Ann Nucl Med (2007) 21:325–330
DOI 10.1007/s12149-007-0030-2

ORIGINAL ARTICLE

Diffuse and diffuse-plus-focal uptake in the thyroid gland identified by using FDG-PET: prevalence of thyroid cancer and Hashimoto's thyroiditis

Seiji Kurata · Masatoshi Ishibashi · Yuji Hiromatsu
Hayato Kaida · Ikuyo Miyake · Masafumi Uchida
Naofumi Hayabuchi

Received: 11 January 2007 / Accepted: 30 March 2007

Abstract
Objective To investigate and evaluate the prevalence of incidental thyroid diffuse and diffuse-plus-focal fluorine-18 fluorodeoxyglucose (FDG) uptake in healthy subjects who underwent cancer screening on positron emission tomography (PET) scan, and also to evaluate the prevalence of thyroid cancer and Hashimoto's thyroiditis.
Methods We carried out a retrospective review of 1626 subjects who underwent PET scanning at our institution. Diffuse uptake was defined as FDG uptake in the whole thyroid gland, whereas diffuse-plus-focal uptake was defined as a thyroid lesion with both diffuse uptake and focal FDG uptake. The maximum standardized uptake value of the thyroid lesions was recorded and reviewed. In each selected subject with positive thyroid FDG uptake, serum thyroid-stimulating hormone, thyroid hormone, and thyroid antibodies were measured. Fine needle aspiration cytology was performed on patients with a definite nodule using ultrasonography.
Results Twenty-nine subjects (1.78%) were identified as having either diffuse FDG uptake (n = 25, 1.53%) or diffuse-plus-focal FDG uptake (n = 4, 0.24%). All subjects with diffuse FDG uptake were diagnosed as having Hashimoto's thyroiditis. In 1 of the 25 subjects with diffuse FDG uptake and two of the four with diffuse-plus-focal FDG uptake, histopathologic diagnosis showed papillary thyroid carcinoma associated with Hashimoto's thyroiditis. However, PET scan did not detect papillary carcinoma associated with Hashimoto's thyroiditis in one of the three subjects.
Conclusions Our results suggest that although diffuse FDG uptake usually indicates Hashimoto's thyroiditis, the risk of thyroid cancer must be recognized in both diffuse FDG uptake and diffuse-plus-focal FDG uptake on PET scan.

Keywords FDG-PET · Diffuse FDG uptake · Cancer screening · Hashimoto's thyroiditis · Thyroid cancer

S. Kurata (✉) · M. Ishibashi · H. Kaida
Division of Nuclear Medicine, Department of Radiology, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan
e-mail: skur@med.kurume-u.ac.jp

Y. Hiromatsu · I. Miyake
Division of Endocrinology and Metabolism, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

M. Uchida · N. Hayabuchi
Department of Radiology, Kurume University School of Medicine, Kurume, Japan

Introduction

Positron emission tomography (PET) is a functional imaging modality, increasingly being used in the diagnosis and staging of patients with neoplastic diseases [1], and has the potential to successfully provide cancer screening in healthy subjects [2, 3]. This imaging modality exploits the fact that many malignancies metabolize glucose at a much higher rate than normal tissue. The normal thyroid gland shows low-grade fluorine-18 fluorodeoxyglucose (FDG) uptake, or is usually not detected on a whole-body PET scan. Occasionally, diffuse or focal increased FDG uptake is seen as an incidental finding in the thyroid gland [4]. In a large series of patients, it was proved that diffuse thyroid FDG uptake could be an indicator of Hashimoto's thyroiditis [5]. Focal FDG uptake has been associated with malignancy

[6]. Thyroid cancer is also one of the most frequent incidental cancers detected on PET scans, and there have been many reports on thyroid cancers diagnosed during the PET evaluation of an unrelated condition [3, 6]. To date, there have been a few reports on thyroid cancer associated with diffuse and diffuse-plus-focal FDG uptake identified incidentally by PET examination as cancer screening. The objective of this study was to evaluate thyroid diffuse and diffuse-plus-focal FDG uptake in healthy subjects and to determine the prevalence of thyroid cancer and Hashimoto's thyroiditis in this population.

