The Clinical Usefulness of ^{18}F -FDG PET/CT in Patients with Systemic Autoimmune Disease

Jong-Ryool Oh · Ho-Chun Song · Sae-Ryung Kang · Su-Woong Yoo · Jahae Kim ·
Ari Chong · Jung-Joon Min · Hee-Seung Bom · Shin-Seok Lee · Yong-Wook Park

Received: 26 April 2011 / Accepted: 22 June 2011 / Published online: 5 August 2011
© Korean Society of Nuclear Medicine 2011

Abstract

Purpose Individuals with systemic autoimmune disease have an increased susceptibility to both inflammation and malignancy. The aim of this study was to evaluate the clinical usefulness of ^{18}F -FDG PET/CT in patients with systemic autoimmune disease.

Methods Forty patients diagnosed with systemic autoimmune disease were enrolled. Diagnostic accuracy of FDG PET/CT for detecting malignancy was assessed. FDG PET/CT findings, including maximum standardized uptake (SUVmax) of lymphadenopathy (LAP), liver, bone marrow, spleen, joint and muscles, were considered for the characterization of LAPs.

Results FDG PET/CT could detect metabolically activated lesions in 36 out of 40 patients (90%) including inflammatory lesions in 28 out of 32 patients (88%). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG PET/CT for the detection of malignancy were 100, 67, 70, 25, and 100%, respectively. Multiple LAPs were found in 25 of 40 patients (63%), and comprised three malignancies, four cases of tuberculosis, and 18 reactive changes. A SUVmax ratio of bone marrow to liver below 0.78 could distinguish malignancy from tuberculosis + reactive change (AUC=1.000, sensitivity:

100%, specificity: 100%). The SUVmax ratio of spleen to liver in the reactive group was also significantly higher than that in the malignancy group ($P=0.014$). SUVmax of LAP in the TB group was significantly higher than that in the reactive group ($P=0.040$).

Conclusions PET/CT is useful in detecting and differentiating inflammation and malignancy in patients with systemic autoimmune disease. Frequent false-positive interpretations can be minimized by consideration of FDG uptake in bone marrow and spleen.

Keywords Autoimmune disease · PET/CT · Neoplasms · Tuberculosis · Reactive lymphoid hyperplasia

Introduction

Systemic autoimmune diseases are a heterogeneous group of disorders in which “self-tolerance” has been overcome by genetic and environmental factors and an immune response has been mounted against the body’s own organs, tissues, and cells [1]. The diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis, dermatomyositis/polymyositis, Sjögren’s syndrome, and polyarthritis nodosa, among others. These chronic inflammatory and immunomodulatory conditions have been suggested to increase the risk of cancers such as lymphoma, lung cancer, esophageal cancer, and pancreatic cancer [2–4]. The treatment of autoimmune diseases is typically with immunosuppression, which decreases the immune response of the body. However, the majority of immunosuppressive agents also increase the incidence of infection, such as reactivated tuberculosis (TB) [5].

J.-R. Oh · H.-C. Song (✉) · S.-R. Kang · S.-W. Yoo · J. Kim ·
A. Chong · J.-J. Min · H.-S. Bom
Department of Nuclear Medicine,
Chonnam National University Medical School and Hospital,
8 Hakdong,
Dongku, Gwangju 501-757, South Korea
e-mail: songhc@jnu.ac.kr

S.-S. Lee · Y.-W. Park
Department of Rheumatology, Chonnam National University
Hospital,
Gwangju, South Korea

^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is a noninvasive metabolic imaging that plays a major role in the management of oncology patients. It is well recognized that FDG accumulates not only in malignant tissue but also at the site of inflammation or infection. This response to inflammation and infection has been considered by many over the years as a shortcoming of the technology and a source of false-positive results in the assessment of malignancy. However, FDG PET/CT is now seen as having increasing potential for use in examining and managing patients with infectious and inflammatory disorders [6, 7]. Nevertheless, the clinical use of FDG PET/CT in patients with systemic autoimmune disease who have increased susceptibility to both malignancy and infection has not been discussed well.

This study therefore aimed to evaluate the clinical usefulness of FDG PET/CT to detect and differentiate malignancy and inflammation in patients with systemic autoimmune disease.

