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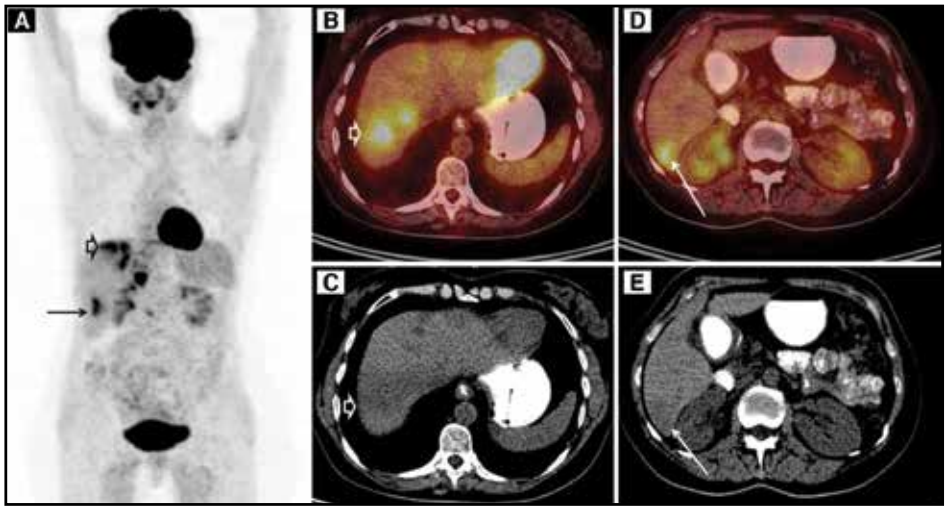

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Article with DOI Number: Erselcan T, Hasbek Z, Tandogan I, Gumus C, Akkurt I. Modification of Diet in Renal Disease equation in the risk stratification of contrast induced acute kidney injury in hospital inpatients. Nefrologia 2009 doi: 10.3265/Nefrologia.2009.29.5.5449.en.full.

Article in a journal published ahead of print: Ludbrook J. Musculovenous pumps in the human lower limb. Am Heart J 2009;00:1-6. (accessed 20 February 2009).

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Books: Greenspan A. Orthopaedic Radiology a Pratical Approach. 3th ed. Philadelphia, Lippincott Williams Wilkins 2000, 295-330.

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CONTENTS

Original Articles

Case Reports

Index

Original Article
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The Diagnostic Value of the Correlation between Serum Anti-p53 Antibody and Positron Emission Tomography Parameters in Lung Cancer

Akciğer Kanserli Hastalarda Pozitron Emisyon Tomografisi Parametreleri ile Serum Anti-p53 Antikoru Arasındaki İlişkinin Diagnostik Değeri

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Abstract

Objective: Mutations in the p53 gene are the most commonly observed genetic abnormalities in malignancies. The purpose of this study was to assess the diagnostic value of serum anti-p53 antibody (Ab) along with the correlation between serum anti-p53 Ab level and quantitative positron emission tomography (PET) parameters such as maximum standardized uptake value (SUV_{max}), SUV_{ave}, metabolic tumor volume, total lesion glycolysis (TLG) and tumor size.

Methods: Serum anti-p53 Ab level was studied in three groups. Patients who underwent ^{18}F-fluorodeoxyglucose (FDG) PET/computed tomography (CT) imaging for staging of previously diagnosed lung cancer constituted the first group, while patients who underwent ^{18}F-FDG PET/CT imaging for evaluation of suspicious pulmonary nodules detected on thorax CT and did not show pathologic FDG accumulation (NAPN=pulmonary nodule with non avid-FDG) were enrolled in the second group. The third group consisted of healthy volunteers.

Results: Twenty-eight patients with lung cancer (median age: 62.5, range: 39-77years), 28 patients with NAPN (median age: 65, range: 33-79 years), and 24 healthy volunteers (median age: 62, range: 44-74 years) were enrolled in the study. The serum anti-p53 Ab level was low in healthy volunteers while it was higher in both lung cancer patients and NAPN patients ($p<0.05$). When serum anti-p53 Ab level and PET parameters were evaluated, there was no significant correlation between serum anti-p53 Ab level and SUV_{max}, SUV_{ave}, TLG, tumor volume and tumor size of patients with lung cancer ($p>0.05$). Besides, there was no significant difference between serum anti-p53 Ab level and lesion size of NAPN patients ($p>0.05$).

Conclusion: It was determined that serum anti-p53 Ab levels are not significantly correlated with PET parameters, and that serum anti-p53 Ab levels increase in any benign or malignant lung parenchyma pathology as compared to healthy volunteers. These results indicate that this Ab cannot be used as a predictor of malignancy in a lung lesion.

Keywords: Anti-p53 antibody, lung cancer, fluorodeoxyglucose, positron emission tomography/computed tomography

Öz

Amaç: p53 gen mutasyonları malignitelerde en sık görülen genetik bozukluktur. Bu çalışmada serum anti-p53 antikor (Ab) düzeyinin tanısal değerinin araştırılması, serum anti-p53 Ab düzeyi ile SUV_{max}, SUV_{ave}, metabolik tümör volümü, total

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lezyon glikolizi (TLG) ve tümör boyutu gibi kantitatif pozitron emisyon tomografisi (PET) parametreleri arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Yöntem: Serum anti-p53 Ab düzeyi üç grupta çalışıldı. Birinci grupta akciğer kanseri nedeniyle evreleme için ^{18}F-florodeoksiglukoz (FDG) PET/bilgisayarlı tomografi (BT) görüntülemesi yapılan hastalar, ikinci grupta ise toraks BT'de şüpheli pulmoner nodül saptanması nedeniyle tanı amacıyla ^{18}F-FDG PET/BT yapılan ancak patolojik FDG tutulumu izlenmeyen hastalar (NAPN=FDG tutmayan pulmoner nodül) vardı. Üçüncü grubu sağlıklı gönüllüler oluşturdu.

Bulgular: Bu çalışmaya akciğer kanseri olan 28 hasta (ortalama yaş: 62,5, aralık: 39-77 yıl), NAPN olan 28 hasta (ortalama yaş: 65, aralık: 33-79 yıl), ve 24 sağlıklı gönüllü (ortalama yaş: 62, aralık: 44-74 yıl) dahil edildi. Serum anti-p53 Ab düzeyi sağlıklı gönüllülerde düşük iken, akciğer kanserli hastalarda ve NAPN hastalarında yüksekti ($p<0,05$). Serum anti-p53 Ab düzeyi ve PET parametreleri değerlendirildiğinde; serum anti-p53 Ab düzeyi ile SUV_{max}, SUV_{ave}, TLG, tümör volümü ve akciğer kanserli hastalardaki tümör boyutu arasında anlamlı korelasyon saptanmadı ($p>0,05$). Ayrıca serum anti-p53 Ab düzeyi ile NAPN hastalarındaki lezyon boyutu arasında anlamlı farklılık yoktu ($p>0,05$).

Sonuç: Serum anti-p53 Ab düzeyi ile PET parametreleri arasında anlamlı korelasyon olmadığı ve serum anti-p53 Ab düzeyinin akciğerde benign veya malign herhangi bir parankim patolojisinde yükseldiği bulundu. Bu sonuçlar serum anti-p53 Ab'nin malign akciğer lezyonları için bir belirteç olamayacağını düşündürmektedir.

Anahtar kelimeler: Anti-p53 antikor, akciğer kanseri, florodeoksiglukoz, pozitron emisyon tomografisi/bilgisayarlı tomografi

Introduction

Lung cancer comprises an important group of malignancies, and is the most common cause of cancer-related deaths with a short survival after initial diagnosis. About 90% of primary lung cancers are non-small cell cancer (NSCLC) (1). Accurate staging is important for determining the choice of treatment and predicting prognosis. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has an important role in staging, and it is the most advanced imaging technique that has been developed to determine the metabolic characterization of the tumor. Maximum standardized uptake value (SUV_{max}), which is acquired by PET imaging, is commonly used in clinical practice as a criterion for malignancy. A high SUV_{max} value is commonly accepted as a poor prognostic factor (2). Due to the development of new software programs, recent studies have shown that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) may be useful quantitative parameters for prognostic evaluation (3). Besides, some reports have suggested that TLG is a better prognostic indicator than SUV_{max} (4).

Recently, there has been an increase in studies on molecular biology of cancer. Prognostic tests have been developed especially for lung cancer, and it has been reported that the presence of auto-antibodies may be used for disease diagnosis at an early stage (5). p53 is a tumor suppressor gene that plays an important role in controlling normal cell proliferation, and is located on the chromosome 17 (17p13.1). It is the most common target of genetic alteration in many tumors (6). Serum p53 protein is present in normal healthy individuals. However, serum anti-p53 antibody (Ab) is extremely rare (7). Mutations in p53 gene cause an accumulation of non-functional proteins and development of anti-p53 Abs, which can be detectable in tissues, blood, slouched cells and other body fluids (8). In many studies conducted up to present, it has been shown that p53 mutation was more frequent in lung, esophagus, stomach, bone, bladder, ovarian, and brain (except glioma) cancers as well as lymphoma and leukemia (8). The rate of p53 gene mutation is higher in patients with small cell lung cancer (SCLC) as compared to NSCLC patients (9). In the literature, there are some publications on the role of p53 gene mutation in the early diagnosis of lung cancer (10).

The purpose of this study was to assess the diagnostic value of serum anti-p53 Ab along with the correlation between serum anti-p53 Ab level and quantitative PET parameters such as SUV_{max}, SUV_{ave}, MTV, TLG and tumor size.

Materials and Methods

Patients

Patients who were referred to our department with the purpose of ^{18}F-FDG PET/CT imaging for staging of previously diagnosed lung cancer and patients who underwent ^{18}F-FDG PET/CT imaging for evaluation of suspicious pulmonary nodules detected on thorax CT and did not show pathologic FDG accumulation (NAPN=pulmonary nodule with non avid-FDG) were enrolled in this prospective and preliminary study. The control group consisted of healthy subjects with no known history of cancer and without any complaints. Only serum anti- p53 Ab was measured in the control group. This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the local ethical committee (2013-03/50). Oral and written consent was obtained from all patients. Patients with previous operations for lung cancer, prior chemotherapy or radiotherapy for lung cancer, those with no definitive histological diagnosis, and those with a blood glucose level greater than 150 mg/dL were excluded from the study. Clinicopathological data of the patients are reported in Table 1.

Detection of Serum Anti-p53 Antibodies

Blood samples were collected from peripheral blood vessels. Blood samples were taken before performing

the FDG administration for ^{18}F-FDG PET/CT. All serum was obtained after complete clotting by centrifugation, immediately frozen and stored at -80 °C until the time of analysis. Serum anti-p53 Abs levels were measured using Enzyme-linked immune-sorbent assay kit (CUSABIO) according to the manufacturer's instructions. The kit was designed to measure circulating p53 antibodies in human serum samples.

Imaging Acquisitions/Analysis

PET imaging was performed prior to any treatment and images were acquired using a combined PET/CT scanner (Discovery 600 PET/CT GE Medical Systems, USA). Each patient fasted for at least 6 h before imaging. After ensuring that blood glucose was <150 mg/dl, approximately 370 MBq ^{18}F-FDG were administered intravenous 1 hour before image acquisition and patients were rested. Attenuation correction of PET images with CT data was performed. First, the CT scan was performed. CT images were acquired with 70 mA, 120 kV, axial slice thickness of 3.75 mm. Right after CT image acquisition, a standard PET imaging protocol was applied from the cranium to the mid-thigh with an acquisition time of 3 min/bed in 3-dimensional mode. All PET studies were acquired in 3-D mode. CT and PET images were matched and fused into transaxial, coronal and sagittal images. The data were transferred via the Digital Imaging and Communications in Medicine protocol to a processing Workstation (AW Volumeshare 5 GE Medical Systems S.C.S, France), and visual and semi-quantitative analyses were performed. Tumor size (three maximum diameters) was measured. SUV_{max}, SUV_{mean} and MTV were calculated from attenuation-corrected ^{18}F-FDG PET images for tumor mass. The SUV_{max} was calculated by using the following formula: maximum pixel value with the return on investment activity (MBq/kg)/ [injected dose (MBq)/body weight (kg)]. SUV_{mean} was determined from the average voxel counts within the tumor region. Automatic volume of interest using an isocontour threshold method was placed over the primary tumor. TLG was then calculated as: "$TLG=SUV_{mean} \times MTV$".

Table 1. Lung cancer patient's characteristics

Patient characteristics	n	%
Age (years)		
Median (range)	62.5 (39-77) years	
Gender		
Male	26	92.9
Female	2	7.1
Histopathology		
Squamous cell carcinoma	18	64.3
Adeno-carcinoma	9	32.1
Large-cell carcinoma	1	3.6
Smoking status		
Smoker	23	82.1
Nonsmoker	5	17.9
Stage		
I	5	17.9
II	2	7.1
III	9	32.1
IV	12	42.9

Statistical Analysis

The statistical tests were performed using SPSS (version 14.0; SPSS, Inc.). The frequencies test was applied to evaluate the statistical significance of the parameters. Correlations among serum anti-p53 Ab levels, tumor volume, tumor size, SUV_{mean}, SUV_{max}, and TLG were examined by the Pearson correlation test. Correlation between serum anti-p53 Ab levels and case groups, histopathologic subtype of cancer patients and stage of cancer were evaluated by using Kolmogorov-Smirnov test since parametric hypothesis could not be tested. Correlation between serum anti-p53 levels and tobacco smoking status, age and sex of cases were evaluated with Mann-Whitney U test. Significance levels were presented as p values. It was assumed that the observed differences were statistically significant at the $p<0.05$ levels.

Results

Twenty-eight lung cancer patients (median age: 62.5, range: 39-77 years), 28 patients with NAPN (median age: 65, range: 33-79 years), and 24 healthy volunteers (median age: 62, range: 44-74 years) were included in this preliminary, prospective study.

According to histopathology results; 18 (64.3%) squamous cell carcinomas, nine (32.1%) adenocarcinomas and one (3.6%) large-cell carcinoma patients were included. The median primary tumor size in patients with lung cancer (n=28) was 52.9 mm (range: 19.6-92.4 mm). The lesion size in NAPN patients (n=28) was 16 mm (range: 10-51 mm). The subjects consisted of 26 (92.9%) males and two (7.1%) females, 21 (75%) males and seven (25%) females, 21 (87.5%) males and three (12.5%) females in lung cancer, NAPN, and healthy volunteers, respectively.

The median serum anti-p53 Ab value was 3.75 ng/mL (range 2.23-104.19 ng/mL) in all cases. The median serum anti-p53 Ab level in epidermoid cancer group, adeno-carcinoma group, and large-cell carcinoma group was 4.10 ng/mL (range: 2.67-52.49 ng/mL), 4.16 ng/mL (3.26-104.19 ng/mL) and 4.5 ng/mL, respectively. The median serum anti-p53 Ab level in lung cancer group, NAPN group and healthy volunteer group was 12.90 ng/mL (range: 2.67-104.19 ng/mL), 17.63 ng/mL (2.52-92.19 ng/mL) and 4.02 ng/mL (2.23-25.72 ng/mL), respectively. Serum

anti-p53 levels were higher in lung cancer and NAPN patient groups in comparison with healthy volunteers (p=0.0001). Figure 1 shows the comparison of serum anti-p53 Ab levels of all cases included in the study. Clinical details of all cases and their relation with serum anti-p53 Ab levels were summarized in Table 2.

