Clinical Case Report

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18F-Fluorodeoxyglucose positron emission tomography computed tomography detection threshold in follicular lymphoma

A case report

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Abstract

Rationale: Follicular Lymphoma in situ is generally identified as reactive follicular hyperplasia in which some of the hyperplastic germinal centers are colonized by few lymphoma cells. These cells can be detected through their strong 18F-Fluorodeoxyglucose avidity.

Patient concerns: We report the case of a 70 year-old patient with arthralgia, weight loss and chronic fever over two months. A paraneoplastic polymyalgia rheumatica was initially suspected on abnormal 18F fluoro-deoxyglucose positron emission tomography (PET) pictures in two inguinal lymph nodes with a standardized uptake value at 8.6 and 5.8.

Diagnoses: The PET lymph nodes were removed and histological examination revealed subtle lymph nodes infiltration by follicular lymphoma in situ. The absolute number of the follicular lymphoma cells determined using virtual imaging and 3D reconstruction appeared very low with a total tumor cell volume estimated at around 0.026 mm^3 for one lymph node and 0.041 mm^3 for the other.

Interventions: The patient has been treated by corticotherapy alone.

Outcomes: A long-time follow-up should be highly suggested for this patient to avoid any risk of clinical progression to follicular lymphoma.

Lessons: Our findings show that low amounts of follicular lymphoma cells in reactive germinal center may reach a threshold of hypermetabolism detectable with positron emission tomography imaging, suggesting that tumor microenvironment also accounts for such as strong fluoro-deoxyglucose avidity. Thus, a systematic immunohistochemistry with anti-BCL2 antibodies should be performed on PET positive lymph node with apparent normal morphological features.

Abbreviations: CRP = C-reactive protein, CT = computed tomography, FDG = fluoro-deoxyglucose, FL= follicular lymphoma, FLIS = follicular lymphoma in situ, HL = Hodgkin lymphoma, LN = lymph node, PET = positron emission tomography, SUV = standardized uptake value.

Keywords: fluoro-deoxyglucose avidity, follicular lymphoma in situ, positron emission tomography

1. Introduction

Follicular lymphoma (FL), the second most common non-Hodgkin B-cell lymphoma occurring in adult, is considered as an indolent tumor but frequently diagnosed at an advanced stage. In FL, cells derive from germinal center B lymphocytes and are characterized in 85% of cases by the t(14;18)(q32;q21) translocation, which juxtaposes the *BCL2* gene with the immunoglobulin heavy chain gene locus resulting in constitutive expression of the antiapoptotic BCL2 protein.[1–3] This molecular abnormality is considered as the initial event in FL and can be

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The study was conducted in accordance with the Helsinki Declaration. This case report was performed with the informed consent from the patient, and the personal information of the patient was made anonymous.

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detected using immunohistochemistry with anti-BCL2 antibodies. As a result, FL cells are strongly BCL2 positive in germinal center and can be easily seen. FL in situ (FLIS), described in 2002 by the Jaffe group, is generally identified as reactive follicular hyperplasia in which some of the hyperplastic germinal centers are colonized by double positive $BCL2^+/CD10^+$ B cells.[1–3] As the overall architecture and cytology of such lymph nodes (LNs) look normal, BCL2 staining is mandatory for the diagnosis, and is usually observed in few, scattered germinal centers. The clinical significance of FLIS remains unclear but in some cases can be considered as an early precursor of FL.[1–3]

Several studies have shown that the majority of lymphomas have a strong avidity for 18F-fluoro-deoxyglucose positron emission tomography/computed tomography (FDG PET/CT) especially FL despite its indolent nature.[4–6] FDG PET imaging is considered as one of the most important tools in FL management and recent official recommendations include FDG PET/CT in FL staging.[7] There is no available information on the usefulness of FDG PET/CT in the detection of FLIS. To the best of our knowledge, we report the first description of FLIS in LN detected by FDG PET imaging.

