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Preliminary PET/CT Study of ^{18}F-FDG Uptake in Cervical and Supraclavicular Brown Adipose Tissue

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OBJECTIVE The clinical use of PET/CT in oncology has led to the realization that ^{18}F-FDG uptake in brown adipose tissue (BAT) can be a common cause of potentially misleading false-positive PET scans. The goal of this study was to study ^{18}F-FDG uptake in cervical and supraclavicular regions and its characteristics with PET/CT.
METHODS All the PET/CT scans obtained at our institution from July 2007 to January 2008 were retrospectively reviewed for increased ^{18}F-FDG uptake in BAT. The cases in which increased ^{18}F-FDG in cervical and supraclavicular regions was not localized to a soft-tissue mass or lymph node or muscle on the CT images, were included in this study. The following features were recorded: body weight, body mass index (BMI) and maximal standardized uptake value (SUVmax). In these selected patients, the BAT uptake in other area of the body was also recorded.
RESULTS PET/CT scans were obtained in 457 patients (259 males and 198 females). In all of the scans, cervical and supraclavicular BAT uptake was observed in 12 patients (2 males and 10 females) and was typically bilateral, symmetric and intense. The range of the SUVmax was 3.6~12.82 (mean 6.9 ± 2.6). BAT uptake was more common in females than in males, showing a significant difference (P = 0.004). Although ^{18}F-FDG uptake in BAT occurred more often in underweight patients with low BMI, there was no difference in the body weight (P = 0.607) or BMI (P = 0.491) of these patients with hypermetabolic BAT compared with controls.
CONCLUSION Hypermetabolic BAT uptake can be localized in cervical and supraclavicular regions with it occurring more commonly in females compared to males. Knowledge of this potential pitfall with PET/CT is important in improving diagnostic interpretation and accurate staging.

KEY WORDS: brown adipose tissue, ^{18}F-FDG, PET/CT.

Introduction

^{18}F-FDG PET has been a useful clinical tool for the diagnosis and staging of various cancers and evaluation of therapeutic responses[1]. However ^{18}F-FDG is not cancer specific, as any biological or pathological process with increased glucose metabolism can lead to accumulation of ^{18}F-FDG similar to malignancy. If not correctly recognized, it might result in a wrong diagnosis.

The cervical and supraclavicular regions are often involved in metastatic disease that derive from cancers of the lung, stomach, breast and esophagus, etc. ^{18}F-FDG PET provides more accurate diagnosis for these cancers, but some nuclear medicine physicians have noticed that curvilinear ^{18}F-FDG uptake in the cervical and supraclavicular regions is not associated with pathology, and that it can be diminished or resolved by muscle relaxants. So it has been recognized to be muscle activity attributed to tension, anxiety or over-exercise[2]. The recent introduction of PET/CT scanners in clinical oncologic imaging combined both PET and CT scanning devices offers fused images of both anatomy and metabolism. This new technology has shown that in some patients the ^{18}F-FDG accumulation in the cervical and supraclavicular regions did not have a corresponding soft-tissue mass or lymph node or muscle, but was adipose tissue on the CT scans. This adipose tissue has been hypothesized to be brown adipose tissue (BAT) which shows an increase in ^{18}F-FDG uptake during periods of cold temperature[3]. Therefore, ^{18}F-FDG uptake in BAT is a potential cause of false-positive findings for PET in the cervical and supraclavicular regions of patients with malignancy.

At our hospital, we have been doing PET/CT scans since July 2007. We also noticed that there were patients with nonpathologic ^{18}F-FDG uptake in the cervical and supraclavicular regions that did not map to soft-tissue mass, lymph nodes or skeletal muscle but to BAT.

Materials and Methods

Patients

All of the whole-body PET/CT scans from July 2007 to January 2008 conducted in our institution were retrospectively reviewed. A total of 457 patients (259 males and 198 females) with mean age 53.5 ± 14.9 (a range of 15~87 years) were assessed for the presence of BAT uptake.

All of the scans were obtained using Siemens Biography Sensation 16 PET/CT (Siemens Medical System, Germany). The patients fasted for at least 4 h before the PET/CT examination, but water was allowed, they received an intravenous injection of 370~740 MBq (10~20 mCi) of ^{18}F-FDG after which a tracer uptake phase of about 60 min was conducted. During that period the patients sat in a quiet room with maintaining a comfortable position without walking, talking or chewing. No specific breathing or breath-holding instructions were given to the patients. The PET and CT scans were performed during quiet tidal breathing.