Serum anti-p53 Ab level was measured as 25 ng/mL in one healthy volunteer while the mean serum anti-p53 Ab level was 3.08±0.43 ng/mL (range: 2.23-4.17 ng/mL) in other healthy volunteers. This volunteer had a history of smoking for almost 45 years. A thorax CT was performed to that volunteer that did not show any mass or nodule. However, emphysema was detected in lung parenchyma.

Evaluation of serum anti-p53 Ab level and PET parameters showed that there was no significant correlation between serum anti-p53 Ab level and SUV_{max}, SUV_{ave}, TLG, tumor volume, and tumor size of patients with lung cancer (p=0.189, 0.123, 0.572, 0.928, 0.421, respectively). Besides, there was no significant difference between serum anti-p53 Ab level and lesion size of NAPN patients (p=0.694). There was no association between serum anti-p53 Ab level and age or sex (p=0.704, p=0.771, respectively). Moreover, there was no significant correlation between histopathologic subtypes or stage of cancer and serum p53-Ab levels (p=0.920, p=0.847, respectively). In the lung cancer group, the mean serum anti-p53 Ab level was higher in stage I patients at the time of diagnosis in comparison with other stage groups; however, the difference was not statistically significant (p=505). On the other hand, there was significant correlation between serum anti-p53 Ab levels and tobacco smoking (p=0.011) (Table 2).

Two patients included in the study had a previous history of cancer. Both patients were in complete remission and follow-up. One of them had colon cancer and the other had renal cell carcinoma. While serum anti-p53 Ab level was 52.49 ng/mL in the patient with colon cancer, it was 3.45 ng/mL in the patient with renal cell carcinoma.

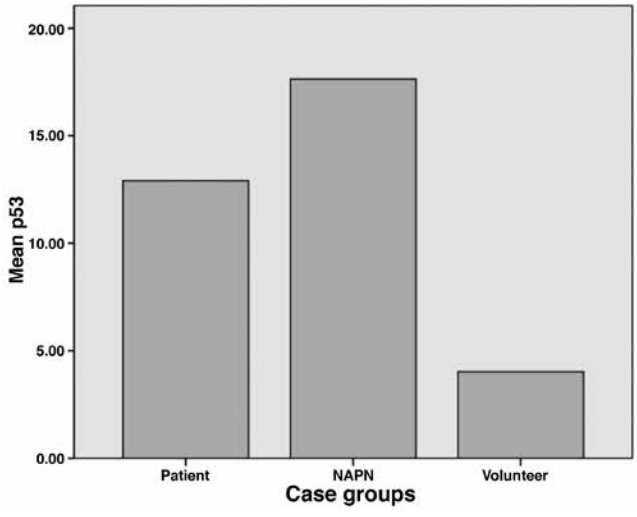

Figure 1. Comparison of serum anti-p53 antibody levels of cases included in the study
NAPN: Pulmonary nodule with non avid-fluorodeoxyglucose

Table 2. Characteristics of the entire study group and comparison of serum anti-p53 antibody levels within sub-groups

	n (%)	p53 (ng/mL) (mean ± SD; median) (range)	p value
Gender			
Female	12 (15%)	10.81±24 (2.52-89.20)	p=0.704
Male	68 (75%)	12.09±23 (2.23-104.19)	
Age			
≤55 years	22 (27.5%)	10.24±18; 4.15 (2.46-70.53)	p=0.771
>55 years	58 (72.5%)	12.52±24; 3.66 (2.23-104.19)	
Case groups			
Lung cancer	28 (35%)	12.90±24; 4.20 (2.67-104.19)	
NAPN	28 (35%)	17.63±29; 4.43 (2.52-92.19)	p=0.0001
Volunteer	14 (30%)	4.02±4.6; 3.18 (2.23-25.72)	
Histopathologic subtype of cancer patients			
Epidermoid Ca	18 (64.3%)	7.20±11; 4.16 (2.67-52.49)	
Adeno Ca	9 (32.1%)	24.95±39; 4.16 (3.26-104.19)	p=0.920
Large-cell Ca	1 (3.6%)	4.5; 4.5*	
Stage			
Stage I	5 (17.9%)	14.77±21; 4.74 (2.73-52.49)	
Stage II	2 (7.1%)	3.35±0.96; 3.35 (2.67-4.04)	p=0.847
Stage III	9 (32.1%)	13.08±25; 4.30 (3.39-81.18)	
Stage IV	12 (42.9%)	13.58±28; 4.13 (3.26-104.19)	
Smoking status (all cases)			
Present	36 (45%)	13.12±23; 4.40 (2.52-104.19)	p=0.011
Absent	44 (55%)	10.89±23; 3.40 (2.23-92.19)	

*: This patient was excluded from statistical analysis because he had a large cell carcinoma, NAPN: Pulmonary nodule with non avid-fluorodeoxyglucose, Ca: Carcinoma, SD: Standard deviation

Discussion

Cancer is among the most serious health problems all over the world. While scientists continue their studies on development of novel cancer treatments, studies on the detection of cancer before it manifests or at an early stage are also being performed. With this purpose, by developing panels of tumor-associated antigens, it is being investigated if these auto-antibodies can be used as markers (11). Lung cancer, as being the most common cause of cancer-related death, is one of the most researched cancer type in this regard.

A p53 mutation appears to be the most common genetic defect identified in malignancies (12). Antibodies against p53 can be detected in the serum. Some studies suggested that serum p53-Ab can be used as a tumor marker (8). In this study, we investigated the correlation between serum anti- p53 Ab and PET parameters in lung cancer patients. In our study, mean serum anti-p53 Ab level was higher in patients with lung cancer and those with non-avid FDG pulmonary nodules in comparison to healthy volunteers. However, there was no significant difference between serum anti-p53 Ab levels of patients with lung cancer and patients with NAPN. These results indicate that this Ab is not specific for lung cancer. Besides, these findings raise the suspicion that any situation inducing hypoxia in the lung (such as lung cancer, solitary pulmonary nodule, or obstructive lung diseases like emphysema) might lead to an increase in serum anti-p53 Ab levels. The number of studies evaluating the correlation between p53 mutation and prognosis in lung cancer has been increasing, but the results of these studies are equivocal. Likewise, there are many studies in the literature on the role of serum anti-p53 Abs in the early diagnosis of lung cancer as well as other cancer types. While some studies practice on panels of other antigens in addition to p53, some studies practice the sensitivity of anti-p53 Abs assay methods (13). Maddau et al. (12) detected p53 expression at 51.7% of 180 NSCLC patients. They reported that patients with p53 and Ki-67 overexpression had worse outcome in stage I adenocarcinoma (but not those with stage II and III or other histologic types). They stated that the effects of p53 alteration may depend on tumor cell type. In our study, the mean serum anti-p53 Ab level in stage I patients was found to be higher than that in other stages (Table 2), although not statistically significant. Ciancio et al. (6) studied anti-p53 and anti-Ki-67 antibodies within specimens obtained by fiber-optic bronchial biopsies, and they reported that the prognosis was better in Ab-negative patients. Gomez et al. (14) reported that p53 protein overexpression in lung adenocarcinoma correlated with lymphatic vessel invasion. Gao et al. (15) also detected p53 mutation in 20% of adenocarcinoma cases and 35% of squamous cell carcinoma cases in their study. In addition to that, although they could not find any correlation between p53 mutation and survival, they found that tumor size and degree of differentiation were predictors of poor survival. Chapman et al. (5) reported that the presence of tumor-associated autoantibodies may be useful in the early prognosis of lung cancer and that it may be used especially on high risk individuals. Similarly, in another study, p53 suprabasal immunostaining was detected in 75% of severely dysplastic or carcinoma in situ lesions, and a "contribution value to predict the biological behavior of pre-neoplastic endobranchial lesions" was expressed (16). On the other hand, it has been reported that the presence of p53 Ab is not cancer specific and that it was also found to be positive in patients with impaired lung function. (17). Moreover, the prognostic role of anti-p53 antibodies in lung cancer remains controversial, as some studies indicate an association with poor prognosis others report no correlation between survival and anti-p53 Abs (18).

SCLC progresses more aggressively than NSCLC since it has a tendency to present with disseminated metastasis at the time of diagnosis. It is also the most responsive type of tumor to treatment as compared to other lung cancer patients. Chapman et al. (11) evaluated SCLC patients for the presence of autoantibodies against certain antigens (p53, CAGE, NY-ESO-1, GBU4-5, Annexin I, SOX2, and Hud), and they found that antibodies existed at least to one of the 6 antigens. The specificity was found to be 90% when compared with the control group, while the specificity was reported to be greater than 99% in the limited panel composed of p53, SOX2 and Hu-D. Park et al. (19) also reported that together with anti-p53 other conventional markers help to increase sensitivity and specificity in lung cancer detection.

Tobacco smoking is still one of the major risk factors inducing lung cancer. Gibbons et al. (20) reported that although p53 mutation rate is high in smoking-related tumors such as lung, bladder, oral cavity and conductive airways, tobacco smoking also produces mutation of the tumor suppressor TP53. In our study, when cases were considered altogether, there was a significant correlation between serum anti-p53 Ab levels and smoking. However; when lung cancer, NAPN, and volunteer groups were considered separately, there was no significant difference between serum anti-p53 Ab levels. Hypoxia induces p53 protein accumulation and p53 dependent apoptosis in oncogenically transformed cells (21). Hypoxic cells might be the reason of elevation in serum anti-p53 Ab levels in smokers. In one healthy volunteer in our study, the serum anti-p53 Ab level was higher in comparison to the mean serum anti-p53 Ab levels of other healthy volunteers. This volunteer had a smoking history of almost 45 years. The thorax CT performed on that volunteer who had no complaint of coughing, sputum, labored breathing or exertion dyspnea revealed emphysema.

Conventionally, CT has been the primary imaging technique for the diagnosis and staging of lung cancer

patients. Similar to normal cells, tumor cells also use glucose for energy production. Therefore, recent advances in combined PET/CT imaging systems have further improved staging and disease management based on the metabolic information in addition to anatomic imaging. Routinely, the most commonly used measure of FDG uptake is the SUV. For this reason, SUV is usually used as a tumor marker indicating tumor aggressiveness, especially in adenocarcinoma (22). SUV is a simple, practically applicable and repeatable parameter. On the other hand, it is time-dependent and affected by several factors such as glucose metabolic rate and partial volume effect (23). That is why the importance of PET parameters such as TLG and MTV is being emphasized for prognostic evaluation (24). In the literature, there are some publications suggesting that the mutation of tumor suppressor genes such as p53 is correlated with an increase in FDG uptake in lung cancer (25). Duan et al. (26) reported that p53 expression is the primary predictive factor for SUV_{max}. Zhou et al. (27) found a significant difference between SUV_{max} and Tp53-induced glycolysis and apoptosis regulator (TIGAR)'s being positive or negative. On the other hand, Watanabe et al. (28) did not find a correlation between p53 alteration and FDG uptake. Similarly in our study, there was no significant correlation between serum anti-p53 Ab level and PET parameters such as SUV_{max}, SUV_{ave}, TLG, and tumor volume. However, this situation might occur because of FDG uptake in tumor tissue is dependent on hypoxia in tumor cell. Hypoxic cancer cells were reported to have significantly higher radiolabeled FDG uptake than normoxic cancer cells in animal studies (29). Unfortunately, the hypoxia condition of tumor cells was not evaluated in our study. Another limitation of the study comprises the relatively small number of patients.

Conclusion

Based on the results, we have found that serum anti-p53 Ab level does not correlate with PET parameters, and that serum anti-p53 Ab level increases in any benign or malignant lung parenchyma pathology as compared to healthy volunteers. These results suggest that this Ab cannot be used as an indicator for malignant lung lesions.

Principally, tobacco smokers and people who work in jobs that highly expose them to carcinogens are well aware of their risk to get cancer. As researchers, are we doing the right thing by introducing additional tests like serum anti-p53 Ab level that cause healthy people more distress on the probability of having lung cancer at any time? Would it be more appropriate to use these tests only on patients with suspected malignancy for early diagnosis until a test with very high sensitivity and specificity is identified? Currently, detecting cancer before it manifests clinically is impossible. However, we believe that future studies on tumor markers like anti-p53 Ab will reveal important tools as reagents of early detection of metastasis/recurrence in previously/already diagnosed cancer patients.

Ethics

Ethics Committee Approval: The study was approved by the Cumhuriyet University of Local Ethics Committee (2013-03/50), Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zekiye Hasbek, Ömer Tamer Doğan, Birsen Yücel, Concept: Zekiye Hasbek, Design: Zekiye Hasbek, Ömer Tamer Doğan, Birsen Yücel, Data Collection or Processing: Zekiye Hasbek, Ömer Tamer Doğan, Serdar Berk, Mehmet Metin Şeker, İsmail Sarı, Yavuz Siliğ, Bülent Turgut, Analysis or Interpretation: Zekiye Hasbek, Birsen Yücel, Ömer Tamer Doğan, Serdar Berk, Literature Search: Zekiye Hasbek, Writing: Zekiye Hasbek.

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Occupational Radiation Exposure to the Extremities of Medical Staff during Hysterosalpingography and Radionuclide Bone Scan Procedures in Several Nigerian Hospitals

Birkaç Nijerya Hastanesinde Histerosalpingografi ve Radyonüklid Kemik Tarama Prosedürleri Sırasında Sağlık Personeli Ekstremitelerinde Mesleki Radyasyona Maruz Kalma

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Abstract

Objective: The practice of regular dose measurement helps to ascertain the level of occupational dose delivered to the staff involved in diagnostic procedures. This study was carried out to evaluate the dose exposed to the hands of radiologists and a radiologic technologist carrying out HSG and radionuclide bone scan examinations in several hospitals in Nigeria.

Methods: Radiation doses exposed to the hands of radiologists and a technician carrying out hysterosalpingography (HSG) and bone scan procedures were measured using calibrated thermo-luminescent dosimeters. Five radiologists and a radiologic technologist were included in the study for dose measurement.

Results: The study indicates that each radiologist carried out approximately 2 examinations per week with the mean dose ranging between 0.49-0.62 mSv per week, resulting in an annual dose of 191 mSv. Similarly, the occupational dose delivered to both the left and right hands of a radiologic technologist administering ^{99m}Tc-methylene diphosphonate (MDP) without cannula and with cannula were 10.68 (720.2) and 13.82 (556.4) mSv per week (and per annum), respectively. It was determined that the left hand of the personnel received higher doses than their right hand.

Conclusion: The estimated annual dose during HSG is far below the annual dose limit for deterministic effects, however, it is greater than 10% of the applicable annual dose limit. Hence, routine monitoring is required to ensure adequate protection of the personnel. The total annual dose received during the bone scan exceeds the annual dose limit for both hands, and the dose to either left or right hand is greater than the dose limit of 500 mSv/yr. The radiologists monitored are not expected to incur any deterministic effects during HSG examinations, however, accumulated doses arising from the scattered radiation to the eyes, legs, and neck could be substantial and might lead to certain effects. More staff are required to administer ^{99m}Tc-MDP in Nigerian institutions to prevent excessive doses to personnel.

