation.5

Despite the challenge in distinguishing malignant nodal lesions from benign adenopathy, FDG-PET/CT may provide additional information even in the staging work-up of patients with already transformed ALPS thanks to the possibility to image the entire body in a single session, increasing the opportunity of finding unsuspected disease sites.8 However there are no reports regarding this clinical setting in literature.

Post-therapy surveillance of patients with histologically confirmed ALPS-associated lymphoma represents an additional indication and the role of FDG-PET/CT is to exclude lymphoma relapse in the background of regenerating ALPS-related adenopathy. However also in this setting there may be some overlapping between SUVmax values of benign adenopathy with those of malignant lesions.6,7

As regards our case report, 18F-FDG-PET/CT was useful because it provided a metabolic map of lymph nodes and allowed to detect the most active lymph nodes, target for a diagnostic biopsy, and to appreciate changes over the time of metabolic activity. Furthermore, it allowed the identification of extranodal locations suspected for lymphoma. This information was essential in order to plan a therapy, to assess the response to the treatment and for the follow up.

In our patient all lesions responded to the treatment with Rituximab: both lymphomatous localizations and inflammatory lymph

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**Fig. 2.** Maximum-intensity-projection (MIP) PET image (a), sagittal CT (b), PET (c) and PET/CT (d) images showed areas of intense 18F-FDG uptake corresponding to multiple vertebrae, some ribs, sacrum, liver and both the lungs. Further areas of increased 18F-FDG uptake were detected in multiple lymph nodes spread in the cervical, thoracic and abdominal stations. By using the CT, PET and PET/CT images as a guide (e-g), a bone marrow biopsy was performed on the left iliac bone (arrow), that revealed the presence of a B-cell non-Hodgkin lymphoma.

**Fig. 3.** Post-treatment sagittal T2 STIR MRI showed residual high intensity signal involving L1 and reduction of the epidural tissue (yellow arrow); abnormal signal intensity is also seen at T9 with prominent vertebral body involvement (red arrow).
nodes showed a marked regression at $^{18}$F-FDG-PET/CT. This probability suggests that the same cells (CD20+) were implicated in all lesions, both in lymphomatous localizations and in ALPS. Interestingly, however, complete remission was achieved only after EBV-specific CTL infusion, indicating that an additional, low toxicity and specifically targeted biological treatment, such as cell therapy, may play an important role in patients with ALPS developing EBV-related lymphoproliferations. The complete disease regression documented by $^{18}$F-FDG-PET/CT after cell therapy, a procedure that works through initial expansion of “therapeutic” T cells at the disease site, suggests that this imaging technique may be employed in the follow-up of patients treated with cell therapy approaches.

Conclusions

$^{18}$F-FDG-PET/CT seems to have several roles in patients with ALPS. It can confirm or rule out diagnosis in patients with suspicion of malignancy, at the same time allowing a proper staging; it also gives important information in monitoring the treatment response and during the follow-up in patients with malignancies; finally, it could be useful to control autoimmune manifestations of symptomatic ALPS, by monitoring the response to the therapy through the evaluation of metabolic activity of involved lymph nodes.

Conflict of interests

The authors declare that they have no conflict of interest.

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