CT scanning

Unenhanced CT scanning was acquired with spiral CT in a helical mode from the base of the skull to the middle of the thigh using the following: 120 Kv peak; 50 mAs; 0.5 s per CT rotation; 5 mm slice thickness and 3 mm interval. The CT data were resized from a 512 × 512 matrix to a 128 × 128 matrix automatically, and were smoothed to match the PET data so that the images could be fused and the CT transmission images could be generated.

PET scanning

The PET scans were conducted after obtaining CT images, requiring 5~8 bed positions. Typically the scans were taken from the base of skull to the mid thigh. PET data were acquired for 2 min at each bed position. PET images were reconstructed using CT for attenuation correction with ordered subsets expectation maximization algorithm (OSEM, 4 iterations, 8 subsets) using a 128 × 128 matrix.

Imaging analysis

All PET/CT scans were interpreted retrospectively by two experienced reviewers. The PET images were analyzed first, followed by the CT images and, finally, the PET/CT fused images. Findings were recorded by consensus.

PET images of the cervical and supraclavicular region were evaluated for the presence of obvious abnormally increased ^{18}F-FDG uptake (clearly exceeding the surrounding background activity) with corresponding fat-density tissue in the fused and CT images.

The following features were recorded: location, appearance and the maximum standardized uptake value (SUVmax) of the ^{18}F-FDG uptake. The CT-measured density at the maximum focus of ^{18}F-FDG uptake was obtained in Hounsfield Units (Hu) using the region of interest (ROI) drawn on the PET image superimposed on the CT image. The body weight and body mass index (BMI) of the patients with ^{18}F-FDG uptake in the BAT, and those of the patients in a control groups, matched for age and sex, randomly selected from the PET/CT scans during the same period, but did not display ^{18}F-FDG uptake in the BAT, were recorded. BMI, an estimate of total body fat, was calculated by dividing the weight (in kilograms) by the square of the height (in meters squared).

Statistical analysis

Data were expressed as mean ± SD. The unpaired *t*-test was used to compare SUVmax, body weight and BMI $P < 0.05$ considered statistically significant. Differences of sex in the incidence of BAT were tested using the chi-square test.

Results

Twelve patients (2 male and 10 female) ranging in age from 28 to 51 years (mean, 39.8 ± 7.0) of the 457 patients (2.6%) demonstrated BAT uptake in the cervical and supraclavicular regions not explained by normal structures or pathologics as seen on the concomitant CT images. These patients had undergone PET/CT scanning for the following: physical examination (5), lung cancer

Table 1. Details of all patients with BAT uptake included in the study.

No.	Age, years	Sex	Diagnosis	^{18}F-FDG uptake (SUVmax)				Density on CT (Hu)
				Cervical	Paravertebral	Periaortic	Axillary	
1	40	Female	Physical examination	6.09	-	-	-	-100.78
2	37	Female	Left lung cancer	9.71	-	-	-	-96.43
3	41	Female	Physical examination	5.18	-	-	-	-71.32
4	30	Female	Right breast cancer	6.63	-	-	-	-74.05
5	44	Female	Left breast cancer	4.98	-	-	-	-91.79
6	35	Female	Intestine mesothelioma	12.82	5.65	3.35	5.18	-78.01
7	28	Female	Ovarian cancer	5.24	-	-	-	-83.24
8	46	Female	Physical examination	6.93	6.14	4.80	-	-78.75
9	45	Male	Physical examination	8.66	-	-	-	-85.63
10	51	Female	Right lung cancer	4.72	-	-	-	-76.69
11	32	Male	Right lung cancer	8.17	-	-	-	-85.54
12	37	Female	Physical examination	3.60	-	-	-	-98.64

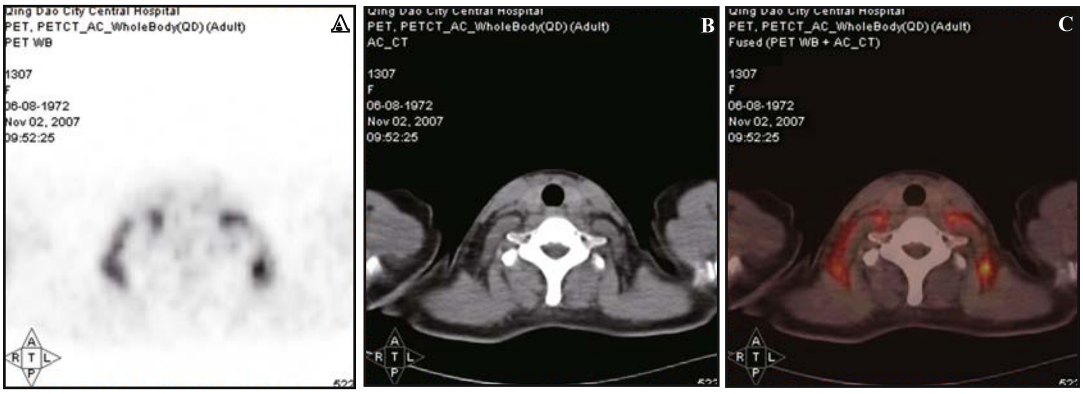

Fig.1. Transaxial slice of PET (A), CT (B) and fusion (C) imaging at the supraclavicular level show ^{18}F-FDG activity mapped to BAT.