Keywords: Radiation dose, hysterosalpingography, bone scan, thermo-luminescent dosimeter, hand dose

Öz

Amaç: Düzenli doz ölçümü uygulaması tanı yöntemlerinde yer alan personele verilen mesleki dozun düzeyini tespit etmek için yardımcı olur. Bu çalışma Nijerya'da çeşitli hastanelerde HSG ve radyonüklid kemik sintigrafisi incelemelerini yürüten bir radyoloji teknisyeni ve radyologların ellerinin maruz kaldığı dozu değerlendirmek amacıyla yapılmıştır.

Yöntem: Histerosalpingografi (HSG) ve radyonüklid kemik sintigrafisi incelemelerini yürüten bir radyoloji teknisyeni ve radyologların ellerinin maruz kaldığı radyasyon dozu kalibre edilmiş termo-lüminesan dozimetreler kullanılarak ölçüldü. Beş radyolog ve bir radyoloji teknisyeni doz ölçümü için çalışmaya dahil edildi.

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Bulgular: Bu çalışma her radyoloğun haftada 2 inceleme yaparak ortalama haftalık dozun 0,49-0,62 mSv arasında değiştiğini, yıllık 191 mSv dozla sonuçlandığını göstermiştir. Benzer şekilde, radyoloji teknisyeninin sol ve sağ ellerine sırasıyla kanülsüz ve kanüllü ^{99m}Tc-metilen difosfonat (MDP) uygulamasında verilen haftalık (ve yıllık) dozlar 10,68 (720,2) ve 13,82 (556,4) mSv olarak bulunmuştur. Personelin sol elinde sağ elden daha yüksek doz aldıkları tespit edilmiştir.

Sonuç: HSG sırasında tahmini yıllık doz deterministik etkiler için bildirilen yıllık doz sınırının çok altındadır, ancak uygulanabilir yıllık doz sınırının %10'undan daha fazladır. Bu nedenle, personelin yeterli korunmasını sağlamak için rutin izleme gereklidir. Kemik taraması sırasında alınan toplam yıllık doz her iki el için yıllık doz sınırını aşmaktadır ve sol veya sağ el dozu 500 mSv/yıl doz sınırından daha fazladır. İzlenen radyologların HSG muayenelerine bağlı herhangi bir deterministik etkiye uğraması beklenmemektedir, ancak gözler, bacaklar ve boyuna saçılan radyasyondan kaynaklanan birikmiş dozlar önemli olabilir ve belirli etkilere yol açabilir. Personele aşırı dozu önlemek için Nijerya kurumlarında ^{99m}Tc-MDP uygulayabilecek daha fazla insan gücü gereklidir.

Anahtar kelimeler: Radyasyon dozu, histerosalpingografi, kemik sintigrafisi, termo-lüminesans dozimetre, el dozu

Introduction

The use of both ionizing and non-ionizing radiations for medical imaging and treatment is rapidly increasing. The use of these medical tools has led to several breakthroughs in both diagnosis and treatment. The rapid development of imaging technology has contributed largely to progress of simple and complex diagnostic procedures as well as interventional radiology (1). Hysterosalpingography (HSG) is a diagnostic procedure performed to determine if the fallopian tubes are patent (open), and to see if the structure and size of the uterine cavity are normal. This is a non-invasive procedure usually performed after the menstrual period has ended to prevent interference with an early pregnancy. It is performed by positioning a woman under a fluoroscope (real-time imager) on a table. The gynecologist or radiologist examines the patient and fills the uterus with contrast medium in order to visualize the outline of the inner size and shape of the uterus and fallopian tubes clearly. X-ray images are obtained during the introduction of the contrast medium using a tube. During the filling of the uterus with the contrast medium, the fingers and the lower extremities of the gynecologist or radiologist is exposed to radiation (2,3).

The HSG is a common procedure carried out in Nigeria essentially in infertile women. This is because of the cultural practice of disparaging women with infertility problems. The HSG procedure is also used a few months after a tubal sterilization procedure to make sure that the fallopian tube has not been completely blocked. The common indication for the use of HSG in Nigeria is infertility. Other indications include, but are not limited to, the evaluation of: pelvic pain, irregular vaginal bleeding, congenital abnormalities or anatomic variants (4). Other alternative procedures to HSG are laparoscopy, sonohysterosalpingogram and hysteroscopy. Nevertheless, HSG remains the most commonly performed procedure to evaluate tubal patency (2).

HSG procedure requires the radiologist or gynecologist (who is not trained to handle ionizing radiation) to hold the cannula and inject the contrast medium into the cervix of the patient while she is being irradiated. The supporting personnel also remain close to the patient. Though, a lead apron is worn, the hands of the radiologist are covered in latex gloves, making their hands vulnerable to x-rays. The exposure of the radiologists' hands to x-rays during this procedure is a continuous and inevitable experience during HSG procedures, hence the need to evaluate the dose exposed to the hands.

The use of ^{99m}Tc has gained wide acceptance in nuclear medicine practice due to its advantages related to its specific characteristics. The physical half-life of ^{99m}Tc used in radionuclide bone scan is 6.02 hours (5,6), thus it exposes a fairly low dose per unit intake due to its short half-life and radiation spectrum (7). It has an energy of 140 keV that is sufficient enough to be detected by the gamma camera through the body. The reason for the choice of ^{99m}Tc in bone scintigraphy arose because of its characteristic qualities. Bone scintigraphy/scan is one of the most common applications of ionizing radiation in nuclear medicine. Radionuclide bone scan is a diagnostic procedure used to evaluate the distribution of active bone formation in the body. The radiopharmaceutical is injected intravenously with and without cannula to the patient by a radiologic technologist and is distributed via blood flow throughout the body. It therefore passively diffuses into the extravascular and extracellular spaces, and bind to hydration shell around the bone crystal (8). The use of ^{99m}Tc in patients undergoing bone scan procedure presents special concerns for the assessment of radiation dose (9) and the attendant risk to the administering staff. As a result of the need for radiation protection of the administering staff, doses exposed to the hands of the radiologic technologist were measured.

More than 92% of all investigations carried out at the Department of Nuclear Medicine, University College Hospital (UCH), Ibadan, is bone scan using ^{99m}Tc. The aim of this present study was to evaluate the radiation doses exposed to the hands of radiologists and a radiologic technologist carrying out HSG and radionuclide bone scan procedure in some selected hospitals in two major cities in Nigeria. The results obtained were compared with the recommended dose limits.

Materials and Methods

The study involving HSG was carried out between February and May 2013 in five selected hospitals in the Mega City of Lagos, while the bone scan study was carried out at the UCH (a teaching hospital), Ibadan. The selection of the study centers in Lagos was based on the availability of facilities for carrying out the HSG procedure at each hospital. In addition, the facilities of the hospitals have been previously monitored in compliance with the Nigerian Nuclear Regulatory Authority (a body responsible for regulation of nuclear activities in Nigeria) policy. Forty-eight patients and five radiologists participated in the HSG study. The goals of the researchers were discussed with the patients and the staff at the beginning of the study. Five private health care centers included in the study are; Rays and Waves Radiological Centre, Ifako (RWRC); Fanic Diagnostic Centre, Dopemu (FDC); Precise Medical Diagnostix, Iju (PMD); Royal Hospital, Ojodu (RHH); and The Shield Hospital, Eko (TSH). Fifty-two patients who have been injected during the HSG procedure carried out within the study period were included in the study. The doses received by the radiologic technologist during the bone scan procedures using ^{99m}Tc-methylene diphosphonate (MDP) were monitored at the Nuclear Medicine Department of UCH, Ibadan. The radiologic technologist who carried out the investigation was permitted to undertake the examination as part of his routine work by the law of UCH. Thermo-luminescent dosimeters (TLD) pellets were attached to his fingers. The HSG procedures were carried out by certified radiologists who were by the law of our country permitted to examine patients as part of their daily duty, and the study was also carried out on the radiologists themselves.

Radiation Dose Measurement during Hysterosalpingography

In order to assess doses exposed to the hands, calibrated TLD pellets obtained from the Lagos State University Radiation Monitoring Service (LASURMS) (a university-based radiation monitoring service provider) were attached to the fingers of both right and left hands of each radiologist prior to the exposure of the patient to radiation. Patients were irradiated with x-ray beam energy ranging between 90 kVp and 99 kVp, and with the tube load in the range of 40-50 mAs depending on patient size. After the first exposure, the used film was removed and a new one was introduced to take the left and right antero-posterior views. This implies that three images were taken while the contrast medium was administered. Each procedure took between 10 and 30 minutes when the patient cooperated fully with the radiologist carrying out the investigation. In certain cases, patients were allowed to rest while the film was being processed and assessed to ensure that the film provided the required diagnostic information. After irradiation, the TLD chips were removed and kept outside the x-ray room to prevent further exposure from scattered radiation. The irradiated dosimeters were calculated by using the RADOS TLD READER RE 2000 of LASURMS.

Radiation Dose Measurement during Whole Body Bone Scan

Thermo-luminescent dosimeter (LiF-TLDs) pellets with dimension of 4.5 mm (diameter) by 0.9 mm (thickness) were used in the study to determine the dose delivered to the base of the index fingers of the radiologic technologist handling the ^{99m}Tc-MDP. TLD pellets with variation of ±5% were selected for the study. The labeled pellets were inserted in a plastic holder that could be adjusted for any size which was worn by the radiologic technologist at the base of index fingers of both hands (left and right). The choice of the index finger was performed according to the convenience of the radiologic technologist and the proximity of the source to the fingers while administering the ^{99m}Tc-MDP. A total of 104 TLD pellets were used during the administration of ^{99m}Tc-MDP and were evaluated later. The TLD pellets were kept outside the radiation area when not in use. Control TLD pellets were also kept outside the radiation area for measuring the background response of the TLD. The background readings were subtracted from the measured doses. TLD reader (Harsaw 3500) obtained from National Institute for Radiation Protection and Research, Department of Physics, University of Ibadan was used to read the TLD pellets.

Results

Result of Finger Doses during Hysterosalpingography

Doses to the patient were measured in terms of personal dose equivalent horsepower (0.07). This is equivalent to the dose in the tissue (soft) below a specified point on the body at a depth of 0.07 mm.

Ten patients were examined by a radiologist in each of the following study centers: RWRC, FDC, PMD and RHH; while eight patients were included in the study carried out in TSH. In each of the centers, one radiologist took part in the study during the period of sixteen (16) weeks. Radiologists were assigned code numbers: R1 (RWRC), R2 (FDC), R3 (PMD), R4 (RHH), and R5 (TSH). Radiologists R1-R4 performed an average of 1.6 HSG procedures per week (≈2) while R5 performed 2 HSG procedures per week.

Table 1 shows the radiation doses (mSv) delivered to the hands of the five radiologists studied during the period of 16 weeks. The range of mean doses to both hands of the radiologists were R1: 0.14-0.31 mSv, R2: 0.21-0.44 mSv, R3: 0.23-0.48 mSv, R4: 0.16-0.36 mSv, and R5: 0.17-0.43 mSv. The radiologist coded R5 carried out eight examinations during the study period. The highest dose during the study was received by the left hand of radiologist R3. A dose close to the maximum value was received by the left hand of radiologist R2. To a large extent, the doses to the left

hands of the radiologists were higher than the doses to their right hands. Relatively lower doses were received by R1, R4 and R5 while examining patients P5, P6, and P8.

Table 2 shows the doses accumulated during 16 weeks, estimated annual dose to both hands, mean doses received on each hand during the 16 weeks, and mean dose accumulated in 16 weeks by both hands. The dose range that was accumulated by both hands was 4.86-6.13 mSv, and the corresponding estimated annual accumulated dose ranged between 15.8-19.9 mSv. Among the five radiologist investigated, R1 received the smallest accumulated annual dose of 15.8 mSv.

Results of Doses Measured during Bone Scan

Tables 3 and Table 4 display the estimated activities of injected radiopharmaceuticals and their administration time. The mean injected activities with and without cannula were 19.6±2.16 mCi and 19.9±1.49 mCi, respectively. The corresponding mean administration times were 33.3±9.4

Table 1. Distribution of occupational doses among different radiologists

Patient (n)		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Radiologist	**Hand dose (mSv)**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**8**
R1	Left	0.34	0.30	0.30	0.23	0.15	0.31	0.23	0.18	0.28	0.33
	Right	0.21	0.22	0.26	0.20	0.13	0.30	0.25	0.14	0.22	0.28
	Mean dose	0.28	0.26	0.28	0.22	0.14	031	0.24	0.16	0.25	0.31
R2	Left	0.38	0.28	0.62	0.29	0.51	0.40	0.22	0.43	0.51	0.31
	Right	0.26	0.25	0.25	0.22	0.34	0.20	0.20	0.19	0.29	0.18
	Mean dose	0.32	0.27	0.44	0.26	0.43	0.30	0.21	0.31	0.40	0.26
R3	Left	0.39	0.63	0.29	0.32	0.40	0.37	0.30	0.31	0.24	0.32
	Right	0.26	0.33	0.17	0.22	0.34	0.32	0.25	0.17	0.22	0.28
	Mean dose	0.31	0.48	0.23	0.27	0.37	0.35	0.28	0.24	0.23	0.30
R4	Left	0.27	0.29	0.37	0.40	0.35	0.19	0.27	0.14	0.29	0.43
	Right	0.23	0.24	0.27	0.26	0.21	0.15	0.25	0.18	0.25	0.29
	Mean dose	0.25	0.27	0.32	0.33	0.28	0.17	0.26	0.16	0.27	0.36
R5	Left	0.48	0.30	0.37	0.28	0.52	0.39	0.29	0.19	–	–
	Right	0.29	0.24	0.26	0.29	0.33	0.31	0.26	0.14	–	–
	Mean dose	0.39	0.27	0.32	0.28	0.43	0.35	0.28	0.17	–	–

Table 2. Mean, accumulated and calculated annual occupational dose

Radiologist (n)	Dose accumulated in 16 weeks (both hands)	Calculated annual dose (mSv) for both hands	Mean dose (mSv)		Mean dose ± SD (mSv) accumulated in 16 weeks
			Left hand	Right hand	Both hands
R1 (10)	4.86 (0.28-0.61)	15.8	0.27	0.22	0.49±0.11
R2 (10)	6.13 (0.42-0.87)	19.9	0.40	0.24	0.61±0.17
R3 (10)	6.13 (0.46-0.96)	19.9	0.36	0.26	0.61±0.16
R4 (10)	5.33 (0.32-0.72)	17.3	0.30	0.23	0.53±0.13
R5 (8)	4.94 (0.33-0.85)	16.1	0.34	0.27	0.62±0.16

SD: Standard deviation

Table 3. Activity of radiopharmaceuticals administered to patients (no cannula)

Statistical parameter	Mean estimated activity (mCi)	Injected activity (mCi)	Residual activity (mCi)	Administration time (s)
Mean	20.6±1.79	19.9±1.49	0.72±0.44	33.3±9.4
Median	20.1	19.9	0.64	33.0
Range	17-24	16.6-22.4	0.11-1.87	18-56

seconds, and 44.7±8.57 seconds for administration without and with a cannula, respectively.