Materials and Methods

Patients

A total of 40 patients (31 women, 9 men; mean age, 49 years; range, 18–67 years) with systemic autoimmune disease were enrolled in this retrospective study. The diagnosis of underlying disease was made based on clinical manifestation, serology, imaging, and/or histopathology, according to the diagnostic criterion of each disease as follows: 10 systemic lupus erythematosus, 9 adult-onset Still's disease, 9 dermatomyositis/polymyositis, 6 rheumatoid arthritis, 4 Sjögren's syndrome, and 2 erythema nodosum (Table 1). Twenty-six patients were newly diagnosed, while 14 patients had been previously diagnosed with systemic autoimmune disease. Among the 14 patients who were previously diagnosed, 10 patients were under immunosuppressive treatment at the time of the PET/CT scan. No patient had received chemotherapy or granulocyte colony-stimulating factor. Chief reasons for PET/CT referral were searching for hidden malignancy in 23 patients, lymphadenopathy (LAP) in 16 patients, and fever of unknown origin in 1 patient. All patients underwent blood testing including white blood cell (WBC), absolute neutrophil count (ANC), hemoglobin (Hgb), platelet, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) within 2 days of PET/CT examination.

Imaging Acquisitions

^{18}F -FDG PET/CT was performed on a Discovery STE PET/CT system (GE Medical Systems, Milwaukee, WI, USA).

Table 1 Patient demography ($n=40$)

Characteristic	Value
Gender	
Female	31 (78%)
Male	9 (22%)
Mean age, range (years)	49, 18–67
Underlying disease	
Systemic lupus erythematosus	10 (25%)
Adult-onset Still's disease	9 (22.5%)
Dermatomyositis/polymyositis	9 (22.5%)
Rheumatoid arthritis	6 (15%)
Sjögren's syndrome	4 (10%)
Erythema nodosum	2 (5%)
Malignancy	
Present	4 (10%)
Absent	36 (90%)
Lymphadenopathy	
Present	25 (62.5%)
Absent	15 (37.5%)

The patients fasted for at least 6 h prior to the intravenous administration of ^{18}F -FDG (7.4 MBq per kg body weight) to ensure a serum glucose level below 8.3 mmol/L. At 60 min after ^{18}F -FDG administration, transmission data were acquired by means of a low-dose CT scan (120 kV, automated from 10 to 130 mA, a 512×512 matrix, a 50 cm field of view (FOV), 3.75 mm slice thickness, and a rotation time of 0.8 s), extending from the base of the skull to the proximal thigh. Immediately after CT acquisition, PET emission scans were acquired in the same anatomic locations with a 15.7-cm axial FOV acquired in three-dimensional mode with a 128×128 matrix. The CT data were used for attenuation correction. The images were reconstructed using a conventional iterative algorithm (ordered-subsets expectation-maximization). Image display and analysis were performed using an Advanced Workstation (GE Medical Systems) providing multiplanar reformatted images.

Image Analysis

PET/CT image was reviewed by two experienced nuclear medicine physicians who were unaware of the clinical manifestation, blood testing, other imaging modalities, or histopathology. The possibility of malignancy was scored as follows by consensus considering the location, distribution, intensity, and nature of FDG uptake: 5 = definitely malignant, 4 = possibly malignant, 3 = equivocal finding, 2 = possibly benign, 1 = definitely benign. Standards of reference were histopathology or clinical follow-up with imaging studies. LAP was defined as one or more enlarged

lymph nodes with a short-axis diameter of 10 mm or more in any site on conventional contrast-enhanced computed tomography or with increased glucose uptake on PET/CT even if the short-axis diameter was less than 1 cm [8]. Semiquantitative analysis using maximum standardized uptake value (SUVmax) based on administered tracer activity and patient body weight was applied. SUV_{LAP} was the highest SUVmax among LAPs. SUV_L and SUV_S were SUVmax in liver and spleen, respectively. SUV_{BM} was a mean of SUVmax from T10 to L3 vertebrae. If there was focal increased FDG activity, the unaffected lesion was used for the measurement in each organ. SUV_J and SUV_M were means of SUVmax in bilateral shoulder joints and in bilateral proximal muscles of the upper arm avoiding venous structures, respectively. Liver was also used as a reference organ. Regions of LAP were also recorded as follows: cervical, axillary, mediastinal, hilar, abdominal (including retroperitoneal, porta-hepatic, para-aortic, and para-caval areas), iliac, and inguinal areas.