2. Case presentation

A 70-year-old man presented with general state alteration (anorexia, weight loss, chronic fever) together with joint pain since 2 months. Biological explorations including blood count, liver function test, immunological analyses, viral serology, blood protein electrophoresis unveiled an inflammatory reaction with C-reactive protein (CRP) rate increase. An infectious disease was ruled out and the diagnosis of polymyalgia rheumatica was proposed. A treatment by corticosteroid (1 mg/kg/day) was initiated with a partial efficacy. A paraneoplastic syndrome was suspected on atypical clinical symptoms and corticotherapy resistance. A whole-body CT-scan completed by FDG PET/CT was performed and revealed multiple positive uptakes in joints and in a few LNs. There were some retroperitoneal LNs and 2 left inguinal LNs, a medial and a lateral LN (1.8 and 1.1 cm, respectively) (Fig. 1) with a standardized uptake value (SUV) at 8.6 and 5.8, respectively. A surgical biopsy of the 2 inguinal LNs was performed. Tissue samples were fixed in 4% buffered formalin, paraffin embedded, and cut into 4 μm thick sections before hematoxylin and eosin (HE) staining. Histological examination on HE sections revealed reactive conditions with preserved architecture and abundance of secondary follicles. There was no sign of specific inflammation, infection, or malignant proliferation. A systematic immunohistochemistry analysis (IHC) were performed on Ventana Benchmark Ultra machine (Ventana, member of Roche group, AZ) with anti-CD20 (L26, Dako), anti-CD3 (CD3, Dako), anti-CD10 (SP67, Ventana), and anti-BCL2 (124, Dako). This analysis revealed the presence of clusters or nests of $CD20^+$, $CD10^+$, and $BCL2^+$ cells within a minority of germinal centers (Fig. 2A–D). The latter cells displayed a very strong staining for BCL2, much higher than that of surrounding reactive lymphoid cells (Fig. 2B, C). The diagnosis of FLIS was proposed. To try to reconcile the results of the histopathogical analyses and those of FDG PET/CT, we sought to determine the absolute amount of FL cells in the 2 LNs, as a possible threshold for FDG PET detection. To do so, the IHC slides were digitalized using Pannoramic 250 Flash II digital microscopes (3DHISTECH, Hungary) and tumor cell count ($BCL2^+$ FL cells) was performed on both LNs using virtual imaging and 3D reconstruction with the Marker Counter module, Pannoramic Viewer 1.15 (3D HISTECH, Hungary) (Fig. 2D). The count was performed on 6 slice levels with an interval of 100 μm for both LN. An average density of tumor cells was deducted (medial LN: 0.187 cells/mm^2; lateral LN: 1.696 cells/mm^2). These data were extrapolated to the total nodal volume assuming a homogeneous distribution of the tumor cells. Altogether, these calculations led to a total tumor cell volume estimated at 0.026 mm^3 for medial LN and 0.041 mm^3 for lateral LN.

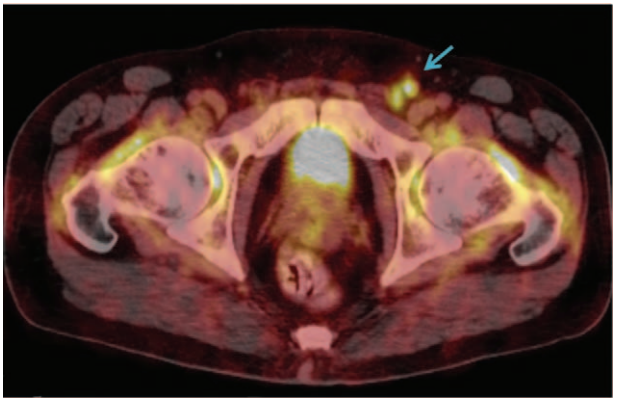

Figure 1. 18 FDG PET/CT images. FDG PET/CT imaging revealed multiple uptakes on pelvic girdle and 2 inguinal lymph nodes: a medial and a lateral lymph node (arrow).