Materials and methods

Subjects

We reviewed our database for all subjects who underwent whole-body PET at our institution. PET scanning was performed as a cancer screening on presumptively healthy individuals with no history of malignancy. A total of 1626 subjects (885 men and 741 women), age 33–82 years (mean age ± standard deviation 58.7 ± 9.3 years), were included in the present study. The data from this study were retrospectively analyzed. All subjects gave informed consent, and the studies were approved by the Research Ethics Committee of Kurume University.

PET method

Positron emission tomography scans were obtained using a dedicated ALLEGRO PET scanner (Philips, Eindhoven, The Netherlands). All subjects fasted, except for water, for more than 4 h before the PET scan was carried out. All subjects showed a normal glucose level (range 80–120 mg/dl) that was measured immediately before the PET scan. Just before injection, they were hydrated with 500 ml of green tea. Image acquisitions for the whole-body scan started approximately 60 min after the intravenous administration of 7.03 ± 1.26 mCi injected dosage of FDG. Then they underwent scanning from the base of skull to midthighs with transmission attenuation correction (2 min and 30 s/bed position emission, 23 s/bed position transmission). Attenuation-corrected emission images were reconstructed using 3D-RAMLA (three-dimensional row action maximum likelihood algorithm; Philips, Eindhoven, the Netherlands).

Image analysis

All the studies were evaluated visually and semiquantitatively using the maximum standardized uptake value (SUV_{max}) by a nuclear medicine specialist with 5 years of PET experience. Thyroid lesion was defined as thyroid FDG uptake incidentally identified on PET study, and it was divided into diffuse type and diffuse-plus-focal type according to the FDG uptake pattern. Diffuse uptake was defined as FDG uptake in the whole thyroid gland. Diffuse-plus-focal uptake was defined as a thyroid lesion with both diffuse uptake and focal FDG uptake. Subjects with focal FDG uptake were excluded from the analysis.

Laboratory data

In each subject with positive thyroid FDG uptake, serum thyroid hormones were measured, including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels. The normal reference ranges are 1.9–3.5 pg/ml for FT3, 0.88–1.56 ng/dl for FT4, and 0.21–3.85 μIU/ml for TSH. Antithyroid antibodies including antithyroperoxidase and antithyroglobulin antibodies were also measured. None of the subjects were taking medications, known to affect the tests of thyroid function.

Ultrasonographic examinations

Ultrasonographic (US) examination of the thyroid was performed by one physician with 10 years of experience in thyroid US. All subjects were examined with a 7.5-MHz annular array transducer (Toshiba SSA250A, Tokyo, Japan). The abnormalities in the US findings were evaluated with respect to thyroid parenchymal change. The scans were interpreted by a single observer, blinded to the results of other imaging studies.

Results

FDG-PET findings

Of the 1626 FDG-PET scans reviewed, 29 subjects (1.78%) met criteria for having thyroid increased FDG uptake. Of these 29 subjects, 26 women and 3 men, with an age range of 33–82 years (mean age ± standard deviation 58.7 ± 9.3 years), and a higher incidence in women than in men, none had a history of thyroid disease. Twenty-five of the 29 subjects showed diffuse type, and the remaining four showed diffuse-plus-focal type. Representative FDG-PET scans of subjects with diffuse and diffuse-plus-focal FDG uptake are shown in Figs. 1 and 2. FDG-PET study, laboratory data, and clinical diagnosis in this study are summarized in Table 1.

Table 1 FDG-PET study, laboratory data, and clinical diagnosis results in 29 subjects