Table 5 shows the results of the total dose delivered with cannula and without cannula to the right and left hands. The mean doses to the right and left hand (without cannula) were 0.20±0.14 and 0.21±0.17 mSv, respectively. Also the mean doses delivered to the left and right hands were 0.25±0.12 and 0.28±0.15 mSv, respectively. Table 6 demonstrates the estimated daily, weekly and annual doses received during the administration of ^{99m}Tc-MDP. The mean doses per day (with cannula) were 1.46±0.56 and 1.31±0.34 mSv for the left and right hand, respectively. Furthermore, the mean doses received per day (without cannula) by the radiologic technologist to the left and right hands were 1.09±0.69 mSv and 1.05±0.64 mSv, respectively.

Discussion

Regular monitoring of radiation doses received by the extremities of radiologists, physicians and technologists involved in HSG is very important in order to ascertain the level of exposure of the unprotected part of the hands of the personnel who carry out the procedure. The regular dose assessment of hands, eyes, gonads, and legs is essential to ensure that occupational doses received by radiologists are within the recommended annual dose limit. The results of this study demonstrated that each radiologist performed an average of 2 HSG procedures per week. The two patients per week schedule on a regular basis amounts to 154 HSG examinations per annum. A mean dose of 0.62 mSv received per examination (maximum mean dose per exam from both hands) yields a total dose of 191 mSv per annum. This is relatively higher than 3/10th (150 mSv) and about 141 mSv higher than 1/10th (50 mSv) of the limit.

Table 4. Activity of radiopharmaceuticals administered to patients (with cannula)

Statistical parameter	Mean estimated activity (mCi)	Injected activity (mCi)	Residual activity (mCi)	Administration time (s)
Mean	20.4±2.40	19.6±2.16	0.84±0.59	44.7±8.57
Median	20.5	19.9	0.84	44.0
Range	16.9-26.9	16.3-24.0	0.04-2.89	24-62

Table 5. Total dose to each hand of the radiologic technologist (with cannula or without cannula)

Doses (mSv)	Administration without cannula	Administration with cannula
Total dose to the left hand (mean)	5.44 (0.21±0.17)	7.29 (0.28±0.15)
Total dose to the right hand (mean)	5.24 (0.20±0.14)	6.53 (0.25±0.12)
Total dose to both hands	10.68	13.82

Table 6. Estimated daily, weekly and annual doses received by administering radiologic technologist

Dose (mSv)	Week	With cannula		Without cannula	
		Left hand	Right hand	Left hand	Right hand
Total dose per week	1	7.29	6.53	–	–
Mean dose per day		1.46±0.56	1.31±0.34	–	–
Total dose per week	2	–	–	5.44	5.24
Mean dose per day		–	–	1.09±0.69	1.05±0.64
Total dose per annum		379.6	340.6	283.4	273.0
Total dose received by the radiologic technologist per annum (for both left and right hands)		720.2		556.4	
Left hand (total) Dose (mSv)		663.0			
Right hand (total)		613.6			

The annual dose limit for deterministic effects to the hands and legs as well as the skin is set to 500 mSv averaged over 1 cm^2 area of skin regardless of the exposed field. Routine dose monitoring is legally required if $1/10^{th}$ of the limit is reached (10). An estimated annual dose for the radiologists monitored during this study was calculated by multiplying the mean dose (upper limit) obtained for an HSG procedure by the estimated workload (number of procedures) for one year. Since the annual dose exceeds $1/10^{th}$ of the limit in the present study, it is essential to routinely monitor the radiation doses received by radiologists.

Although, the annual estimated dose obtained from the workload (HSG) is greater than $3/10^{th}$ of the limit, it is not unlikely that the radiologists also perform other procedures such as interventional radiology and cardiac radiological procedures which involve long fluoroscopic times, hence leading to higher doses (11,12). Besides, doses to the legs and lens of the eyes were not measured. Measurement of these values might significantly increase the annual dose.

Table 1 shows that relatively higher doses were delivered to the left hands of most of the radiologists. The doses to the left hand for all radiologists ranged from 0.15-0.63 mSv while the range of doses to the right hand was 0.13-0.34 mSv. The few exceptions to this trend are R1 (P7) and R4 (P8), while the results of R5 (P4) were comparable. The reason for higher doses could be attributed to the irradiation of the left hand that is used to hold the cannula in place and to prevent slipping off. This could also be attributed to most radiologist's leaning their left hands towards the cathode of the x-ray tubes, thus increasing received doses due to heel effects. The reported doses to the left hand in this study are in agreement with an earlier study, which reported that (interventional) physicians received higher doses on their left wrist during interventional radiology and cardiology procedures (13). It is evident from Table 1 that slight variations exist among received doses by radiologists. The variation could be attributed to various factors such as patient's body size (14), skill and the experience of the physicians (15), and the exposure parameter selected (16) during examinations.

Using the accumulated dose during the study period as seen in Table 2, the calculated accumulated annual doses indicate a range of 15.8-19.9 mSv, which implies that it is still within the recommended limit of 500 mSv/yr. The occupational doses received by radiologists in this study are below the acceptable dose limit and therefore, does not constitute serious health hazards if doses to other extremities are not considered. However, the calculated occupational dose based on the typical workload of a radiologist indicates that routine dose monitoring is required in Nigerian hospitals for effective radiation protection of radiology staff.

With regards to radionuclide bone scan procedures, a comparison of Table 3 and Table 4 show that the exposure time of the procedures carried out with a cannula is longer than the duration of administration without one. This excess mean time of 11.4 seconds between the two modes of administering the radiopharmaceutical could be due to the difficulty in applying the cannula. The extra time spent in the administration might have led to the apparently higher dose received by the radiologic technologist using the cannula, which is evident in Table 5. Apparently, the mean dose received by radiologic technologists is higher when a cannula was used to administer the ^{99m}Tc-MDP. Table 5 indicates that the dose delivered to the left hand was higher than the dose delivered to the right hand of the staff by a factor of 1.04 without a cannula, and was higher by a factor of 1.12 when a cannula was used. In addition, the total dose received while using a cannula is higher than the total dose received when a cannula was not used by the administering staff by a factor of 1.30.

The estimated total doses per annum received by a staff administering ^{99m}Tc-MDP with and without a cannula were 720.2 mSv and 556.4 mSv, respectively. We assumed that each radiologic technologist worked five days per week, and that he was available to administer the radiopharmaceutical throughout 52 weeks of the year. The total doses received by the radiologic technologist without and with a cannula were 10.68 mSv and 13.82 mSv, respectively. Based on the assumption that the staff does not go on vacation but rests only on weekends, the total annual dose that could be delivered to the staff would be 1276.6 mSv. The estimated occupational dose per annum exceeds the annual limit of 500 mSv to the extremities, hands and feet, and skin (17,18) by a factor of 2.6. The relatively higher dose recorded in this study could be related to the assumption that the radiologic technologist handling ^{99m}Tc-MDP carries out the administration throughout the whole year as opposed to working on a rotating schedule as has been earlier reported by Pant et al. (17). Moreover, these results are the upper limit of the estimated dose data. The trend found in the present study calls for the engagement of more technical staff who could administer the radiopharmaceuticals in turn or on rotation basis, which in turn will help reduce the dose received by an individual staff per year.

The total dose delivered to the left and right hands were 663.0 and 613.6 mSv, respectively, with a mean dose of 638.3 mSv to each hand. The mean total dose to each hand exceeds the annual dose limit of 500 mSv.

Conclusion

The radiation doses delivered to the hands of the radiologists who carry out HSG procedures were measured in five hospitals in Nigeria (within Lagos). Mostly, higher doses were delivered to their left hands. The estimated annual dose calculated according to the workload revealed that the recommended annual limit for the extremities are not surpassed. Nevertheless, the estimated annual dose exceeds 10 percent of the annual dose to the extremities,

thus indicating the need for monitoring individual doses to the extremities of the radiologists.

However, the estimated annual dose received by a staff administering the ^{99m}Tc-MDP during bone scan exceeded the annual dose limit for health workers. The high dose recorded during the bone scan indicates the need for involvement of additional technical staff in the injection of ^{99m}Tc-MDP so as to reduce the dose received by the few radiologic technologists involved in the administration of the radionuclide.

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Ethics

Ethics Committee Approval: The radiologic technologist who carried out the investigation was permitted to undertake the examination as part of his routine work by the law of University College Hospital. Thermo-luminescent dosimeters pellets were attached to his fingers. The hysterosalpingography procedures were carried out by certified radiologists who were by the law of our country permitted to examine patients as part of their daily duty, and the study was also carried out on the radiologists themselves, Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

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Assessment of Heart Rate Recovery with GATED-Myocardial Perfusion Scintigraphy Outcome in Patients with Coronary Artery Disease: A Retrospective Study and Institutional Experience

Koroner Arter Hastalarında GATED-Miyokard Perfüzyon Sintigrafisi Sonuçlarının Kalp Hızı Toparlanma İndeksi ile Birlikte Değerlendirilmesi: Retrospektif Çalışma ve Kendi Deneyimlerimiz

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Abstract

Objective: This study aimed to investigate the effects of assessment with myocardial perfusion scintigraphy (MPS) and heart rate recovery (HRrec) measurements in combination to evaluate the current status of patients with a diagnosis or suspicion of coronary artery disease (CAD).

Methods: A total of 350 patients were included in the study. CAD group consisted of 200 patients with stable angina pectoris and a known history of CAD, while the control group consisted of 150 patients with suspicious stress test who had no history of known CAD. In order to calculate the HRrec index, the treadmill exercise test was performed in all patients according to the Bruce protocol. The MPS results were evaluated for the presence or absence of myocardial ischemia and infarction by visual and quantitative (summed stress score and summed difference score) assessments.

Results: When the MPS results and HRrec were evaluated together, there was no statistically significant difference in the non-CAD group. But, when GATED-MPS was evaluated alone in the triple-vessel patient group, 27 (36%) patients were found to be normal while evaluated with HRrec, four (5.3%) patients were found to be normal.

Conclusion: HRrec measurements obtained during stress MPS is important in patient evaluation. Therefore, evaluation of MPS results and HRrec measurements together may provide a more accurate estimation of possible presence of CAD in patients.

Keywords: Coronary artery disease, heart rate recovery, stress myocardial perfusion scintigraphy

Öz

Amaç: Bu çalışmada koroner arter hastalığı (KAH) olan ya da şüphesiyle incelenen hastaların mevcut durumlarının daha iyi değerlendirilmesi için miyokard perfüzyon sintigrafisi (MPS) ve kalp toparlanma hızlarının birlikte değerlendirilmesinin sonuçlar üzerine olan etkisi araştırıldı.

Yöntem: Çalışma retrospektif özellikte olup toplam üç yüz elli hasta dahil edildi. Anjina pektoris ve KAH öyküsü bulunan 200 kişi hasta grubunu, KAH öyküsü bulunmayan 150 hasta ise kontrol grubunu oluşturdu. Hastalara Bruce protokolüne göre efor testleri yaptırılarak kalp toparlanma hızları ölçüldü. MPS sonuçları kalp hızı toparlanma indeksleri ile birlikte değerlendirildi.

Bulgular: Koroner hastalığı olmayan hasta grubunda MPS sonuçları ve kalp hızı toparlanma indeksleri birlikte değerlendirildiğinde istatiksel olarak anlamlı fark bulunmadı. Ancak, üç damar hasta grubunun değerlendirilmesinde sadece MPS sonuçları yapılan

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değerlendirmede hastaların 27'si (%36) normal bulunurken, kalp hızı toparlanma indeksleri ile birlikte değerlendirildiğinde hastaların dördü (%5,3) normal olarak saptandı.
Sonuç: Stres MPS sırasında elde edilen kalp hızı toparlanma ölçümleri hastaların değerlendirilmesinde önemlidir. Bu nedenle, MPS sonuçlarının kalp hızı toparlanma ölçümleri ile birlikte değerlendirilmesi olası KAH varlığını daha doğru öngörebilir.
Anahtar kelimeler: Koroner arter hastalığı, kalp hızı toparlanma indeksi, stres miyokard perfüzyon sintigrafisi

Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality in developed countries.

Due to the incidence of CAD, there is a need for accurate, inexpensive, and non-invasive imaging methods for both diagnosis and monitoring. Exercise tests were the initial tests employed in diagnosis of CAD.

Changes in heart rate during and immediately after exercise determine the balance between the sympathetic system and vagal activity. During the recovery period after exercise, as the sympathetic activity that increased during exercise reduces, parasympathetic activity increases and causes a reduction in heart rate (1).

Heart rate recovery (HRrec) refers to the decrease in heart rate after exercise. HRrec index is calculated by subtracting the heart rate at the 1st, 2nd and 3rd minutes of the recovery period from the maximum heart rate in a patient performing a submaximal or maximal stress test (2).

HRrec index is an important marker of vagal activity, and there are many studies showing that it is a strong predictor of deaths due to all causes as well as cardiovascular reasons (3,4,5).

Many studies have shown that the HRrec index in the 1st and 2nd minutes strongly predicts prognosis in coronary artery patients and reported that those with low HRrec have a significantly higher risk of mortality (5).

GATED-myocardial perfusion scintigrapy (MPS) is a nuclear medicine method that is currently being used widely for the diagnosis and monitoring of CAD (6).

GATED-MPS uses a radioactive marker such as ^{99m}Tc-methoxyisobutylisonitrile or Tl201 in patients undergoing treadmill or pharmacological stress. Data obtained under stress and rest conditions using MPS-single photon emission computed tomography (SPECT) and GATED [simultaneous with electrocardiography (ECG)] methods is used to investigate myocardial perfusion in the left ventricle and heart wall movements on segmentary analyses on polar graphics prepared on slices in transaxial, coronal and sagittal planes.

MPS results can be assessed both visually and quantitatively. Abnormal perfusion images may be observed in balanced ischaemia cases with triple vessel disease and also in cases with insufficient stress test (7).

Both exercise and GATED-MPS provide false positive and false negative results if used alone for the assessment of CAD. Therefore, in this study we aimed to investigate the effects of assessment with MPS and HRrec measurements in combination to evaluate the current status of patients with a diagnosis or suspicion of CAD.

Materials and Methods

Study Population

The study was retrospectively planned on patients who applied to Çanakkale University Faculty of Medicine, Nuclear Medicine Department for MPS with the aim of investigating CAD. The study included 350 patients comprising 225 women and 125 men. The CAD group consisted of 200 patients with known history of CAD and stable angina pectoris, while the control group included 150 patients with no known history of CAD and who had a suspicious stress test.

Patients were excluded from the study if they had congestive heart failure, advanced degree of aortic stenosis, severe hypertrophic cardiomyopathy, malignant hypertension, uncontrolled rhythm disorders, acute ischemia, chest pain within the previous two days, if they could not perform stress test due to orthopedic problems, those with musculo-skeletal problems, peripheral artery disease, psychiatric problems, those using medications affecting the autonomic system, and those under the age of 20 and above the age of 65 years.