Statistical Analysis

Statistical analysis was performed with MedCalc software version 11.5 (Mariakerke, Belgium). To determine the optimal score demonstrating the highest diagnostic performance of PET/CT in detecting malignancy, the receiver-operating-characteristic (ROC) analysis was applied. The sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated using standard statistical formulae. The Kruskal-Wallis test was used for comparing hematologic and metabolic variables between subgroups. A p -value of <0.05 was considered to indicate a statistically significant difference.

Results

Standards of Reference and PET/CT Findings

PET/CT showed metabolically activated lesions in 36 out of 40 patients (90%) and PET/CT was also helpful as a guide for biopsy in 15 patients (38%). Histopathology revealed four patients having malignancy—two primary lung malignancies (adenocarcinoma) and two lymphomas (one intravascular B-cell lymphoma and one nodal marginal zone B-cell lymphoma)—and four patients with TB—one involving breast, lung, and lymph nodes, and three involving lymph nodes only. Among 32 patients without evidence of malignancy or TB infection, PET/CT could also successfully visualize one or more hyperactive lesions in 28 patients (88%); lymph nodes in 18 patients (56%), bone marrow in 15 patients (47%), spleen in 13 patients (41%), joints in 11 patients (34%), muscle and soft tissue in 7

Fig. 1 Incidences of metabolically activated organs in patients with systemic autoimmune disease but not with malignancy or tuberculosis infection. *NED* No evidence of disease

patients (22%), lung in 6 patients (19%), and liver in 1 patient (3%) (Fig. 1). Fourteen patients were evaluated with histopathology, and 18 patients were evaluated with clinical follow-up with imaging or serologic studies for confirming the absence of malignancy or TB infection.

Diagnostic Performance

PET score >3 was the best predictor in detecting malignancy, resulting in sensitivity, specificity, accuracy, positive

Fig. 2 Receiver-operating-characteristic analysis of ^{18}F -FDG PET/CT in detecting malignancy in patients with systemic autoimmune disease

Table 2 Diagnostic performance of ^{18}F -FDG PET/CT in detecting malignancy in patients with systemic autoimmune disease

	TP (<i>n</i>)	FP (<i>n</i>)	FN (<i>n</i>)	TN (<i>n</i>)	Sensitivity	Specificity	DA	PPV	NPV
PET/CT	4	12	0	24	100%	67%	70%	25%	100%

TP True positive, FP false positive, FN false negative, TN true negative, DA diagnostic accuracy, PPV positive predictive value, NPV negative predictive value

predictive value, and negative predictive value of 100, 67, 70, 25, and 100%, respectively (Fig. 2, Table 2; AUC=0.847, 95% CI=0.698–0.941). PET scores were 5 in 3 patients (1 malignancy, 1 TB, and 1 reactive LAP), 4 in 13 patients (3 malignancies, 3 TB, 7 reactive LAP), 3 in 4 patients, 2 in 3 patients, and 1 in 17 patients. Twenty-four true negative findings included 10 reactive LAP and 14 nonspecific findings.

Characterization of Lymphadenopathy

Subgroup analysis was performed to characterize LAPs. The SUVmax ratio of bone marrow to liver ($\text{SUV}_{\text{BM/L}}$) in the reactive group was significantly higher than those in the TB and malignancy groups (30 and 86%, respectively) (Table 3). The SUVmax ratio of spleen to liver ($\text{SUV}_{\text{S/L}}$) in the reactive group was also significantly higher (88%) than

that in the malignancy group. SUV_{LAP} in TB group was significantly higher (120%) than that in the reactive group. In contrast, SUV_{L} , $\text{SUV}_{\text{J/L}}$, and $\text{SUV}_{\text{M/L}}$ did not differ significantly among the three groups. All hematologic variables, i.e., WBC, ANC, Hgb, platelet, CRP, ESR, and LDH, were also not significantly different among the three groups (Table 3). $\text{SUV}_{\text{BM/L}} \leq 0.78$ could distinguish malignancy from TB + reactive group with 100% sensitivity, specificity, diagnostic accuracy, PPV, and NPV (Fig. 3).

