Reactive Tonsillar Enlargement Showing Strong ^{18}F -Fdg Uptake During the Follow-Up of Follicular Lymphoma

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Abstract The ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has become a standard procedure for the diagnosis, staging, and restaging in lymphoma patients. However, a relative high rate of false-positive results has been reported. We report a case of a 40-year-old man with a previous history of a nodal follicular lymphoma, stage IVA, treated with R-CHOP, which showed strong ^{18}F -FDG uptake in the Waldeyer's tonsillar ring during his follow-up, being considered highly suspicious of relapsed lymphoma. A surgical removal of the palatine tonsils and adenoids was

performed, which showed reactive follicular hyperplasia. Furthermore, bone marrow biopsy revealed absence of neoplasia. The patient is still in follow-up with no signs of recurrent lymphoma. This case illustrates that, despite the high sensitivity for the detection of recurrent lymphoma, ^{18}F -FDG uptake should be interpreted with great caution and confirmatory studies should be performed before any therapy.

Keywords Tonsillar enlargement · Reactive follicular Hyperplasia · Lymphoma · Chemotherapy · ^{18}F -FDG-PET

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Introduction

The 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) has been effective for the diagnosis, staging, and restaging of malignancies of the head and neck region, including carcinoma, melanoma, and lymphoma. During the follow-up, negative FDG-PET/CT scans almost exclude a relapse of the disease, but ^{18}F -FDG uptake does not necessarily mean its returns [1, 2].

To interpret FDG-PET/CT scans accurately, it is essential to be fully familiar with the normal patterns, intensities, and frequencies of ^{18}F -FDG distribution. The degree of FDG uptake is often measured to allow comparison within and between different patients and diseases by the standardized uptake value (SUV) [3]. In normal head and neck structures, ^{18}F -FDG uptake is usually seen in the palatine tonsils, soft palate, and lingual tonsils. ^{18}F -FDG accumulation in the major salivary glands, spinal cord, and vocal cords is variable; whereas in the inferior concha, thyroid gland, and tongue is typically minimal [4]. In lymphoma patients, unfortunately, false-positive results

are possible, because an infection, inflammation, hypermetabolic brown fat surrounding lymph nodes or reactive process producing strong ^{18}F -FDG uptake might be present [2, 5–8]. In these cases, and not uncommonly after chemotherapy, reactive enlargement of the lymph nodes, tonsils, and thymus gland can be detected [8–12]. Thus, to accurately interpret FDG-PET/CT images, one must be fully familiar with the variable patterns and intensities of uptake and with the frequencies of physiologic and non-physiologic uptake [13, 14]. Moreover, it is interesting that only few oral lymphoma cases using FDG-PET/CT images for diagnosis and staging purposes have been previously and recently reported [15–17]. So, is needed that a larger number of properly documented oral lymphoma cases are reported in order that the variable patterns of physiologic and nonphysiologic ^{18}F -FDG uptake are accurately recognized.

In the current study, we present an interesting case with strong ^{18}F -FDG uptake in the palatine tonsils, adenoids, and weak uptake in the cervical lymph nodes, which were diagnosed as reactive follicular hyperplasia (RFH), in a patient with previous history of nodal follicular lymphoma (FL). To our knowledge, it is the second case of histology-proven RFH affecting the palatine tonsil with strong ^{18}F -FDG uptake [8] and we suggested that chemotherapy is probably related with this finding.

Case Report

A 40-year-old man was referred to the oncologic service for diagnosis and evaluation of an enlargement of the palatine tonsils for several weeks accompanied by discomfort when speaking and swallowing.

Medical history revealed a low grade (Grade 1–2) stage IV nodal FL diagnosed 5 years ago, with cervical and left inguinal lymph node involvement as well as bone marrow infiltration. The chemotherapeutic regimen consisted of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) every 4 weeks for 8 cycles, followed by a maintenance treatment with rituximab for a period of 2 years. Initial treatment yielded a complete response. After the completion of chemotherapy, and during the follow-up, there was no evidence of residual disease by FDG-PET/CT scans.

Physical examination revealed bilateral enlarged palatine tonsils, being more evident on the right side. The FDG-PET/CT scan of the palatine tonsils demonstrated a slight bilateral hyperthrophy with a high maximum standardized uptake value (SUV_{max}) of 17.4, and a less ^{18}F -FDG uptake in both right (SUV_{max} of 3.9) and left (SUV_{max} of 5.1) jugulocarotid chain lymph nodes, which was compatible with a relapsed lymphoma (Fig. 1). All relevant blood

tests, including complete blood counts and lactate dehydrogenase levels, were normal. A surgical removal of the right palatine tonsil and a bone marrow trephine biopsy for staging purposes, were indicated.