Subject no.	FDG uptake pattern	Diffuse SUV_{max}	Focal SUV_{max}	Sex	Age (years)	TSH μIU/ml	Antithyroid antibody	Thyroid function	Clinical diagnosis
1	Diffuse	2.5	–	F	66	1.5	Positive	Euthyroid	Hashimoto's thyroiditis
2	Diffuse	7.8	–	F	50	1.4	Positive	Euthyroid	Hashimoto's thyroiditis
3	Diffuse	2.4	–	F	62	1.6	Positive	Euthyroid	Hashimoto's thyroiditis
4	Diffuse	3.5	–	F	66	1.5	Positive	Euthyroid	Hashimoto's thyroiditis
5	Diffuse	3.8	–	F	65	2.4	Positive	Euthyroid	Hashimoto's thyroiditis
6	Diffuse	2.8	–	F	68	2.7	Positive	Euthyroid	Hashimoto'sthyroiditis
7	Diffuse	6.9	–	M	82	2	Positive	Euthyroid	Hashimoto's thyroiditis
8	Diffuse	2.4	–	F	56	1.4	Positive	Euthyroid	Hashimoto's thyroiditis
9	Diffuse	2.6	–	F	58	2.2	Positive	Euthyroid	Hashimoto's thyroiditis
10	Diffuse	3.6	–	F	65	2	Positive	Euthyroid	Hashimoto's thyroiditis
11	Diffuse	2.3	–	F	50	1.3	Positive	Euthyroid	Hashimoto's thyroiditis
12	Diffuse	1.8	–	F	60	2.8	Positive	Euthyroid	Hashimoto's thyroiditis
13	Diffuse	1.7	–	F	62	2.6	Positive	Euthyroid	Hashimoto's thyroiditis
14	Diffuse	1.6	–	F	58	1.4	Positive	Euthyroid	Hashimoto's thyroiditis
15	Diffuse	3.6	–	F	56	3.6	Positive	Euthyroid	Hashimoto's thyroiditis
16	Diffuse	4.2	–	F	33	2.1	Positive	Euthyroid	Hashimoto's thyroiditis
17	Diffuse	5.2	–	F	61	9.4	Positive	Subclinical hypothyroidism	Hashimoto's thyroiditis
18	Diffuse	3.4	–	F	61	7	Positive	Subclinical hypothyroidism	Hashimoto's thyroiditis
19	Diffuse	3.3	–	F	52	5	Positive	Subclinical hypothyroidism	Hashimoto's thyroiditis
20	Diffuse	4.3	–	F	64	4	Positive	Subclinical hypothyroidism	Hashimoto's thyroiditis
21	Diffuse	5.9	–	M	59	12.2	Positive	Subclinical hypothyroidism	Hashimoto's thyroiditis
22	Diffuse	3.0	–	F	47	4.6	Positive	Subclinical hypothyroidism	Hashimoto's thyroiditis
23	Diffuse	2.6	–	F	51	2.4	Positive	Euthyroid	Papillary carcinoma associated with HT[a]
24	Diffuse	2.6	–	F	72	1.3	Positive	Euthyroid	Adenomatous goiter associated with HT
25	Diffuse	3.8	–	F	60	1.3	Positive	Euthyroid	Adenomatous goiter associated with HT
26	Diffuse-plus-focal	4.4	8.8	F	59	5.3	Positive	Subclinical hypothyroidism	Papillary carcinoma associated with HT[a]
27	Diffuse-plus-focal	1.9	2.7	F	56	2.7	Negative	Euthyroid	Papillary carcinoma associated with HT[a]
28	Diffuse-plus-focal	1.5	2.8	M	63	7.9	Positive	Subclinical hypothyroidism	Adenomatous goiter associated with HT
29	Diffuse-plus-focal	1.6	2.1	F	42	3.3	Positive	Euthyroid	Adenomatous goiter associated with HT

FDG-PET fluorine-18 fluorodeoxyglucose positron emission tomography, *HT* Hashimoto's thyroiditis, SUV_{max} maximum standardized uptake value, *TSH* thyroid-stimulating hormone, normal range for serum TSH is 0.21–3.85 μIU/ml, *F* female, *M* male

[a] Subjects who received partial thyroidectomy and histopathologically reconfirmed to have papillary carcinoma with HT

Subjects with diffuse FDG uptake ($n = 25$)

Six of the 25 subjects were diagnosed as having subclinical hypothyroidism on the basis of the findings of laboratory examination. The remaining 19 subjects were euthyroid. One or both the antithyroid antibodies were positive in all subjects. There were diffuse parenchymal changes in all subjects on US. On the basis of these findings, all subjects were diagnosed as having Hashimoto's thyroiditis. One (subject 23) of the 25 subjects had a microcalcified solid nodule (size 0.6×0.5 cm), indicated by diffuse parenchymal changes of the right lobe of the thyroid gland on US. The FDG-PET scan and thyroid US findings of subject 23 are shown in Fig. 3a, b. It was diagnosed as papillary carcinoma by US-guided fine-needle aspiration (FNA) cytology. Two of the 25 subjects showed a low echoic nodule, as indicated by diffuse parenchymal change on US. US findings in these two patients revealed adenomatous goiter. US-guided FNA was not performed on these subjects because they refused.