(3), breast cancer (2), ovarian cancer (1) and intestine mesothelioma (1). The results are shown in Table 1. The incidence of BAT uptake in the cervical and supraclavicular regions was 0.8% in the scans of male patients and 5.1% in the scans of female patients. These differences in sex were statistically significant (P = 0.004).

The appearance of ^{18}F-FDG in the cervical and supraclavicular BAT was bilateral, symmetric, linear and intense, elongated extending from the neck inferiorly to the shoulders mapped to the adipose tissue (Figs.1 and 2). Additionally, 2 of these 12 patients had associated extra-cervical and supraclavicular hypermetabolic BAT in the paravertebral (Fig.3) and periaortic regions (n = 2); axillary regions (n = 1). The SUVmax of cervical and supraclavicular regions showed wide variation, ranging from 3.60 to 12.82, with a SUVmax average of 6.9 ± 2.6. This was a significant difference from the controls (average SUVmax was 1.0 ± 0.2, P = 0.001).

The mean body weight of patients showing ^{18}F-FDG uptake in the cervical and supraclavicular BAT was 62.3 ± 7.5 kg (range, 50~77 kg) and the mean BMI was 22.6 ± 2.2 (range, 18.8~26.2). Although the patients with BAT uptake tended to be thinner with lower BMI[3], no statistically significant difference was found with age- and sex-matched control groups (mean, 65.5 ± 8.4 kg and 23.9 ± 1.7, respectively) for body weight (P = 0.607) or for BMI (P = 0.491).

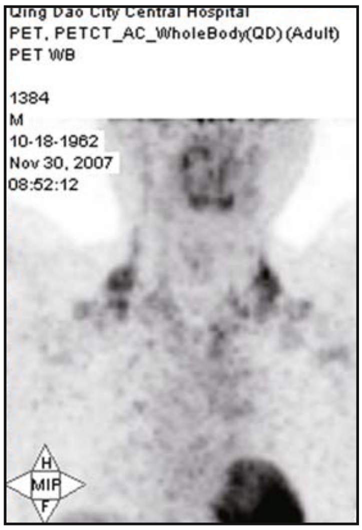

Fig.2. Coronal imaging shows curvilinear ^{18}F-FDG uptake in cervical and supraclavicular regions bilaterally, not associated with any radiologic or clinically evident pathology.

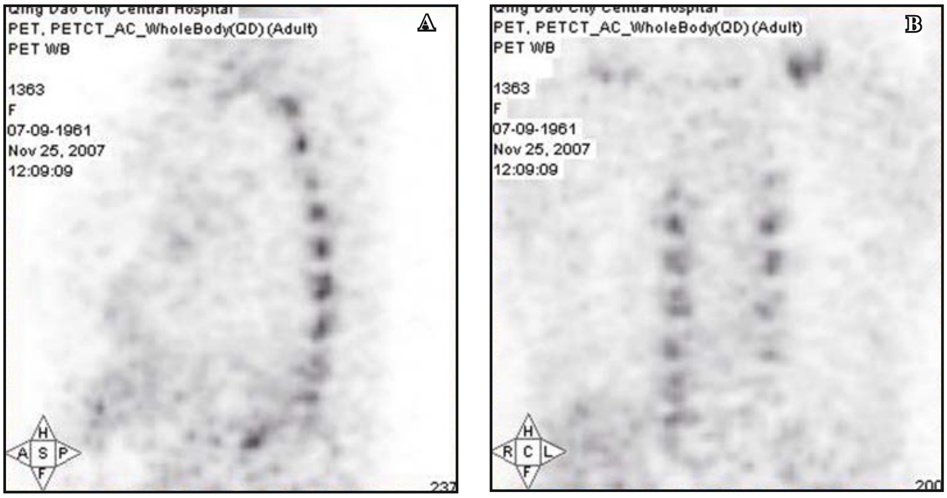

Fig.3. Sagittal slice (A) and coronal slice (B) show foci of ^{18}F-FDG activity along the thoracic spine bilaterally, mapped to the paravertebral intercostal space.