The microscopic analysis of the palatine tonsil exhibited several well-formed lymphoid follicles (Fig. 2a, b). By immunohistochemistry, the interfollicular areas showed a mixed pattern of staining for CD20 and CD3. The germinal centers (GCs) were positive for CD20, CD10, bcl-6, and negative for bcl-2. Ki-67 labeling index was 10 %, being that the lymphoid follicles displayed a polarized proliferation pattern. Cyclin D1 was negative. Furthermore, the bone marrow biopsy revealed absence of neoplasia (Fig. 3), which was confirmed by negativity for CD20. Thus, according to the microscopic and immunohistochemical findings the diagnosis was RFH.

After 3 months, another FDG-PET/CT scans were performed, which showed a decrease ^{18}F -FDG uptake in the right palatine tonsil area, and remarkably a slight increase and persistent hypercaptation in the left palatine tonsil, adenoids, and bilateral jugulocarotid chain lymph nodes, when compared with previous scans. A surgical excision of these lymphoid tissues was performed. The diagnosis of all specimens was RFH. Moreover, all laboratory exams showed normal results. After 2-years, the patient is still in follow-up with no signs of relapse or recurrence.

Discussion

The FDG, as an analogue of glucose, is taken up by cell membrane glucose receptors. Malignant tumors have a higher metabolic rate and generally express more numbers of specific membrane transporter proteins than normal cells and as an effect the FDG become trapped in these tumors cells [3]. However, physiologic ^{18}F -FDG uptake in Waldeyer's tonsillar ring, the gastrointestinal tract, orbital muscles, cerebral cortex, myocardium, renal collecting systems, bladder, gonads, and brown fat is observed. Also, ^{18}F -FDG may accumulate in inflammatory processes, followed by injury conditions, and benign tumors. Knowledge of these potentially false-positive lesions is essential for accurate FDG-PET/CT scan interpretation in oncologic patients [14, 18]. Increased ^{18}F -FDG uptake in inflammation may be explained by the recruitment of granulocytes, lymphocytes, and macrophages, which have enhanced levels of glucose transporters (GLUTs) [14]. Infections in the head and neck region are common, as it may involve the sinonasal cavities, pharynx, tonsils, ears, mastoids, salivary glands, and dental tissues. Occasionally, it may be impossible to differentiate lymphoma from inflammation on the FDG-PET/CT scans. In these cases, it is necessary clinical, pathological, and imaging follow-up correlations

Fig. 1 **a** Sagittal PET showing hypermetabolic foci involving the area of the Waldeyer's tonsillar ring. ^{18}F -FDG-PET/CT axial image (PET in **b**; CT in **c**; and fused PET/CT in **d**) of the current patient with

previous history of nodal follicular lymphoma. Strong ^{18}F -FDG uptake is observed in both palatine tonsils (*arrows*), as well as in a jugulo-digastric lymph node (*arrowhead*)

Fig. 2 Histopathological features of the reactive follicular hyperplasia affecting the palatine tonsil (H&E stain). The irregular size of the reactive follicles is evident; however, the *clear* and *dark zones* as well as the attenuated *thin mantle zones* are well-defined. The

interfollicular areas are broad and well-defined (**a**, $\times 10$). In high-power view the reactive follicles of the Fig. 1a showed the germinal centre cells (*upper left*) clearly separated from the mantle/marginal zone cells (*lower right*) (**b**, $\times 40$)

Fig. 3 On hematoxylin and eosin-stained bone marrow sections, immature and mature myeloid cells, including erythroid lineage cells and a normal complement of megakaryocytes as well as adipose cells were observed (**a**, $\times 10$; **b**, $\times 40$)

[5, 14, 18]. Such as showed in our case, reactive tonsils and lymph nodes are responsible for decreased specificity of FDG-PET/CT scans for nodal or extranodal staging of many malignancies [14].