Subjects with diffuse-plus-focal FDG uptake ($n = 4$)

Two of the four subjects were diagnosed with subclinical hypothyroidism. The remaining two subjects were euthyroid. One or both the antithyroid antibodies were positive in three subjects, and both the antithyroid antibodies were negative in one (subject 27). All subjects had solid nodules, as indicated by diffuse parenchymal changes on US. Two (subjects 26 and 27) of the four subjects had solid nodules with microcalcifications. All subjects had

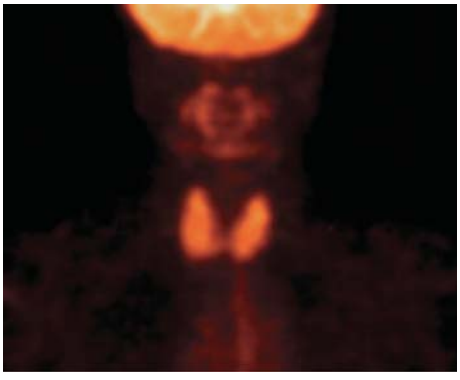

Fig. 1 Frontal maximum intensity projection from fluorodeoxyglucose positron emission tomography (FDG-PET) scan in subject 20 with diagnosed Hashimoto's thyroiditis. Intense diffuse FDG uptake (maximum standardized uptake value, SUV_{max} 4.3) is shown in the whole thyroid gland

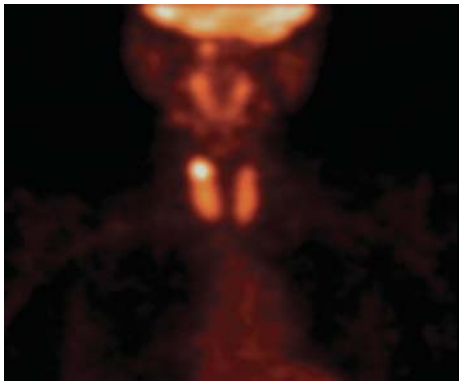

Fig. 2 Frontal maximum intensity projection from FDG-PET scan on subject 26 with diagnosed papillary carcinoma associated with Hashimoto's thyroiditis. Intense diffuse FDG uptake (SUV_{max} 4.4) can be seen in the whole thyroid gland, and focal FGD uptake (SUV_{max} 8.8) in the upper portion of the right lobe of the thyroid gland

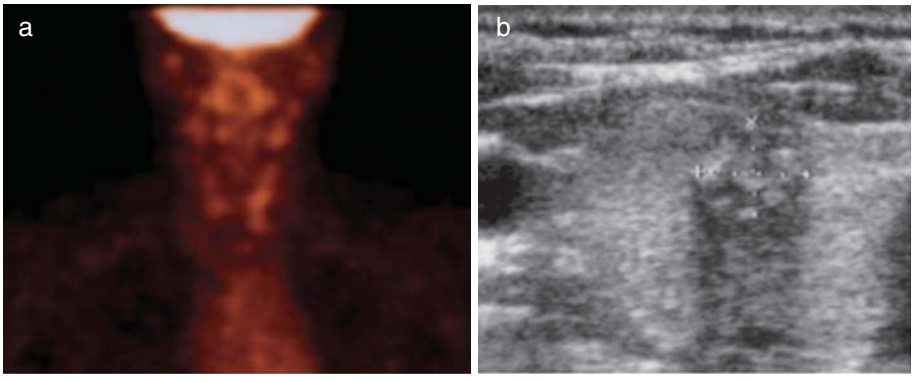

Fig. 3 **a** Frontal maximum intensity projection from a FDG-PET scan in subject 23 with diagnosed papillary carcinoma associated with Hashimoto's thyroiditis. Diffuse thyroid FDG uptake (SUV_{max} 2.6) can be seen in the whole thyroid gland. Focal FDG uptake is not visible in the right lobe of the thyroid gland. **b** Transverse thyroid ultrasonographic image for subject 23 shows an irregularly shaped hypoechogenic nodule (calipers) with microcalcified foci in diffuse parenchymal change, not palpable on the clinical examination. US-guided fine-needle aspiration cytology and surgery confirmed papillary carcinoma associated with Hashimoto's thyroiditis

thyroid US-guided FNA cytology: two subjects had papillary carcinoma associated with Hashimoto's thyroiditis, and the remaining two subjects had adenomatous goiter associated with Hashimoto's thyroiditis.