Discussion

^{18}F-FDG uptake in the cervical and supraclavicular regions is often seen in PET/CT scans. Metastases are the most common causes but muscle uptake is the other usual explanation for this kind of uptake. However, PET/CT shows that in most cases ^{18}F-FDG uptake in these areas has no corresponding lymph nodes or muscle, so it is now considered to be BAT. If not regarded carefully, it may be falsely interpreted and potentially lead to a false-positive finding. With the clinical application of PET/CT, this phenomenon has gained more and more acceptance[4].

There are two types of adipose tissue in mammals: white adipose tissue and BAT. The former stores energy and serves as insulation, but BAT also plays an important role in temperature regulation, cold resistance, obesity prevention, energy balance regulation and anti-infection. In 1551, Gessner found BAT in marmots, and in 1992 Polimanti proposed that BAT may be involved in substance exchange and energy regulation.

In the fetus and neonate, BAT is abundant because it serves an important role in thermoregulation. But BAT deposits diminish with age, even virtually disappear in adults. BAT is generally in deep cervical and supraclavicular areas, infrascapular, intercostal, paravertebraland periaortal areas, axillary fossa and areas near the large vessels. BAT is rich in mitochondria, vascularity, sympathetic nerves and adrenergic receptors and exclusively expresses a mitochondrial uncoupling protein, which causes uncoupling of oxidative phosphorylation and generation of heat. During this process, anaerobic metabolism of glucose is increased to produce ATP[4,5].

BAT uptake of glucose is associated with the temperature, region, environment, sex and age[3]. Glucose carriers and utilization in BAT increase with cold stimulation. Furthermore, cold can stimulate sympathetic nerves to produce heat without shivering, so cold is an important stimulator for BAT metabolic activity.

Uptake of ^{18}F-FDG in BAT has been reported to occur in 2.5%~4% of the patients undergoing PET/CT scans, a finding to be more common in women and in the winter[6-9]. Utilization of ^{18}F-FDG by BAT can increase significantly by stimulation of sympathetic nerves. This may explain the effectiveness of muscle relaxants and sedatives such as diazepam in abolishing the neck and shoulder ^{18}F-FDG uptake as reported previously[10,11]. Anxiety causing increased sympathetic nervous activity may also cause increased ^{18}F-FDG uptake by BAT. Tatsumi's study[12] with Lewis Rats revealed that ^{18}F-FDG uptake in BAT was extremely high after ketamine-based anesthesia, which was presumed to have stimulated the sympathetic nerves system. However, cold stimulation increased ^{18}F-FDG uptake in BAT to levels 4.9 times that of the controls. ^{18}F-FDG uptake in BAT was significantly decreased to less than 30% of the control level after propranolol or reserpine administration.

The BAT thermogenic response to cold has been found to be sex dependent[13]. In a study by Cohade et al.[7], they observed a high female-to-male ratio (6:1) in the BAT uptake group. Aged women have been reported to maintain higher temperatures during cold exposure compared to men of a similar age. So in the cold season, females with lower BMI exhibit more ^{18}F-FDG uptake in their BAT. ^{18}F-FDG uptake in BAT has been reported to occur more often in underweight patients with low BMI[3], but in our study patient body weight and BMI had no influence on ^{18}F-FDG uptake in BAT compared to the control groups, a result similar to other studies[7,8]. Hypermetabolic BAT has been shown to be more common in children compared to adults, but because we had few adolescent patients among our cases, we can not draw a comparison.

In our study, a high incidence of BAT uptake mainly occurred during the coldest period of the year and BAT uptake was mostly seen in the cervical and supraclavicular region, followed by the paravertebral and other regions. The range of the SUVmax was wide and therefore not helpful in differentiating between malignant and benign etiology. But ^{18}F-FDG-avid foci fused to tissues of fat density on CT images. The corresponding measured Hu was within the reported fat-density range (-100.78~-71.32). It seems improbable that there would be malignant pathologic foci of this intensity. On the other hand, the appearance of BAT uptake is usually specific as follows: curvilinear, usually fusiform-shaped, in the cervical and supraclavicular region; focal nodular ^{18}F-FDG activity bilaterially along the thorax, mapped to the paravertebral intercostal spaces. Garcia et al.[14] recommend that keeping the patient warm and controlling the indoor temperature can effectively reduce the occurrence and level of BAT uptake, especially in winter. Additionally, avoiding stimulation of sympathetic nerves by mental stress and anxiety can also decrease the incidence of ^{18}F-FDG uptake in BAT[15].

In conclusion, cervical and supraclavicular ^{18}F-FDG uptake by BAT can easily be recognized as a malignancy in PET scans. PET/CT allows us to verify by CT scanning that these foci had no corresponding anatomic soft-tissue mass, lymph node or muscle. Knowledge of this potential pitfall and the use of PET/CT to precisely localize ^{18}F-FDG uptake are important techniques to improve diagnostic interpretation and accurate staging.

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