In the reactive group, the predominant sites of LAP were cervical and iliac areas (78%, 14/18, each), followed by abdomen (72%, 13/18), axilla (67%, 12/18), mediastinum (56%, 10/18), and hilar and inguinal areas (33%, 8/18, each).

Discussion

In the presented study, FDG PET/CT was useful for detecting inflammatory or infectious foci in patients with systemic autoimmune disease. It also showed high sensitivity and negative predictive value in detecting and excluding malignancy. Frequent false-positive interpretations associated with inflammation and infection could also be remedied through consideration of PET/CT findings in bone marrow and spleen (Fig. 4). Overactivity measured by FDG uptake in bone marrow and spleen was found in a majority of patients with reactive LAP, to a lesser extent in TB, and not significantly in malignant patients.

Systemic autoimmune diseases are characterized as a group by the presence of spontaneous overactivity of the immune system that results in the production of extra antibodies. The diseases can afflict every organ and tissue in body, especially lymphoid tissues, joints, skin, muscles, salivary glands, and bone marrow, with the targets differing according to disease entity and status [1, 5]. Although they result in a wide array of clinical signs and symptoms, constitutional symptoms such as fever, anorexia, muscle and joint ache, fatigue, and weight loss are present in the majority of patients with systemic autoimmune disease, and some diseases can coexist and overlap [9]. In this study, FDG PET/CT could successfully visualize the degree and extent of the disease in the entire body. It is well documented in the previous literature that FDG PET/CT has great potential in evaluating patients with systemic

Table 3 Comparison of metabolic and hematologic variables among the three groups presenting lymphadenopathy

	Reactive (<i>n</i> =18)	TB (<i>n</i> =4)	Malignancy (<i>n</i> =3)	<i>p</i> value
Metabolic variables				
$\text{SUV}_{\text{BM/L}}$	1.3±0.4	1.0±0.1	0.7±0.2	0.004 ^a
$\text{SUV}_{\text{S/L}}$	1.5±0.6	1.1±0.3	0.8±0.02	0.014 ^b
SUV_{LAP}	6.4±3.6	14.1±6.2	7.5±4.5	0.040 ^c
$\text{SUV}_{\text{J/L}}$	1.1±0.9	0.8±0.4	0.5±0.02	0.114
$\text{SUV}_{\text{M/L}}$	0.5±0.3	0.4±0.1	0.6±0.3	0.638
Hematologic variables				
WBC (count, ×10 ³)	8.8±4.8	6.4±3.8	5.8±3.8	0.459
Hgb	9.9±1.5	7.9±0.7	9.9±3.0	0.056
Platelet	295±173	302±15	142±170	0.407
ANC (count, ×10 ³)	6.6±3.5	4.6±3.3	3.4±3.2	0.154
ESR	66±43	76±33	76±44	0.765
CRP	6.1±5.5	9.2±5.4	5.8±4.6	0.450
LDH	1,172±783	445±177	777±231	0.097

TB Tuberculosis, SUV standardized uptake value, BM bone marrow, S spleen, L liver, LAP lymphadenopathy, J joint, M muscle, WBC white blood cell, ANC absolute neutrophil count, Hgb hemoglobin, ESR erythrocyte sedimentation rate, CRP c-reactive protein, LDH lactate dehydrogenase

^a Reactive vs. malignancy, reactive vs. TB

^b Reactive vs. malignancy

^c Reactive vs. TB

Fig. 3 Comparisons of $SUV_{BM/L}$ (a), $SUV_{S/L}$ (b), and SUV_{LAP} (c) among reactive, tuberculosis (TB), and malignancy groups