Discussion

FDG-PET is widely used in metastasis work-up of cancer patients [7] and cancer screening in healthy subjects without a previous history of cancer [8, 9]. In the present study, the prevalence of thyroid diffuse FDG uptake was 1.53%, a rate that is similar to that in other reports [5, 9–11]. The prevalence of diffuse-plus-focal FDG uptake was 0.24%, but there have been a few reports on diffuse-plus-focal FDG uptake in earlier studies [12].

In the present study, on the basis of thyroid hormonal levels, antithyroid antibodies levels, and US findings, diffuse FDG uptake was considered to indicate Hashimoto's thyroiditis. Yasuda et al. [5] have reported that diffuse thyroid uptake may be an indicator of chronic thyroiditis. Diffuse FDG uptake is most possibly benign, usually caused by chronic thyroiditis, whereas markedly increased focal FDG uptake in the thyroid gland has a significant risk of being malignant [10]. Although 1 of the 25 subjects with diffuse FDG uptake had no focal FDG uptake, this subject had a small papillary carcinoma associated with Hashimoto's thyroiditis. In this subject, the diameter of the carcinoma was less than 1 cm. False-negative results may be owing to a reduction in tumor metabolism or to the small size of the cancer. The small size of the nodule may be overlooked in diffuse FDG uptake by using PET scan; hence US and US-guided FNA was useful for the evaluation of thyroid nodules [13].

The clinical significance of a thyroid lesion with diffuse and focal FDG uptake is not well known. Choi et al. [12] have reported that a diffuse-plus-focal FDG uptake pattern might be associated with a benign condition, similar to a diffuse FDG uptake pattern. In our study, however, two of the four (50%) subjects with diffuse-plus-focal FDG uptake showed papillary carcinoma associated with Hashimoto's thyroiditis. This result may indicate the risk of malignancy in diffuse-plus-focal FDG uptake.

In this study, 3 of the 29 subjects (10%) had papillary carcinoma associated with Hashimoto's thyroiditis. All these subjects were women. The prevalence of autoimmune thyroiditis was significantly higher in patients with papillary carcinoma than in those with adenomatous goiter or follicular adenoma in Japanese women [14]. An increased incidence of thyroid carcinomas has been seen particularly in patients with Hashimoto's thyroiditis [15, 16]. However, there have been a few reports on papillary carcinoma associated with Hashimoto's disease in FDG-PET scan. Hashimoto's thyroiditis is caused by an immune response to thyroid antigens. The enhancement of cell death is considered to be caused by lymphocytic infiltration, targeting follicular epithelia owing to autoimmune phenomena [15]. The mechanism of FDG uptake in Hashimoto's thyroiditis is not yet known. Increased glucose transporters have been proposed as one of the reasons why malignant cells have increased FDG accumulation. However, this phenomenon is not tumor specific. Inflammatory cells have also increased the expression of glucose transporters when they are activated [17–20]. The result of inflammatory reactions may affect thyroid FDG uptake in Hashimoto's thyroiditis. Apoptosis may play an important role in cancer development. Enhanced cell death in chronic thyroiditis might include cell necrosis as well as apoptotic cell death [15, 16]. Hashimoto's thyroiditis may include malignant transformation by increased cell death and cell proliferation caused by chronic lymphocyte infiltration. We therefore believe that the risk of cancer related to diffuse thyroid uptake as observed by FDG-PET must be recognized.

Conclusions

Twenty-nine (1.78%) of 1626 subjects who underwent FDG-PET scans showed 25 diffuse uptake and 4 diffuse-plus-focal uptake patterns. Three (one diffuse uptake pattern, two diffuse-plus-focal uptake pattern) of the 29 subjects showed papillary carcinoma associated with Hashimoto's thyroiditis. Even if focal uptake is not detected in thyroid diffuse uptake on FDG-PET scans, we must evaluate thyroid malignancies in the thyroid gland. Our data suggest that subjects with diffuse and diffuse-plus-focal uptake on FDG-PET scans should receive both clinical and US follow-up. FDG-PET has a potential clinical impact on the incidental detection of possible thyroid cancer and Hashimoto's thyroiditis, but further studies, in which a larger number of patients are evaluated, are necessary.