The study was completed after receiving permission from the local ethics committee.

Heart rate and recovery index measurements;

Basal heart rate: All patients had a basal ECG performed in a quiet room at body temperature, with the patient awake and resting, before the study to measure basal heart rate (HRrest).

Maximum heart rate (HRmax): The HRmax is the highest heart rate obtained by exercise linked to age. HRmax was measured with the aid of the Fox et al. (8) formula [HRmax: 220-(age)].

Target heart rate (THR) measurement: THR was calculated using the Karvonen (9) method. Maximal effort performance THR was accepted as a test reaching 85% and above.

Treadmill stress test and HRrec index measurements: A treadmill stress test was performed in accordance with the Bruce protocol prior to GATED-MPS in order to increase myocardial perfusion in all patients. The stress test was stopped when 85% of the calculated maximal heart rate

according to age was reached. To calculate the HRrec index, when maximal heart rate was reached, the heart rates at the 1st, 2nd and 3rd minutes of the recovery period before beginning a relaxing walk were subtracted from the maximal heart rate and were recorded as Rec 1, Rec 2 and Rec 3 HRrec index.

HRrec index cut-off values: In our study, instead of using our own cut-off values for normal and abnormal HRrec, we benefitted from the cut-off values obtained in previous studies. The HRR was accepted abnormal if < or =12 beats/min during the first minute after exercise (10).

GATED-MPS: Patients underwent stress-rest protocols in a single day. All patients discontinued cardiac glycosides one week prior to the test while other antihypertensive medications were stopped 48 hours before the procedure. Stress images were taken 45 minutes after 10 mCi ^{99m}Tc-sestamibi injection, with resting images obtained 4 hours after initial imaging and 60 minutes after 30 mCi ^{99m}Tc sestamibi injection.

GATED-MPS images were taken with a low energy, high resolution, double head gamma camera (GE, Infinia) fitted with a parallel-slit collimator synchronized to ECG from 45° right anterior to 45° left posterior oblique, with 140±20% keV energy peak, 64x64 matrix, in supine position. Each image took 35 seconds and a total of 32 images were obtained.

After processing the raw data obtained from the patients with the aid of a computer, it was then evaluated both quantitatively and visually.

Statistical Analysis

Research data was uploaded to the SPSS 19.0 statistical program in the electronic environment and the analyses were performed. Statistical evaluation used the chi-square analysis, and $p<0.05$ was accepted as significant.

Results

The clinical characteristics of patients in coronary artery and control groups are presented in Table 1. The mean age in the CAD group was 56±9 years, and was 52±11 years in the control group. The CAD patients comprised 70% female and 30% male, while the control group comprised 56.6% female and 43.3% male. Comparison of the clinical characteristics and cardiac risk factors between the groups did not reveal any statistically significant difference in terms of age distribution. However, it was observed that the number of female cases was greater than the number of male cases. In terms of cardiac risk, there was no significant difference between the CAD

Table 1. Baseline patient characteristics of the coronary artery disease and the control groups

	Patients with CAD (n=200)		No CAD (n=150)		
	n (%)	Mean ± SD	n (%)	Mean ± SD	p value
Age (years)		56±9		52±11	0.420
Sex					
Female	140 (70%)		85 (56.6%)		
Male	60 (30%)		65 (43.3%)		0.350
Family history	60 (30%)		43 (28.6%)		0.210
Hypertension	80 (40%)		57 (38%)		0.230
Dyslipidemia	47 (23.5%)		19 (12.6%)		0.150
Diabetes mellitus	80 (40%)		55 (36.6%)		0.170
Smoking	51 (25.5%)		46 (30.6%)		0.200
Obesite (kg/m^2)	30 (15%)		18 (12%)		0.150
Previous MI	50 (25%)		0		
Previous CABG	15 (7.5)		0		
B Blocker	60 (30%)		25 (16.6%)		
Ca channel blockers	40 (20%)		55 (36.6%)		0.250
Alpha blockers	0		0		
Angiotensin receptor blocker	110 (55%)		60 (40%)		0.150
Single vessel CAD	110 (55%)		0		
Double vessel CAD	15 (7.5%)		0		
Three-vessel CAD	75 (37.5%)		0		

CAD: Coronary artery disease, SD: Standard deviation, MI: Myocardial infarction, CABG: Coronary artery bypass graft, Ca: Calcium

group and the control group (p>0.005). In the CAD group 55% had single vessel, 7.5% had double vessel and 37.5% had triple vessel disease (Table 1). While there was no clear difference between the HRrec in the single and double vessel disease cases in the CAD group, the HRrec in the triple vessel disease group was clearly lower than the other two sub-groups (Figure 1). When the HRrec values are compared in the patient and control groups, the HRrec in the 1st and 2nd minute in the CAD group was identified to be significantly lower than the control group (p=0.002, Table 2).

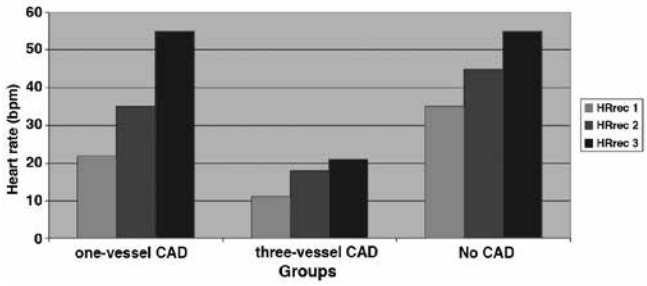

Figure 1. Heart rate recovery index shows that in patients with three-vessel lower than the other groups
CAD: Coronary artery disease, HRrec: Heart rate recovery

The GATED-MPS results of all participants are presented in Table 3. In the CAD group, 47/200 (23.5%) of patients were normal and 153/200 (76.5%) had ischemia; while in the control group, 128/150 (85.3%) were normal and 22/150 (14.6%) were found to have ischemia (p<0.001, Table 3).

When the MPS results are evaluated together with the HRrec, there was no statistical difference observed in the control group. When evaluated with HRrec in the CAD group in single vessel patients 9% had ischemia of the 21.8% of patients found to be normal, while there was no difference for double vessel patients. A patient with three-vessel disease was presented Figure 2A, 2B. When GATED-MPS is evaluated alone for the triple vessel patient group, 27 (36%) patients were found to be normal while evaluated with HRrec, four (5.3%) were found to be normal (Table 4).

Table 2. Heart rate recovery indices of the groups

HRrec	CAD			No CAD	p value
	One-vessel	Two-vessel	Three-vessel		
HRrec 1	22.4±8.4	21.6±7.2	11±7.5	35.3±8.1	0.002
HRrec 2	35.3±8.1	22.4±6.4	18.3±6.1	45.3±8.1	0.035
HRrec 3	55.4±6.5	40.4±8.4	21.6±5.1	55.4±6.5	0.015

HRrec: Heart rate recovery, CAD: Coronary artery disease

Table 3. Myocardial perfusion imaging findings in the coronary artery disease and control groups

MPS findings n (%)	One-vessel CAD n=110	Two-vessel CAD n=15	Three-vessel CAD n=75	No CAD n=150	p value*
SSS <4	18 (16.3%)	2 (13.3%)	27 (36%)	128 (85.3%)	<0.001
SSS 4-8	67 (60.9%)	8 (53.3%)	25 (33.3%)	12 (8%)	
SSS 9-13	20 (18.1%)	3 (20%)	13 (17.3%)	10 (6%)	
SSS >13	5 (4.5%)	2 (13.3%)	10 (13.3%)	0	
SDS 0-1	24 (21.8%)	2 (13.3%)	32 (42.6%)	133 (88.6%)	<0.001
SDS 2-4	50 (45.4%)	8 (53.3%)	28 (37.3%)	17 (11.3%)	
SDS 5-7	30 (27.2%)	3 (20%)	8 (10.6%)	0	
SDS ≥8	6 (5.4%)	2 (13.3%)	7 (9.3%)	0	
SLVEF <35	9 (8.1%)	2 (13.3%)	30 (40%)	0	<0.001
SLVEF 35-49	41 (37.2%)	10 (66.6%)	25 (33.3%)	0	
SLVEF ≥50	60 (54.5%)	3 (20%)	10 (13.3%)	150	

CAD: Coronary artery disease, MPS: Myocardial perfusion scintigraphy, SSS: Summed stress score, SDS: Summed difference score, SLVEF: Stress left ventricular ejection fraction, *Chi-square test, SSS <4; normal, SSS 4-8; mildly abnormal, SSS >13 severely abnormal, SDS 0-1; normal, SDS; 2-4; mild ischemia, SDS 5-7; moderate ischemia; SDS ≥8; severe ischemia, SLVEF ≥50; normal, SLVEF 35-49; mild-moderately abnormal, SLVEF <35; severely abnormal

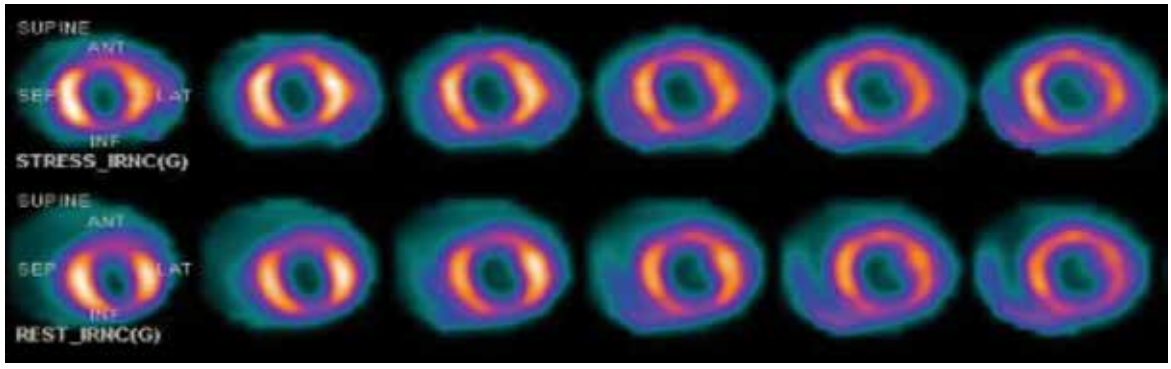

Figure 2A. The view of a 50-year-old male patient with myocardial perfusion scintigraphy. Myocardial perfusion scintigraphy in all areas are monitored reduced and heterogeneous uptake. Three-vessel disease was detected in the patient's coronary angiography

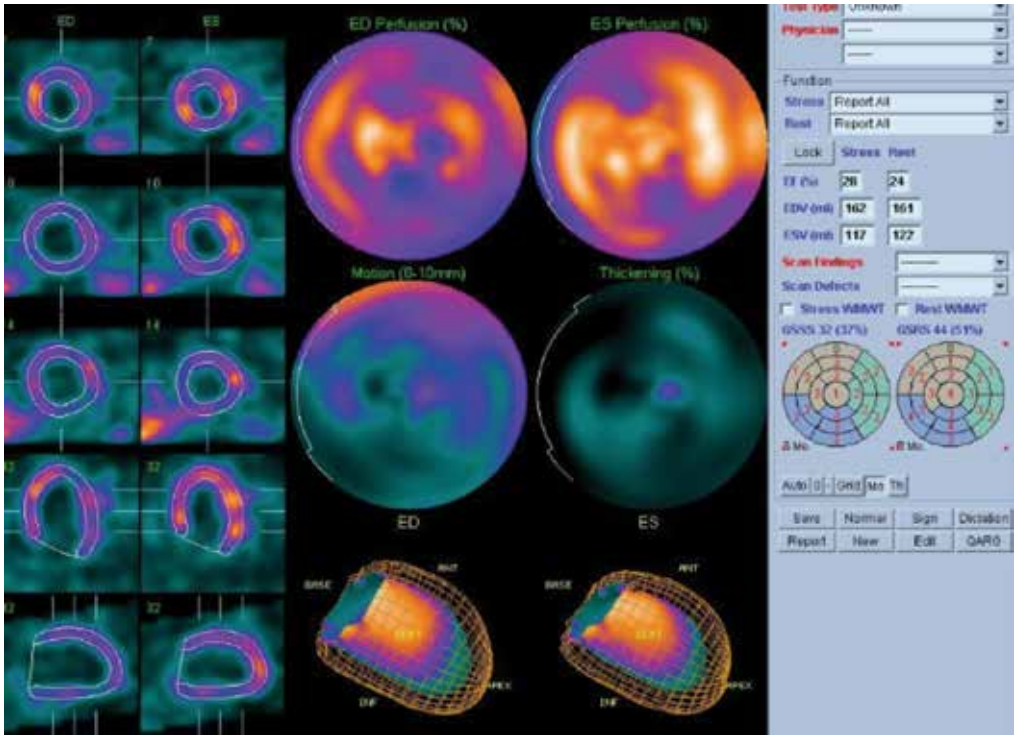

Figure 2B. Quantitative gated single photon emission computed tomography findings of the same patient. In the GATED-single photon emission computed tomography imaging were found stress ejection fraction: 31%, resting ejection fraction: 24%

Table 4. Comparison of myocardial perfusion imaging findings and heart rate recovery with coronary artery disease

	CAD						
	One-vessel n=110		Two-vessel n=15		Three-vessel n=75		p value*
Measures (n, %)	**N* (≥12 bpm) n, %**	**AN** (<12 bpm) n,%**	**N (≥12 bpm) n,%**	**AN (<12 bpm) n,%**	**N (≥12 bpm) n, %**	**AN (<12 bpm) n, %**	
SDS <1 (normal)	14 (12.7%)	10 (9%)	0	2	4 (5.3%)	28 (37.3%)	<0.001
SDS >2 (ischemia)	32/86 (37.2%)	54/86 (62.7%)	3/13 (23%)	10/13 (76.9%)	13 (17.3%)	30 (40%)	

SDS: Summed difference score, SDS <1; (0-1); normal, SDS >2; 2 ischemia (4; mild ischemia, SDS 5-7; moderate ischemia; SDS ≥8; severe ischemia), CAD: Coronary artery disease, HRrec: Heart rate recovery, BPM: Beat per minute, *Normal HRrec (≥12 bpm); N, **Abnormal HRrec (<12 bpm); AN, *Chi-square test

Discussion

The results of this study, similar to previous studies, indicate that the HRrec index for the first and second minutes was lower in CAD patients as compared to controls. The other significant finding of the study is that the HRrec index correlated with the extent of CAD. These findings indicate that it may be an important parameter to evaluate in patients with CAD. Additionally, the positive contribution of evaluation with HRrec and MPS in combination was shown with the reduced false negative results.

Heart rate is stated as the number of heart beats per unit time. Heart rate changes in many situations depending on the body's needs, oxygen and carbon dioxide levels in the blood, physical and mental activity, etc. (11). There are many studies showing that a low resting heart rate reduces mortality. In healthy and asymptomatic individuals, the heart rate falls rapidly within the first 30 seconds after exercise followed by a slower reduction (12).

There are studies showing that heart rate is disrupted in uncomplicated heart diseases even before the development of symptomatic CAD (13).