inflammatory disease [10–18]. However, it should also not be ignored that those patients have increased susceptibility to various malignancies. Although the reported risk levels have typically varied, several autoimmune and chronic inflammatory conditions have been consistently linked with an increased risk of malignancies in a large number of studies in different populations and with different designs [19–21]. The reported average relative increased risks of malignant lymphoma from the largest studies range from about 2-fold in rheumatoid arthritis, to 3- to 6-fold in SLE, and 9- to 18-fold in Sjögren's syndrome [20]. It has been reported that patients with a history of autoimmune disease have a 2.4-fold excess risk of esophageal cancer and 2-fold increased risk of pancreatic cancer [22]. The incidence of cancer in patients with dermatomyositis and polymyositis was approximately seven times that of the general population [4]. Males with rheumatoid arthritis have also been known to have significantly higher risks (up to twofold) of

lung, liver, melanoma, and esophageal malignancy [23]. FDG PET/CT could successfully detect and exclude malignancy in patients with systemic autoimmune disease in the presented study.

However, frequent false-positive findings associated with inflammation and infection considerably negated the diagnostic performance of PET/CT. Herein we suggested a possible remedy for that limitation: frequently, overactivity in bone marrow and spleen can be helpful to differentiate systemic inflammatory change from malignancy. Bone marrow and spleen are common sites involved in lymphoma, and the incidences have been reported to be 5–80% and 20–40%, respectively [24–27], with patterns of FDG uptake that can be diffuse or focal [25]. Of the two patients diagnosed with lymphoma in this study, one patient showed focal splenic FDG uptake and neither showed abnormal bone marrow FDG uptake (Fig. 5). However, most patients with reactive LAP showed diffuse bone marrow (89%, 16/

Fig. 4 A 45-year-old woman with a 30-year history of rheumatoid arthritis who was referred for FDG PET/CT to evaluate fever. Anterior maximum intensity projection (MIP) image (a) and axial PET/CT fusion image (b, c) showed multiple hypermetabolic lymph nodes (LN) and diffusely increased FDG uptake in bilateral shoulder joints, spleen, and bone marrow (arrows). Histopathology in right supraclavicular LN (arrowhead, SUVmax: 4.9) and bone marrow revealed them as reactive changes

Fig. 5 A 58-year-old female with a 13-year history of systemic lupus erythematosus who was referred for FDG PET/CT to evaluate lymphadenopathy (LAP). Anterior MIP image (a) and axial PET/CT fusion image (b, c) showed multiple hypermetabolic LAPs in whole body, hepatosplenomegaly, and focal splenic FDG uptake (arrowhead). Excisional biopsy for right supraclavicular LN (arrow; SUVmax: 12.4) revealed it as nodal marginal zone b-cell lymphoma

18) and splenic (78%, 14/18) uptake exceeding hepatic uptake, except for one patient who showed focal splenic uptake. Those incidences are significantly higher than those in lymphoma.

Although it did not reach statistical difference, FDG uptake in the joints of the reactive group was also higher than in the malignancy group (Table 3). Overactivity in joints ($SUV_{JL} > 1$) was observed in 8 of 25 patients with LAP. Among them, seven patients were in the reactive group, one in the TB group, and none in the malignancy group. In addition to bone marrow and spleen, joint activity may also be helpful to differentiate reactive LAP from malignancy.

The treatment of autoimmune diseases is typically with immunosuppression to decrease the immune response of the body using nonsteroidal anti-inflammatory drugs, glucocorticoids, disease-modifying anti-rheumatic drugs, or biologic drugs such as antitumor necrosis factor alpha (anti-TNF α) agents. Several agents are known to increase the susceptibility to infection, such as reactivated TB [5]. It is estimated that at least 50% of patients with SLE and up to 30% of patients with dermatomyositis/polymyositis will suffer a severe infectious episode during the course of the disease [28, 29]. High-dose glucocorticoids are well recognized to increase the risk of infectious complications. A recent cohort study of 15,597 rheumatoid arthritis

Fig. 6 A 51-year-old female with a 5-year history of Sjögren's disease who was referred for FDG PET/CT to evaluate lymphadenopathy (LAP). Anterior MIP image (a) and axial PET/CT fusion image (b, c) showed multiple hypermetabolic LAPs in the abdomen. Excisional biopsy for para-aortic LN (arrow; SUVmax: 16.3) revealed it as TB infection

patients from a Medicare beneficiary database found that glucocorticoid use doubled the rate of serious bacterial infections compared with methotrexate use [30]. Anti-TNF α agents also involve a higher risk (1.5- to 2-fold) of serious infections [31]. Of the four patients affected with TB in this study, two were under treatment with immunosuppressive agents.