3. Discussion

The limitation of FDG PET results in reduced spatial resolution[8] and lack of specificity.[8–10] To circumvent this poor specificity, semi-quantitative parameters are used including SUV. SUV is correlated to FDG avidity, differs from the benign or neoplastic nature of the lesion, from the type and tumor aggressiveness. There is a substantial overlap in SUV values leading to false-positive results.[4,10] In patients treated for lymphoma, SUV is higher on average for neoplastic than non-neoplastic LNs (average SUV of 7.8 and 5.5, respectively), but there is a considerable overlap rendering SUV an unsuitable selection criterion.[10] The SUV is usually linked to proliferative activity and tumor volume, but recent studies have demonstrated that it is also correlated to tumor cell microenvironment.[11,12] For instance, no correlation has been found in Hodgkin lymphoma (HL) between glucose receptor (GLUT1) expression in tumor cells and FDG SUV.[11] This hypothesis could explain the strong FDG avidity of some indolent lymphoma such as HL and FL. Thus, one can hypothesize that FDG PET imaging could detect LNs with few tumor cells as in HL where malignant cells account for ~1% of all cell compartments.[11,13]

In our case, the absolute amount of lymphoma cells appears low, but the SUV of the removed LNs was high enough to suspect a malignant proliferation. Given the high FDG avidity of FL, we can assume that this minimal clonal proliferation has a strong FDG avidity partly due to tumor microenvironment. However, there was no other pathological explanation for LN hypermetabolism. Non-neoplastic LN can be detected in case of inflammatory conditions such as granulomas or in a clinical ground of cancer. One can suspect that this nonspecific uptake is due to the inflammatory status of patients. This was also the case for our patient, but he presented with a low number of

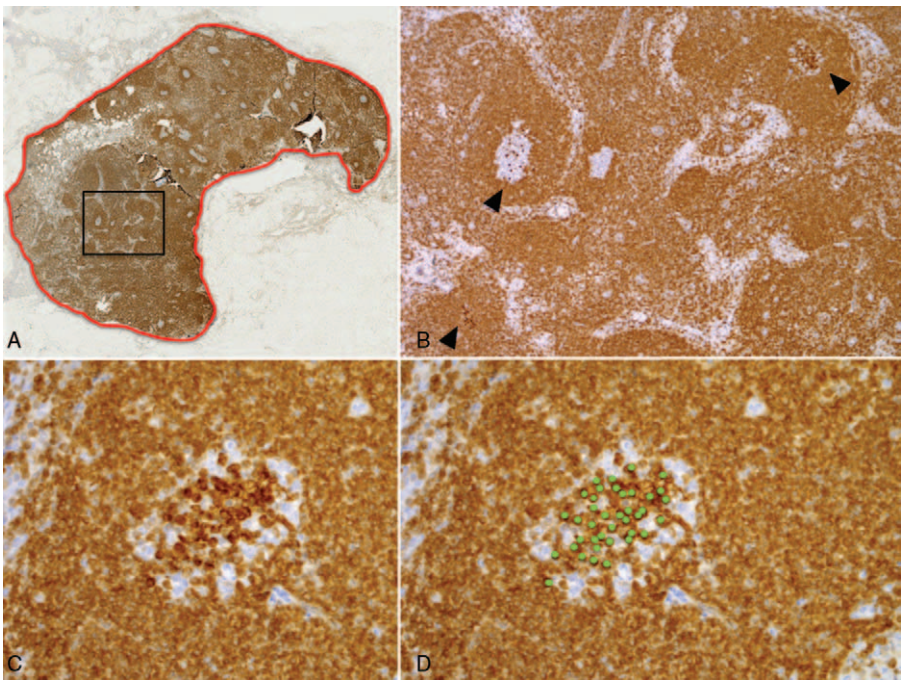

Figure 2. Screenshot of virtual imaging. Immunohistochemistry of lateral lymph node reveals cluster of cells strongly stained with anti-BCL2 (A–D). (A) Immunohistochemistry of LN with anti-BCL2; the red line delineates the lymph node total area (magnification ×10), (B) Focus on a pathological zone in A; arrows indicate the strongly $BCL2^+$ tumor cells in germinal centers (magnification ×50), (C) Example of germinal center used for cell counting (magnification ×200), (D) Example of marker counter analyses (3D HISTECH): green points tag the strongest $BCL2^+$ cells in germinal centers observed in C, (magnification ×200).

hypermetabolic LNs, and those with FLIS displayed the highest SUV.

4. Conclusion

This observation shows that low amount of FL cells in LN may reach a threshold of hypermetabolism detectable with FDG PET imaging. This suggests that LNs with apparent normal histologic features but increasing FDG uptakes should be systematically tested by immunohistochemistry with anti-BCL2 antibodies to diagnose FL early forms or FLIS, which could be associated with overt FL synchronously or metachronoulsy.

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