Cole et al. (14) showed that the lack of expected decrease in heart rate in the 1st minute after exercise (≥12 beats/min) is a marker of reduced vagal activity. This situation may be a strong marker for general mortality independent of heart rate changes due to work load, the presence of myocardial perfusion defect, and during exercise.

A study by Lima et al. (15) reported that there was no dependent relationship between abnormal HRrec and summed different score. In contrast, Georgoulias et al. (16) showed that abnormal HRrec index was an important indicator of ischemia identified on MPS-SPECT images.

Inconsistency between the results of MPS and coronary angiography (CAG) is frequently encountered. The lack of clear coronary artery stenosis on CAG of patients with ischemic perfusion findings is thought to be due to false positive results of scintigraphy. In circumstances that affect the diagnostic accuracy of MPS, such as insufficient stress administration and triple vessel disease, the sensitivity decreases to 60% (17,18,19).

Vivekananthan et al. (20) reported that angiographic severity of CAD, left ventricle function, exercise capacity and HRrec index may be independent predictors of mortality.

HRr is also affected by other factors such as age, heart failure, previous myocardial infarction (MI), diabetes, hypertension and smoking.

In our study, we encountered false positive results in 17 patients (11.3%) with normal CAG. There was no ECG or echocardiography finding to explain the false positivity of MPS. We encountered false positive results in 19.2% of those with single vessel disease on CAG, and in 42.6% of those with multiple vessel disease. The main aim of our study was to investigate how could the current situation of patients with a diagnosis or suspicion of CAD be evaluated more accurately. As a result, when we evaluated the HRrec and MPS results together for all participants, we found that accuracy was higher than that obtained from HRrec or MPS alone. We believe that the false negative evaluations on MPS results, similar to those with triple vessel disease, may be reduced with this approach.

Study Limitations

The first limitation of the study is that the stress test before MPS was completed according to the Bruce protocol. Patients reaching maximum heart rate on the treadmill continued with a slow walking pace for up to a minute after the end of stress. As a result, the HRrec obtained from the 2nd minute were evaluated as the cooling period. Second, in the CAD group, patients were not assessed for MI and coronary artery bypass graft (CABG). There is a need for studies that take MI and CABG durations into account. Finally, our study is a retrospective study conducted on a small group of patients, this issue should be studied in larger groups in the future.

Conclusion

Evaluation of HRrec measurements obtained during GATED-MPS provided a positive contribution and may be used to estimate the current situation of CAD patients more accurately.

Ethics

Ethics Committee Approval: The study was approved by the Çanakkale Onsekiz Mart University Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yusuf Ziya Tan, Burak Altun, Concept: Yusuf Ziya Tan, Burak Altun, Design: Yusuf Ziya Tan, Semra Özdemir, Data Collection or Processing: Yusuf Ziya Tan, Semra Özdemir, Analysis or Interpretation: Yusuf Ziya Tan, Burak Altun, Literature Search: Fatmanur Çelik, Writing: Yusuf Ziya Tan, Semra Özdemir, Burak Altun.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article
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Adverse Reactions to Radioiodine ^{131}I Therapy of Goiter in West African Tertiary Hospital

Üçüncü Düzey Bir Batı Afrika Hastanesinde Guatr Tedavisinde Radyoiyot ^{131}I'in Yan Etkileri

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Abstract

Objective: Radioactive iodine therapy (RAIT) is established as an efficient means of treating toxic goiter (TG) globally. The field of nuclear medicine (NM) still appears novel to many Nigerian clinicians and patients. A culturally embedded dread of radiation may raise ethical and moral concerns about potential adverse effects in the wake of RAIT in our setting. An adverse drug reaction may be described as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man". This study therefore, seeks to review adverse reactions (ARs) experienced following RAIT. We would also like to improve patient and physician education about the safety profile of RAIT.

Methods: This is a retrospective analysis of all patients who had received RAIT for thyroid disease from August 2006 to June 2015.

Results: Forty typical ARs were experienced following 36 therapy sessions (18.65%) with RAIT in 35 patients (21.47%) aged 17-78 years, of which three had multiple sessions for well-differentiated thyroid carcinoma (WDTC).

Conclusion: RAIT remains a safe option for the treatment of benign and TG. The experienced ARs are mainly mild to moderate in severity and mostly short-lived. As larger doses of radioactive iodine for WDTC and TG were more commonly associated with ARs, our study suggests that these patients merit stronger prophylactic measures as well as closer monitoring for earlier detection and management of these reactions.

Keywords: Adverse reactions, radiotherapy, thyroid neoplasms, nuclear medicine

Öz

Amaç: Radyoaktif iyot tedavisi (RAIT) tüm dünyada toksik guatr (TG) tedavisinde etkin bir araç olarak kullanılmaktadır. Nükleer tıp (NM) alanı hala birçok Nijeryalı klinisyen ve hasta için yeni kabul edilmektedir. Radyasyondan kültürel bir korku RAIT kullanımında olası yan etkilerle ilgili etik ve ahlaki kaygıları arttırabilir. Bir ilaç yan etkisi "bir ilaca karşı normal insanlarda kullanılan dozlarda oluşan zararlı ve istenmeyen tepki" olarak tarif edilebilir. Bu çalışma bu nedenle RAIT'ye bağlı yan etkileri gözden geçirmeyi amaçlamıştır. Aynı zamanda RAIT güvenlik profili hakkında hastaları ve hekimleri eğitmeyi de arzu ediyoruz.

Yöntem: Bu çalışma Ağustos 2006-Haziran 2015 tarihleri arasında tiroid hastalığı için RAIT almış tüm hastaların retrospektif bir analizidir.

Bulgular: Yaşları 17-78 arasında 35 RAIT (%21,47) hastasının 36 (%18,65) tedavi seansında kırk yan etki gözlenmiştir, üç hastaya iyi diferansiye tiroid karsinomu nedeniyle çoklu seans uygulanmıştır.

Sonuç: RAIT iyi huylu ve TG tedavisi için güvenli bir seçenek olmaya devam etmektedir. Gözlenen yan etkiler genellikle hafif-orta şiddette ve çoğunlukla kısa ömürlüdür. İyi diferansiye tiroid kanseri ve TG için uygulanan yüksek dozlar daha çok yan etki ile ilişkili olduğundan çalışmamız bu hastalarda daha güçlü profilaktik tedbirlerin yanı sıra bu reaksiyonların erken saptanması ve yönetimi için daha yakından izlenmelerini önermektedir.

Anahtar kelimeler: Yan etki, radyoterapi, tiroid neoplazmlar, nükleer tıp

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Introduction

^{131}I radioactive iodine (RAI) is one of the 15 known radioisotopes of iodine, and is the most widely used in the diagnosis and therapy of thyroid diseases. RAI is reactor produced from the fission of ^{235}U (1,2). RAI is one of the most widely used radioisotopes in nuclear medicine (NM), the most popular being ^{99m}Tc. RAI, like stable iodine, is trapped and organified in the thyroid gland. It emits two types of radiation: 364 and 664 keV gamma rays (for imaging) and 192 keV beta particles (for therapy), respectively (3). Its beta particles deliver a lethal radiation dose to the thyroid cells that accumulate them.

Radioactive iodine therapy (RAIT) has been in use for the treatment of thyroid diseases for more than seven decades (4). It has been established as an efficient means of treating toxic goiter (TG) globally. Indications for RAIT include well-differentiated thyroid carcinoma (WDTC), primary hyperthyroidism due to Graves' disease (GD), toxic multinodular goiter and toxic adenomas, and for thyroid size reduction in cases of sporadic non-toxic/euthyroid goiter (EUG). There has been an increase in the use of RAIT as first line therapy for GD and the treatment of choice for recurrent GD and toxic nodular hyperthyroidism (5,6).

RAIT has recently been introduced to the management of patients with benign and malignant thyroid disease in Nigeria. The field of NM still appears novel to many Nigerian clinicians and patients (7,8). Unfamiliarity of clinicians with the efficacy of this modality has been encountered and its consequence on patient referral is unknown. Earlier studies in our environment reported acceptable treatment response rates of 83.87% and 77.3%, respectively, confirming the efficacy of RAIT for hyperthyroidism (9,10). A culturally embedded dread of radiation may raise ethical and moral concerns about potential adverse effects in the wake of RAIT in our setting such as infertility (11,12).

An adverse drug reaction may be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (13). It has also been described as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man" (14,15). Unlike radiotracers, RAI has ARs related to its associated radioactivity and not due to an "unanticipated physiologic response to the vehicle (tracer) carrying the radioactivity" (16). The previously reported frequency of ARs to radiopharmaceuticals are 11/100.000 in Europe, 2.3/100.000 in the US, and more recently, 0.8/100.000 in Japan (17,18,19). The figure quoted for the US remains relatively unchanged from the earlier frequency of 2.3/100.000 (20). The prevalence of ARs in NM is approximately 1000fold less than that quoted for iodinated contrast media and drugs; these are as high as 19.4% (21,22). Side effects of the treatment of goiter are known to negatively impact patient care (Table 1).

This study therefore, seeks to retrospectively review ARs experienced following RAIT. We would also like to improve patient and physician education about the safety profile of RAIT. This would further enhance patient care and safety in relation to RAIT. To the best of our knowledge, this is the first West African study to address this issue.

Materials and Methods

This is a retrospective analysis of all patients who had received RAIT for thyroid disease from August 2006-June 2015. Patients were treated based on empirical estimates for benign goiter [(TG) and EUG] as well as WDTC. Their management protocols are as follows:

General measures: RAIT is given as empirical doses; its capsules have been initially ordered from Amersham, South Africa, but they were ordered from IBA Molecular, France since February 2011. All patients fasted for at least two hours prior to RAIT, and two hours afterwards. At radioactive doses less than or equal to 555 MBq, patients were treated on an outpatient basis and discharged home after having been observed for possible ARs.

On admission: Patients who received radioactivity exceeding 555 MBq were admitted to our isolation wards, typically those with EUG and WDTC. Patients with TG who received doses exceeding 555 MBq of ^{131}I also followed this protocol. Prophylactic measures against ARs were taken; the prescription of pain relievers (paracetamol or non-steroidal anti-inflammatory drugs unless contraindicated), mist magnesium trisilicate or other antacid, lime juice or chewing gum for salivary gland protection, as well as

Table 1. Previously reported frequency of adverse reactions to radiopharmaceuticals

Country/region	Time period	NM institutions	Radiopharmaceutical administrations	Frequency of ARS
Silberstein and Ryan (20), North America	1989-1995	18	783 525	2.3/100.000
Hesslewood and Keeling (17), Europe	1996	17	71 046	11/100.000
Silberstein (18), North America	2007-2011	15	1 024 077	2.1/100.000
Matsuda et al. (19), Japan	2013	997	1 056 876	0.8/100.000

*NM: Nuclear medicine, ARS: Adverse reactions

liberal oral fluid intake as tolerated. Admitted patients were monitored daily and patients were discharged home at radiation dose readings ≤555 MBq at one meter from the patient. From August 2012, metoclopramide prophylaxis has been strictly enforced to prevent vomiting.

Follow-up clinic visits were scheduled at one month post-RAIT for all patients in order to assess their clinical status and to assess their hematological profiles for possible cytocidal effects of radiation. Patients were asked to report any ARs experienced following treatment during their admission and at follow-up sessions.

In addition, statistical analysis of patients who had received radioiodine therapy was performed using IBM statistics SPSS software version 21. The chi-square test was performed to test for significant association between presence or absence of adverse effects according to patient age groups (less than or equal to 44 years, or greater than 44 years), gender, type of diagnosis (TG, EUG, WDTC) and malignancy of goiter (benign or malignant), RAI treatment (less than or equal to 64 mCi-being the upper dose limit for benign goiters, or more than 64 mCi).

Nausea and vomiting, being the most common AR, was also tested for significant association with the above factors, as well as presence or absence of antiemetic therapy pre-RAI.

Results

Records were available for a total of 193 RAI treatments administered to 163 patients between 23 August, 2006 and June 8, 2015. Patient characteristics are presented in Table 2.

Forty typical ARs were experienced following 36 therapy sessions (18.65%) with RAIT in 35 patients (21.47%) aged 17-78 years, of which three had multiple sessions for WDTC (Table 3). All observed ARs were classified as early, relative to the period of occurrence post RAIT, and were also grouped as being mild to moderate in severity (67.5% mild, 32.5% moderate) (Table 4) (23). There were no mortalities. ARs were most common in WDTC (27 reactions; 67.5%), less so with TG (nine reactions; 22.5%) and the least in those with EUG (four reactions; 10%). The overall frequency of ARs in all NM procedures, whether diagnostic or therapeutic, performed during the study period was 0.78%.

A female preponderance was noted in reported ARs (male: female ratio of 1:5). This is likely subsequent to the pre-existing bias in the patient population.

Regarding goiter size, the greater the quantity of residual thyroid tissue the greater was the frequency of ARs observed (13 had no prior thyroid surgery, 12 had subtotal or near-total thyroidectomies, three had total thyroidectomies, two had lobectomies, while the nature of surgery was not known for five). Of the 12 patients who had been operated upon, the intense "star artifact" was seen in four patients in the thyroid bed on ^{131}I scanning, implying significant residual functioning thyroid tissue. In an additional seven, both thyroid lobes were visualized. However, the extent of thyroid visualization despite thyroidectomy varied depending on the operating surgeons. Two patients who had been operated upon subsequently developed metastatic disease prior to RAIT.

Table 2. Characteristics of patients treated with radioactive iodine therapy between August 2006-June 2015

	TG* (n=94)	EUG* (n=18)	WDTC* (n=81)	Total (n=163)
Age (years)				
Age range	17-74	26-79	13-77	13-79
Age average	45±13.96	49.5±15.15	42.12±13.47	44.3±13.98
Gender				
Males	15	0	21	36
Females	79	18	60	157
Sex ratio (M:F)	1:5	-	1:3	1:5
Doses (MBq)				
Number of doses	94	18	81	193
Dose (range)	301.5-2164.5	413.7-2360.6	1028.6-12210	301.5-12210
Dose (mean)	532.8	51.65±16.21	125.42±46.80	63.74
Single doses	81	12	40	133
Two doses	5	3	13	42
Three doses	1	0	5	18

RAIT: Radioactive iodine therapy, M: Male, F: Female, WDTC: Well-differentiated thyroid carcinoma, EUG: Euthyroid goiter, TG: Toxic goiter

RAI therapy patients with doses of ^{131}I less than or equal to 64 mCi were significantly less likely to experience ARs than those treated with higher doses; p=0.042. Also, patients with benign goiter (TG or EUG) were less prone to have ARs as compared to those with malignant goiters (WDTC); however, this was not significant; p=0.06. Despite the preponderance of female patients having ARs, gender proved non-significant; p=0.11. Other variables tested proved to be statistically insignificant.