We also found that FDG uptake of LAP in the TB group was higher than that in the reactive group (Fig. 6). This result corresponds to the study performed by Sathekge et al. They reported that FDG uptake in lymph nodes of TB-positive and human immunodeficiency virus (HIV)-positive patients was significantly higher than that of TB-negative and HIV-positive patients [32]. It is well known that activated macrophages and lymphocytes take up glucose in lymph nodes. Deol et al. showed that down-regulation of the protein kinase PknF significantly increased uptake of glucose in mycobacterium tuberculosis [33]. That could be an additional source of FDG uptake in LAP infected by TB.

A limitation of this study is the small set of patients in the malignancy and TB groups. Those groups also include patients afflicted with disease in extra-lymphatic organs, as well as only in the lymphatic system. However, to the best of our knowledge, this is the first report that demonstrates the characteristics of FDG PET findings in a considerable number of patients with systemic autoimmune disease. Further research with a larger population should be undertaken to validate the clinical usefulness of FDG PET/CT in systemic autoimmune disease.

In conclusion, our preliminary data showed that PET/CT was useful in evaluating the degree and extent of inflammation in patients with systemic autoimmune disease. It can also be helpful to detect and differentiate malignancy and coexisting inflammatory or infectious change in the entire body. Diffusely increased FDG uptake in bone marrow and spleen suggests the LAP to be representative of reactive change rather than malignancy, and higher FDG activity in LAP suggests TB infection rather than reactive change. Those findings can minimize frequent false-positive interpretations in this clinical setting.

Conflict of interest None declared.

References

- Ramos-Casals M, Brito-Zeron P, Lopez-Soto A, Font J. Systemic autoimmune diseases in elderly patients: atypical presentation and association with neoplasia. *Autoimmun Rev*. 2004;3:376–82.
- Kiss E, Kovacs L, Szodoray P. Malignancies in systemic lupus erythematosus. *Autoimmun Rev*. 2010;9:195–9.
- O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. *Br J Cancer*. 2001;85:473–83.
- Sela O, Shoenfeld Y. Cancer in autoimmune diseases. *Semin Arthritis Rheum*. 1988;18:77–87.
- Carter PH, Zhao Q. Clinically validated approaches to the treatment of autoimmune diseases. *Expert Opin Investig Drugs*. 2010;19:195–213.
- Basu S, Chrysosikios T, Moghadam-Kia S, Zhuang H, Torigian DA, Alavi A. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. *Semin Nucl Med*. 2009;39:36–51.
- Gotthardt M, Bleeker-Rovers CP, Boerman OC, Oyen WJ. Imaging of inflammation by PET, conventional scintigraphy, and other imaging techniques. *J Nucl Med*. 2010;51:1937–49.
- Chung HH, Nam BH, Kim JW, Kang KW, Park NH, Song YS, et al. Preoperative [18F]FDG PET/CT maximum standardized uptake value predicts recurrence of uterine cervical cancer. *Eur J Nucl Med Mol Imaging*. 2010;37:1467–73.
- Kumar TS, Aggarwal A. Approach to a patient with connective tissue disease. *Indian J Pediatr*. 2010;77:1157–64.
- Beckers C, Ribbens C, Andre B, Marcelis S, Kaye O, Mathy L, et al. Assessment of disease activity in rheumatoid arthritis with (18)F-FDG PET. *J Nucl Med*. 2004;45:956–64.
- Choe JY, Chung DS, Park SH, Kwon HH, Kim SK. Clinical significance of (1)F-fluoro-dexoxyglucose positron emission tomography in patients with adult-onset Still's disease: report of two cases and review of literatures. *Rheumatol Int*. 2010;30:1673–6.
- dos Anjos DA, do Vale GF, Campos Cde M, do Prado LF, Sobrinho AB, da Cunha AL et al. Extra-articular inflammatory sites detected by F-18 FDG PET/CT in a patient with rheumatoid arthritis. *Clin Nucl Med*. 2010;35:540–1.
- Elzinga EH, van der Laken CJ, Comans EF, Boellaard R, Hoekstra OS, Dijkmans BA, et al. 18F-FDG PET as a tool to predict the clinical outcome of infliximab treatment of rheumatoid arthritis: an explorative study. *J Nucl Med*. 2011;52:77–80.
- Funauchi M, Ikoma S, Kishimoto K, Shimazu H, Nozaki Y, Sugiyama M, et al. A case of adult onset Still's disease showing marked accumulation in the liver and spleen, on positron emission tomography-CT images. *Rheumatol Int*. 2008;28:1061–4.
- Jadvar H, Bonyadlou S, Iagaru A, Colletti PM. FDG PET-CT demonstration of Sjogren's sialoadenitis. *Clin Nucl Med*. 2005;30:698–9.
- Kubota K, Ito K, Morooka M, Mitsumoto T, Kurihara K, Yamashita H, et al. Whole-body FDG-PET/CT on rheumatoid arthritis of large joints. *Ann Nucl Med*. 2009;23:783–91.
- Nishiyama Y, Yamamoto Y, Dobashi H, Kameda T. Clinical value of 18F-fluorodeoxyglucose positron emission tomography in patients with connective tissue disease. *Jpn J Radiol*. 2010;28:405–13.
- Nowak M, Carrasquillo JA, Yarburo CH, Bacharach SL, Whatley M, Valencia X, et al. A pilot study of the use of 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography to assess the distribution of activated lymphocytes in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2004;50:1233–8.
- Anderson LA, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *Int J Cancer*. 2009;125:398–405.
- Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas—an update. *J Intern Med*. 2008;264:514–27.
- Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. *Eur J Cancer*. 2006;42:3028–33.