References

1. Bomanji JB, Costa DC, Ell PJ. Clinical role of positron emission tomography in oncology. Lancet Oncol 2001;2:157–64.
2. Yasuda S, Shohtsu A. Cancer screening with whole-body 18F-fluorodeoxyglucose positron-emission tomography. Lancet 1997;350:1819.
3. Chen YK, Ding HJ, Chen KT, Chen YL, Liao AC, Shen YY, et al. Prevalence and risk of cancer of focal thyroid inciden-

taloma identified by ^{18}F-fluorodeoxyglucose positron emission tomography for cancer screening in healthy subjects. Anticancer Res 2005;25:1421–6.
4. Schoder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. Semin Nucl Med 2004;34:180–97.
5. Yasuda S, Shohtsu A, Ide M, Takagi S, Takahashi W, Suzuki Y, et al. Chronic thyroiditis: diffuse uptake of FDG at PET. Radiology 1998;207:775–8.
6. Ramos CD, Chisin R, Yeung HW, Larson SM, Macapinlac HA. Incidental focal thyroid uptake on FDG positron emission tomographic scans may represent a second primary tumor. Clin Nucl Med 2001;26:193–7.
7. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. Radiology 2004;231:305–32.
8. Yasuda S, Ide M, Fujii H, Nakahara T, Mochizuki Y, Takahashi W, et al. Application of positron emission tomography imaging to cancer screening. Br J Cancer 2000;83: 1607–11.
9. Kang KW, Kim SK, Kang HS, Lee ES, Sim JS, Lee IG, et al. Prevalence and risk of cancer of focal thyroid incidentaloma identified by ^{18}F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. J Clin Endocrinol Metab 2003;88: 4100–4.
10. Kim TY, Kim WB, Ryu JS, Gong G, Hong SJ, Shong YK. ^{18}F-fluorodeoxyglucose uptake in thyroid from positron emission tomogram (PET) for evaluation in cancer patients: high prevalence of malignancy in thyroid PET incidentaloma. Laryngoscope 2005;115:1074–8.
11. Cohen MS, Arslan N, Dehdashti F, Doherty GM, Lairmore TC, Brunt LM, et al. Risk of malignancy in thyroid incidentalomas identified by fluorodeoxyglucose-positron emission tomography. Surgery 2001;130:941–6.
12. Choi JY, Lee KS, Kim HJ, Shim YM, Kwon OJ, Park K, et al. Focal thyroid lesions incidentally identified by integrated ^{18}F-FDG PET/CT: clinical significance and improved characterization. J Nucl Med 2006;47:609–15.
13. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid 1998;8:283–9.
14. Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma: a study of surgical cases among Japanese, and white and African Americans. Cancer 1995;76:2312–8.
15. Okayasu I, Saegusa M, Fujiwara M, Hara Y, Rose NR. Enhanced cellular proliferative activity and cell death in chronic thyroiditis and thyroid papillary carcinoma. J Cancer Res Clin Oncol 1995;121:746–52.
16. Andrikoula M, Tsatsoulis A. The role of Fas-mediated apoptosis in thyroid disease. Eur J Endocrinol 1999;144:561–8.
17. Chakrabarti R, Jung CY, Lee TP, Liu H, Mookerjee BK. Changes in glucose transport and transporter isoforms during the activation of human peripheral blood lymphocytes by phytohemagglutinin. J Immunol 1994;152:2660–8.
18. Gamelli RL, Liu H, He LK, Hofmann CA. Augmentations of glucose uptake and glucose transporter-1 in macrophages following thermal injury and sepsis in mice. J Leukoc Biol 1996;59:639–47.
19. 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;33:1972–80.
20. Schmid DT, Kneifel S, Stoeckli SJ, Padberg BC, Merrill G, Goerres GW. Increased 18F-FDG uptake mimicking thyroid cancer in a patient with Hashimoto's thyroiditis. Eur Radiol 2003;13:2119–21.