Discussion

The use of RAI in thyroid disease therapy is well established due to its efficacy and simplicity, and is well tolerated although with some recorded side effects that are relatively less severe than other treatment modalities and that can be prevented or minimized if appropriate measures are taken (24). These include nausea and vomiting, and less commonly, radiation thyroiditis, gastritis and sialadenitis, the latter usually involving the parotid glands (25,26). The development of exacerbation of hyperthyroidism and hypersensitivity to RAIT are considered extremely rare (27,28). Iatrogenic hypothyroidism as a side effect is an expected outcome. In our hospital setting, due to economic constraints, most patients advocate for earlier hypothyroidism, and thus avoid the possibility of repeat RAIT.

Table 3. Adverse reactions experienced from radioactive iodine therapy displayed by gender

	Male	Female	Total (%)
Nausea		3	3 (7.5%)
Vomiting	2	16	18 (45%)
Acute sialadenitis		3	3 (7.5)
Radiation thyroiditis	2	9	11 (27.5)
Dysphagia		1	1 (2.5)
Dyspnea		1	1 (2.5)
Radiation pneumonitis		1	1 (2.5)
Xerostomia		1	1 (2.5)
Voice change		1	1 (2.5)
Total	4	36	40

The side effects of RAIT are found to be significantly dose-dependent or deterministic, hence the increasing severity of side effects proportional to the quantity of RAI received. Thus, ARs are more common in patients with WDTC and EUG than those with TG, and significantly more common with RAI for malignant than benign goiter. Most studies reporting ARs from RAIT involve patients with WDTC. We hope to do likewise when we have enough number of patients to achieve statistical significance.

The most common AR observed in our study was nausea and vomiting, consistent with the range of 50-67% cited in the literature (29). Other authors have described vomiting as being less common than nausea (30).

The frequency of radiation thyroiditis in our study, 27.5%, has been attributed to the large proportion of patients presenting for RAIT with substantial amount of functioning native thyroid tissue. This figure is higher than the predicted 1-5% range for patients treated with residual thyroid tissue (31). It has been frequently observed that both thyroid lobes are seen on radioiodine scans post-total thyroidectomy. In addition, dysphagia and dyspnea were observed after RAIT in these patients with significant residual thyroid tissue.

Radiation sialadenitis was not as common in our study, whereas it had been described as the most common side effect of RAIT in 11.5-67% of patients with WDTC treated with RAI (32,33,34). Despite the relatively low rate of ARs experienced overall, our goal would be no AR, as reported by Silberstein from 13200 sessions (17). Dysgeusia and xerostomia have been attributed to sialadenitis. Dysgeusia is caused by radioactive impairment of the taste buds leading to a change in the perception of taste (30).

The DoTS method classifies ARs as dose-related (augmented), non-dose-related (bizarre), dose-related and

Table 4. Grading of adverse reactions from radioactive iodine therapy (23)

Events	Frequency	Grade	Comment
Nausea	3	1	A disorder characterized by a queasy sensation and/or the urge to vomit
Vomiting	18	1	A disorder characterized by a queasy sensation and/or the urge to vomit
Acute sialadenitis	3	2	Asymptomatic or mild symptoms
Radiation thyroiditis	11	2	Minimal, local or non-invasive intervention indicated
Dysphagia	1	1	Asymptomatic or mild symptoms
Dyspnea	1	1	Asymptomatic or mild symptoms
Radiation pneumonitis	1	1	Asymptomatic, clinical or diagnostic observations only; intervention not indicated
Xerostomia	1	1	A disorder characterized by reduced salivary flow in the oral cavity
Voice change	1	1	Mild or intermittent change from normal voice

time-related (chronic), time-related (delayed), withdrawal (end of use), and failure of therapy (failure). Those RAIT related ARs described herein are dose-and time-related (13). The dose here would actually refer to the quantity of radioactivity administered, and not to the quantity of drug (iodide). Thus radioactivity-related side effects would be deterministic in nature (35,36). It is expected that these dose-related events will occur more commonly in patients treated with relatively higher therapy doses of ^{131}I as for EUG and WDTC than those with TG. This held true for WDTC. However, TG patients had more reactions than EUG patients; this may be due to the fact that TG patients had more avid uptake of RAI than those with EUG, and thus a longer thyroid residence time.

The female preponderance of ARs was attributed to the pre-existing bias in the evaluated patients. Nevertheless, it has previously been noted that female patients were more likely to develop adverse drug reactions (37). The possible etiologies suggested include differences in cytochrome enzymes, hepatic and renal drug metabolism, body mass, as well as hormonal and immunologic factors (38,39). In all, women are 50-75% more likely to experience an AR than men (37).

Study Limitations

The main limitations experienced were as follows: Routine neck ultrasonography to determine gland size was not performed on all patients. Thus, correlation between anatomical size and frequency of ARs could not be performed. Also, there is no formal system in place for reporting ARs from the use of radioisotopes and radiopharmaceuticals regionally or nationally. Protocols and standard operating procedures addressing the prevention and the management of these ARs should be instituted both nationally and for the West African region. In addition, ARs experienced after patient discharge might not have been reported promptly at the exact time of their occurrence. In instances when ARs are self-limiting, patients might forget to report them (36).

Conclusion

RAIT remains a safe option for the treatment of benign and TG. ARs experienced are mainly mild to moderate in severity and mostly short-lived. The incidence of 0.8% in this study compares favorably with global figures. As larger doses of RAI for WDTC and TG were more commonly associated with ARs, our study suggests that these patients merit stronger prophylactic measures as well as closer monitoring for earlier detection and management of these reactions. Moreover, nuclear physicians administering RAIT should be prepared to treat adverse events should they arise despite preventive measures.

Ethics

Ethics Committee Approval: Waived (retrospective study), Informed Consent: Not obtained (retrospective study).

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yetunde A. Onimode, Akintunde T. Orunmuyi, Concept: Yetunde A. Onimode, Design: Yetunde A. Onimode, Data Collection or Processing: Yetunde A. Onimode, Analysis or Interpretation: Yetunde A. Onimode, Literature Search: Yetunde A. Onimode, John E. Ejeh, Akintunde T. Orunmuyi, Writing: Yetunde A. Onimode, John E. Ejeh, Akintunde T. Orunmuyi.

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Case Report
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Aggressive Disease Course of Papillary Thyroid Carcinoma with Focal Undifferentiated Component: A Case Report

Fokal Andiferansiye Komponentli Agresif Seyirli Papiller Tiroid Karsinomu: Olgu Sunumu

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Abstract

We report an aggressive papillary thyroid carcinoma (PTC) with focal undifferentiated component in a 32-year-old female. She had limited disease confined within the thyroid gland at diagnosis. Within 12 months of thyroidectomy and radioiodine ablation, thyroglobulin (Tg) levels were elevated. Second radioiodine ablative dose was given, however, stimulated Tg levels showed an upward trend with negative iodine scan within 12 months. An ^{18}F fludeoxyglucose-avid solitary pulmonary nodule that was detected on positron emission tomography/computed tomography scan was resected followed by empiric radioiodine therapy. Within the next 10 months she developed multifocal bone metastases. The multifocal disease was rendered inoperable and treated with external beam radiation. The patient is on follow-up, and the Tg level continues to rise with local disease progression. In a small percentage of patients, PTC behaves as a very aggressive disease despite treatment. Focally undifferentiated thyroid carcinoma is an expression of the extreme end of the spectrum of differentiated thyroid carcinoma.

Keywords: Papillary thyroid carcinoma, undifferentiated thyroid carcinoma, thyroglobulin, radioiodine therapy, fludeoxyglucose positron emission tomography

Öz

Otuz iki yaşında bir kadında saptanan fokal andiferansiye komponentli agresif seyirli papiller tiroid karsinomu sunulmaktadır. Tanı anında tiroid bezi ile sınırlı hastalığı mevcuttu. Tiroidektomi ve radyoiyot ablasyondan 12 ay sonra tiroglobulin (Tg) değerleri yükselmeye başladı. İkinci radyoiyot ablasyon dozu uygulandı, ancak stimule Tg düzeyleri yükselme eğiliminde idi ve 12. ayda iyot sintingrafisi negatif idi. Pozitron emisyon tomografisi/bilgisayarlı tomografi ile ^{18}F florodeoksiglukoz-avid soliter pulmoner nodül saptandı, rezeke edildi ve ampirik radyoiyot tedavisi uygulandı. Takip eden 10 ay içinde multifokal kemik metastazları saptandı. Multifokal hastalık inoperabl olarak değerlendirildi ve eksternal radyasyon ile tedavi edildi. Hasta halen takip altında olup Tg değeri lokal hastalık progresyonu ile birlikte yükselmeye devam etmektedir. Hastaların küçük bir bölümünde papiller tiroid karsinomu tedaviye rağmen agresif seyirli olabilir. Fokal andiferansiye tiroid karsinomu diferansiye tiroid karsinom spektrumunun en aşırı ucunu temsil etmektedir.

Anahtar kelimeler: Papiller tiroid karsinomu, andiferansiye tiroid karsinomu, tiroglobulin, radyoiyot tedavisi, florodeoksiglukoz pozitron emisyon tomografisi

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Introduction

Thyroid carcinoma has been classified according to the degree of differentiation at two ends of the disease spectrum; the well differentiated and the undifferentiated (anaplastic) carcinomas. There is a definite morphological and behavioral distinction between these two entities. The well-differentiated carcinomas are classified as papillary and follicular carcinomas. At the other end of the spectrum, the undifferentiated group includes anaplastic, insular and other types of carcinomas. Behavior-wise, the papillary and follicular carcinomas are relatively indolent and curable, while the anaplastic variant is highly aggressive (1).

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, generally with an indolent clinical course. The overall 5-year relative survival rate has been reported as high as 97.5%, and only a small percentage of papillary carcinomas show aggressive clinical behavior (2).

The aggressive subtypes of PTC include tall cell, columnar cell, diffuse sclerosing variant and hobnail variant. These variants have been associated with higher rates of extra-thyroidal extension, multi-focality, nodal and distant metastasis, recurrence, and resistance to radioactive iodine therapy (3,4). The case we describe here had a discrete undifferentiated focus in the background of classical PTC.

Case Report

In September 2010, a 32-year-old female presented for the evaluation of a right thyroid nodule, which has gradually increased in size over the past 5 years. There were no associated compression symptoms. She underwent right lobectomy and isthmectomy on June 3' 2010. The histopathologic findings were consistent with a neoplastic lesion with vascular invasion. Completion thyroidectomy was performed on June 28' 2016 and histology showed papillary carcinoma with a focal undifferentiated component (T3 N0 M0) (Figure 1a, b).

In view of the undifferentiated component within a background of PTC, a bone scan and computed tomography (CT) scan (chest, abdomen and pelvis) were acquired for staging. All baseline work-up was negative for metastatic disease. After thyroidectomy she received a radioactive iodine ablative dose of 120 mCi in September 2010. Stimulated thyroglobulin (Tg) levels were 17.4 ng/ml. An iodine avid remnant was detectedin the thyroid bed on post-therapy whole body scan.

At 12 months, stimulated Tg levels were elevated at 109 ng/ml. A diagnostic ^{131}I whole body scan showed uptake in the thyroid bed. A second ablative dose of 100 mCi was given in January 2012. Post-therapy scan showed delivery of iodine to the thyroid remnant in the neck (Figure 2).

In February 2013, the patient was clinically symptom free. Stimulated Tg rose to 34 ng/ml. A diagnostic ^{131}I scan did not show any abnormal uptake.

To search for occult metastases, a ^{18}F fludeoxyglucose (FDG) positron emission tomography (PET)/CT scan was acquired that revealed a 1.8 cm hypermetabolic, round, right lower lobe pulmonary nodule with a standardized uptake value (SUV_{max}) of 3.3 (Figure 3).

In March 2013, the patient underwent a right sided video assisted thoracoscopic surgery and lower lobe nodulectomy. Histopathology was consistent with metastatic papillary carcinoma (2.0 cm), and the resection margin was disease free. An empiric dose ^{131}I (150 mCi) was given in June 2013 (stimulated Tg=295 ng/ml).

In December 2013, the patient presented with a palpable scalp swelling in the posterior parietal region, that was noticed only 10-12 days ago. On thyroxine, the Tg was 452

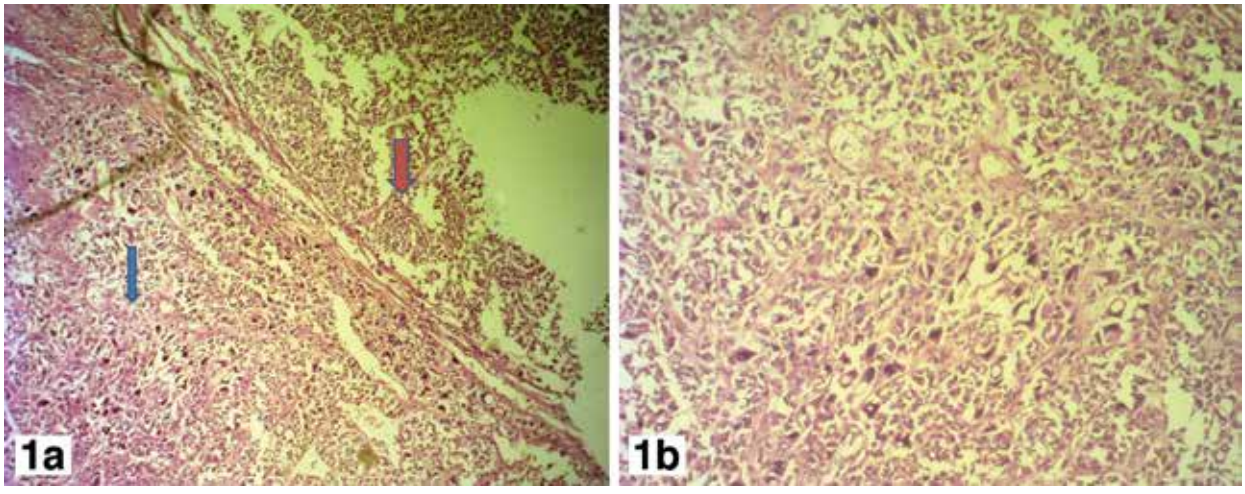

Figure 1. a) The histopathology slide (blue arrow) indicating undifferentiated component in the tumor with large, hyperchromatic and bizarre looking nuclei. The red arrow points towards the conventional papillary carcinoma, b) High power view of the focal undifferentiated component

ng/ml. A three phase bone scan showed osseous uptake in the right parietal bone (Figure 4a). This lesion was hypermetabolic (SUV_{max} 4.4) on PET/CT scan with erosion of the inner and outer tables of the right parietal bone and an associated subcutaneous and intracranial (extradural) soft tissue component. No obvious intra-axial lesion was identified (Figure 4b).

Magnetic resonance imaging (MRI) scan of the brain confirmed a 3-cm expansile lesion in the right parietal region. The mass was T1 hypointense, T2 heterogeneous with post-contrast enhancement, and with associated extra-axial soft tissue on either side of the calvarium (Figure 4c).