22. Völkers N. Do autoimmune diseases raise the risk of cancer? *J Natl Cancer Inst.* 1999;91:1992–3.
23. Parikh-Patel A, White RH, Allen M, Cress R. Risk of cancer among rheumatoid arthritis patients in California. *Cancer Causes Control.* 2009;20:1001–10.
24. Moulin-Romsee G, Hindie E, Cuenca X, Brice P, Decaudin D, Benamor M, et al. (18)F-FDG PET/CT bone/bone marrow findings in Hodgkin's lymphoma may circumvent the use of bone marrow trephine biopsy at diagnosis staging. *Eur J Nucl Med Mol Imaging.* 2010;37:1095–105.
25. Paes FM, Kalkanis DG, Sideras PA, Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. *Radiographics.* 2010;30:269–91.
26. Pelosi E, Penna D, Douroukas A, Bello M, Amati A, Arena V et al. Bone marrow disease detection with FDG-PET/CT and bone marrow biopsy during the staging of malignant lymphoma: results from a large multicentre study. *Q J Nucl Med Mol Imaging.* 2010. Dec 9. [Epub ahead of print]
27. Salaun PY, Gastinne T, Bodet-Milin C, Campion L, Cambefort P, Moreau A, et al. Analysis of 18F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? *Eur J Nucl Med Mol Imaging.* 2009;36:1813–21.
28. Zampieri S, Ghirardello A, Iaccarino L, Briani C, Sarzi-Puttini P, Atzeni F, et al. Polymyositis-dermatomyositis and infections. *Autoimmunity.* 2006;39:191–6.
29. Zandman-Goddard G, Shoenfeld Y. Infections and SLE. *Autoimmunity.* 2005;38:473–85.
30. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum.* 2007;56:1754–64.
31. Patkar NM, Teng GG, Curtis JR, Saag KG. Association of infections and tuberculosis with antitumor necrosis factor alpha therapy. *Curr Opin Rheumatol.* 2008;20:320–6.
32. Sathekge M, Maes A, Kgomo M, Pottel H, Stolz A, Van De Wiele C. FDG uptake in lymph-nodes of HIV+ and tuberculosis patients: implications for cancer staging. *Q J Nucl Med Mol Imaging.* 2010;54:698–703.
33. Deol P, Vohra R, Saini AK, Singh A, Chandra H, Chopra P, et al. Role of *Mycobacterium tuberculosis* Ser/Thr kinase PknF: implications in glucose transport and cell division. *J Bacteriol.* 2005;187:3415–20.