The intensity and symmetry of ^{18}F -FDG uptake are not useful in differentiating between benign and malignant etiology [5, 18]. Elevated or asymmetric head and neck ^{18}F -FDG accumulation without a correlating morphological lesion can frequently be found [19]. The normal SUV_{max} of the palatine tonsil in FDG-PET/CT scan shows values between 0.88 and 13.65 [19]. In our case, the SUV_{max} of the palatine tonsils was 17.4, a greater value when compared with physiological values. Moreover, it has been showed that the grade of follicular hyperplasia is significantly higher in false-positive lymph nodes than those true-negative lymph nodes. This can be explained by the finding that, besides the inflammatory component above mentioned, dendritic follicular cells consistently express GLUT protein [20, 21].

Similar to our case, several studies have reported FDG-PET/CT false-positives in patients with previous history of lymphoma. A 30-year-old, HIV-positive man, with a previous history of an atypical nasopharyngeal Burkitt lymphoma developed ^{18}F -FDG avidity on the area of his initial disease. An open biopsy, however, revealed nodal RFH [6]. Similar findings were observed by Beker et al. [2] in a 7-year-old child with Hodgkin lymphoma. The patient was considered cured, but ^{18}F -FDG uptake in the abdomen was observed, which microscopically revealed RFH. To the best of our knowledge, there is only one case of palatine tonsil RFH showing ^{18}F -FDG uptake in a 14-year-old boy after 6 cycles of aggressive chemotherapy for diffuse large B cell lymphoma [8]. It is interesting the fact that several RFH cases, usually affecting the tonsils, lymph nodes and thymus gland, in patients with hematological malignancies after chemotherapy have been reported [8, 11, 12, 22]. In these cases, it is often difficult to distinguish RFH from residual or recurrent disease, even if various imaging

modalities are used. Furthermore, chemotherapy can lead to a diffusely increased ^{18}F -FDG uptake within the whole bone marrow due to its activation [5]. Thus, considering these studies and the findings of our case; it is plausible to think that chemotherapy is probably related with this finding.

FL is one of the most common lymphoma entities, constituting about 22 % of adult lymphoma cases worldwide. Upon presentation, most patients have disseminated disease affecting peripheral lymph nodes and/or bone marrow, while only about 1/3 has limited stage disease. Probably the most challenging task is the characterization of lesions through imaging modalities, in order to distinguish potentially curable (stage I/II) from advanced disease (stage III/IV), and after completion of therapy [23]. The current case after 5-years of recurrence-free follow-up, showed an intense ^{18}F -FDG uptake in the Waldeyer's tonsillar ring, strongly suspicious of recurrent lymphoma. In these cases, a biopsy is tightly recommended to rule out a relapse or secondary transformation into aggressive lymphoma. Based on the morphologic appearance of the present case, initial considerations included RFH, "in situ" FL, and possibly "in situ" mantle cell lymphoma (MCL). However, because the previous history of nodal FL (CD20+, CD10+, bcl-2+, bcl-6+), the possibility of relapse affecting the palatine tonsil was strongly considered. However, immunostaining of serial sections showed that Ki-67 stained strongly all the GCs, usually showing a polarized proliferation pattern, while bcl-2 was negative. Moreover, cyclin D1 was uniformly negative.

The follicular pattern in RFH typically results of a humoral immune reaction, involving proliferation of B cells. RFH is commonly seen in children and young adults, as they are exposed to a variety of new antigens [24]. Microscopically, the lymphoid follicles are more numerous, with considerable variation in the size and shape, and may not be confined to the peripheral areas. The GCs are hyperplastic and compartmentalized and the mantle zones

are usually well-developed [24]. Moreover, it is interesting that RFH can occur after therapy for hematological malignancies. In fact, Kojima et al. [12] reported a case of a 30-year-old man who presented with swelling of the left tonsil diagnosed as RFH and with previous history of FL, treated with R-CHOP. Unfortunately, no FDG-PET/CT scans in this case were performed. Nevertheless, microscopically, different from findings of our case, numerous enlarged, bizarre-shaped coalescing lymphoid follicles with extensive follicular lysis were visualized [12].

For those patients without overt or with previous history of lymphoma and in the suspect of disease-related symptoms or signs of organ involvement, a clinical examination, based mostly on careful history and symptoms, and FDG-PET/CT scans should be highly considered. After careful analysis and unless otherwise indicated, the biopsy of new extranodal or nodal lesion, suspicious for lymphoma or relapse, is mandatory in all cases. Furthermore, a comprehensive knowledge of physiologic and altered physiologic ^{18}F -FDG uptake in the head and neck, as well as an awareness of potential pitfalls is necessary to minimize false-positive ^{18}F -FDG results.

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