According to the neurosurgical consultation, surgical removal of the solitary skull metastasis was planned. However, there was a three month delay due to patient logistics, and pre-surgery Tg level rose to 1623 ng/ml. A repeat FDG PET/CT scan revealed progression of the parietal bone metastasis. Additional hypermetabolic, expansile, lytic lesions (with soft tissue component) were identified in the 5th left rib postero-laterally (SUV_{max} of 3.4), and in the right pedicle and transverse process of the L4 vertebra without

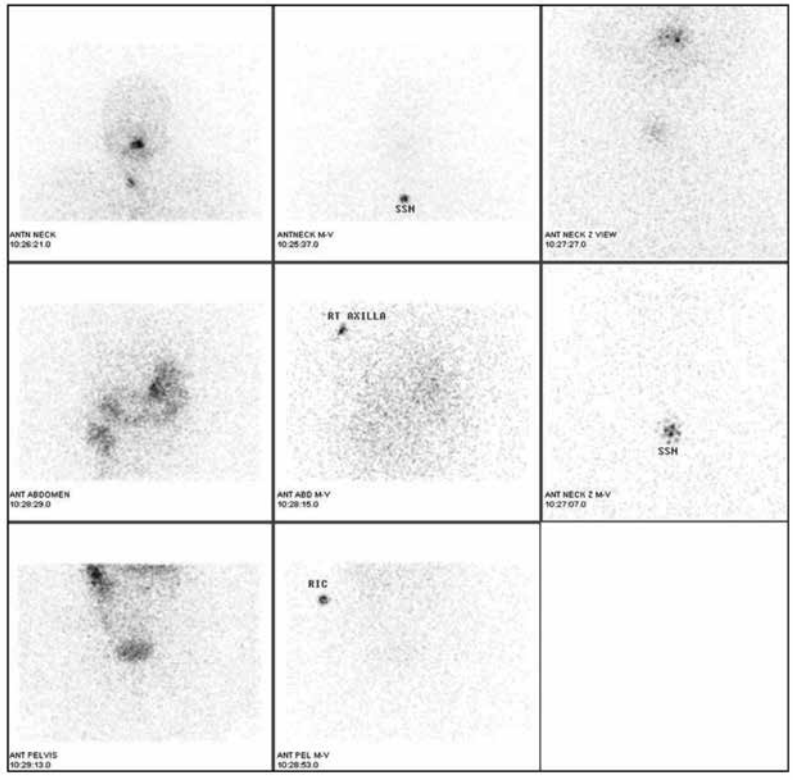

Figure 2. Post-radioiodine therapy whole body spot views showing avid uptake by the residual thyroid tissue. Physiological tracer distribution is detected in the nasopharynx, gut and urinary bladder

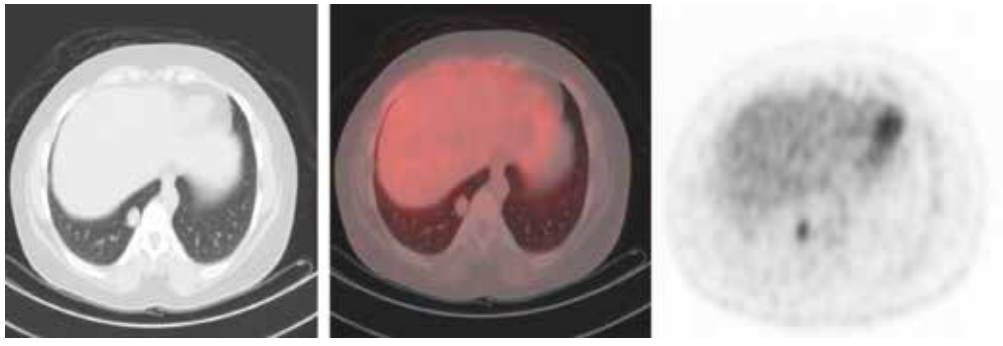

Figure 3. Trans-axial computed tomography, fusion positron emission tomography/computed tomography and positron emission tomography images of the chest showing hypermetabolic, 1.8 cm, round right lower lobe pulmonary nodule with a SUV_{max} of 3.3

intra-spinal extension (SUV of 4.1) (Figure 5). In retrospect, these lesions were also faintly visible on the baseline FDG PET/CT scan.

A CT-guided biopsy of the soft tissue component of the most accessible L4 vertebra lesion confirmed metastatic PTC. The patient underwent palliative radiotherapy to the skull, left

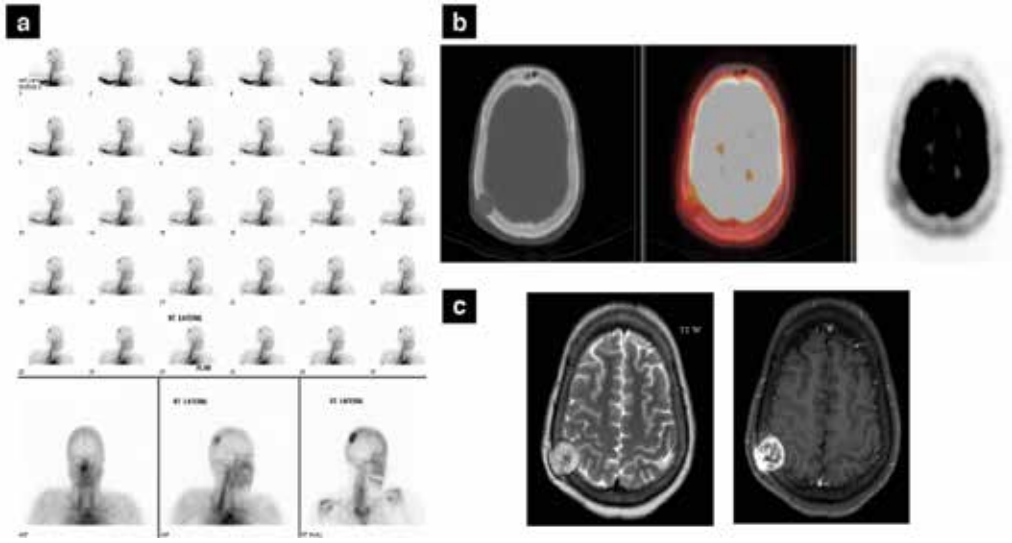

Figure 4. a) Three phase bone scan of the skull showing increased blood flow, focal hyperemia and osteoblastic activity in the right parietal bone, b) Trans-axial computed tomography, fusion positron emission tomography/computed tomography, and positron emission tomography views of the skull demonstrating a large lytic lesion at the posterior aspect of the right parietal bone, eroding both inner and outer tables with an associated subcutaneous and intracranial (extradural) soft tissue component (SUV_{max} of 4.4). No obvious intra axial lesion is identified, c) Trans-axial magnetic resonance imaging scan of the skull showing a 3 cm right parietal expansile lesion. The mass is T1 hypointense, T2 heterogeneous with avid post-contrast enhancement and associated extra-axial soft tissue involvement on either side of the calvarium

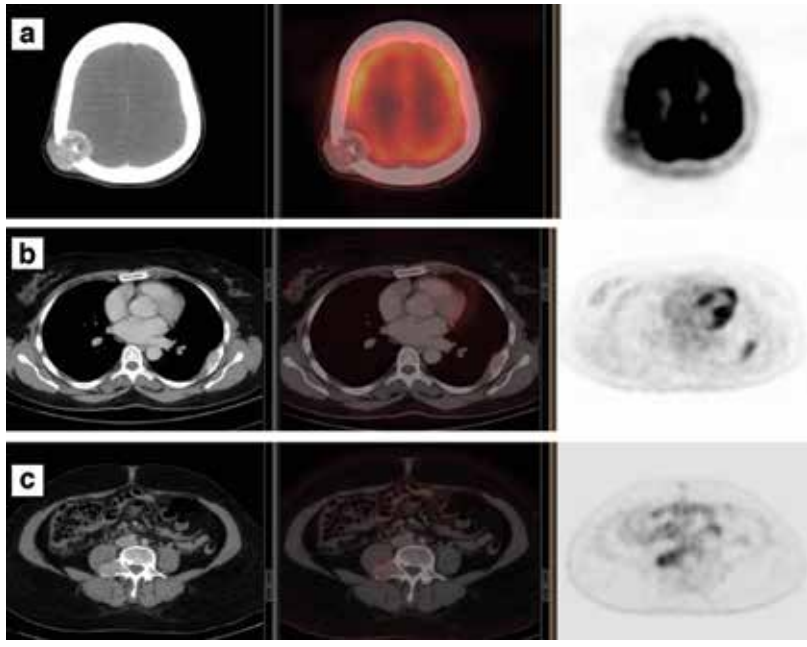

Figure 5. a) Trans-axial computed tomography, fusion positron emission tomography/computed tomography (PET/CT) and PET views of the skull showing metastatic deposit in the right parietal bone postero-laterally with interval progression in size and increase in both intracranial (extra-axial) and subcutaneous soft tissue components, b) Trans-axial computed tomography, fusion PET/CT and PET views of the chest showing a lytic lesion with a large soft tissue component in the 5th left rib postero-laterally which is mildly metabolically active (SUV_{max} of 3.4), c) Trans-axial CT, fusion PET/CT and PET views of the pelvis showing an expansile mass appreciable in the right pedicle and transverse process of the L4 vertebra without intra-spinal extension (SUV_{max} of 4.1)

rib and the lumbar vertebra with 20 Gy/5 fractions. She is on follow-up with complaints of mild pain along the rib and the L4 lesion that require PRN oral analgesics. FDG PET/CT performed 6 months post-XRT showed local progression at the three lesion sites, with no new identifiable lesion.

Discussion

PTC is the most common thyroid malignancy and represents 75 to 85 percent of all thyroid cancers. PTC is frequently found in women of the 20 to 55-year age group (5).

Papillary carcinoma usually has an indolent course rarely showing aggressive behavior. This small percentage has been referred as "real carcinomas" of the thyroid, bringing a challenge to management (6).

The undifferentiated anaplastic carcinoma comprises only 1.7% of thyroid cancers. It is an extremely malignant neoplasm. Its incidence typically peaks at the 6-7th decade of life with a median survival of 3 months following diagnosis. Despite the use of multimodality treatment combining surgery, external beam radiation and chemotherapy, long term survival is possible in only selected patients (7,8,9).

Undifferentiated (anaplastic) cancers commonly metastasize to the regional lymph nodes and lungs. Because of its aggressive behavior, all anaplastic thyroid tumors are classified as stage IV regardless of tumor size, location or metastasis (10).

Differentiated and undifferentiated variants may arise simultaneously in neoplastic lesions. Perri et al. (11) and Foote et al. (12) showed that in certain cases a portion of an otherwise well-differentiated carcinoma may containun differentiated (anaplastic) carcinoma. This has been observed in middle-aged or elderly patients, with grave prognosis. A small focus measuring only a few millimeters in diameter may have little effect on the long-term survival. However, in some patients, this can present with aggressive disease as in the case presented herein.

Undifferentiated (anaplastic) carcinomas progress rapidly and require immediate management with multimodality treatment. Neither surgery nor radiotherapy or chemotherapy is efficient alone (13).

At baseline, our patient had limited disease confined to the thyroid with no nodal involvement. The majority of patients under 45 years of age who have differentiated thyroid cancer (DTC) confined to the thyroid have an excellent prognosis (14). Clinico-pathological features that confer a poor prognosis include age over 70 years, distant metastases, lymph-node metastases >3 cm, follicular histology, and a poorly differentiated component in the primary thyroid neoplasm (15).

Interestingly, in our patient, the histopathologic findings of the lung and L4 vertebra metastases corresponded to the classical papillary component of the primary tumor in the thyroid gland and not the undifferentiated focus. This fact favors the hypothesis that, in our patient, PTC was inherently aggressive and the undifferentiated focus in the primary thyroid tumor represented the most extreme component of the same disease spectrum.

Our patient received two ablative dosages of ^{131}I therapy and became ^{131}I resistant with progressive elevation in Tg levels on subsequent follow-up. Thyroid carcinomas with little or no iodine activity tend to have higher glucose metabolism and positive FDG-PET scans representative of tumor dedifferentiation. Patients in this group have a higher mortality rate over 3-year follow-up as compared to patients with no FDG uptake (16). Surgery is the mainstay of management. However, in our case, radiotherapy was offered to improve local control since radioactive iodine therapy was inefficient and surgical resection of the metastases was not possible.

The primary goals for treatment at each step are to decrease morbidity from metastatic disease and to improve overall survival. Thus, local radiotherapy may be helpful in disease control in cases with potentially aggressive DTC variants, and such patients should be followed up closely.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Humayun Bashir, Aamna Hassan, Arif Jamshed, Sajid Mushtaq, Ahmad Murtaza, Concept: Humayun Bashir, Design: Saima Riaz, Data Collection or Processing: Saima Riaz, Analysis or Interpretation: Saima Riaz, Literature Search: Saima Riaz, Writing: Saima Riaz.

Conflict of Interest: No conflict of interest was declared by the authors.

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^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging in a Patient with HIV (-) Kaposi Sarcoma

HIV (-) Kaposi Sarkomu Olgusunda ^{18}F-Florodeoksiglukoz Pozitron Emisyon Tomografi/ Bilgisayarlı Tomografi Görüntüleme

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Abstract

Kaposi sarcoma (KS) is a vascular neoplasm that often manifests with multiple vascular nodules on the skin and other organs. Various imaging modalities can be used to display disease extent. Herein we present a 65-year-old female patient with human immunodeficiency virus negative KS along with her whole-body positron emission tomography/computed tomography imaging findings.
Keywords: Positron emission tomography/computed tomography, kaposi sarcoma, HIV

Öz

Kaposi sarkomu (KS), deri ve diğer organlarda yaygın vasküler nodüllerle ortaya çıkan vasküler bir tümördür. Hastalığın yaygınlığını göstermek için çeşitli görüntüleme modaliteleri kullanılabilmektedir. Bu çalışmada 65 yaşında insan bağışıklık yetmezlik virüsü negatif KS olan bir kadın hastayı ve bu hastanın tüm vücut pozitron emisyon tomografi/bilgisayarlı tomografi görüntüleme bulgularını sunduk.
Anahtar kelimeler: Pozitron emisyon tomografi/bilgisayarlı tomografi, kaposi sarkomu, HIV

Introduction

Kaposi sarcoma (KS) is an immunodeficiency syndrome-related disease that has been reported to be strongly associated with human herpes virus-8 (1,2). The skin, mucosal surfaces and lung are the main sites of involvement. Visceral involvement predicts survival especially in patients with acquired immune deficiency syndrome (AIDS)-associated KS, thus accurate staging and identification of diseased sites with fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is useful in the management of these patients (3). Herein we present a patient with human immunodeficiency virus (HIV)-negative KS staged by ^{18}F-FDG PET/CT imaging.

Case Report

A 65-year-old female patient was referred to our hospital with complaints of swelling and nodular skin lesions on both legs. She had a history of rheumatoid arthritis and treatment with corticosteroid medication for five years. On physical examination, dark blue-purplish macular

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and nodular skin lesions were observed on the legs along with pretibial edema (Figure 1). The lesions that had appeared within a few months were not painful. She was diagnosed with KS with biopsy of the skin lesions (Figure 2). Laboratory tests were within normal limits except an elevated erythrocyte sedimentation rate. Anti-HIV antibody was negative. She was referred to our department for initial staging with ^{18}F-FDG PET/CT imaging. A whole body ^{18}F-FDG PET/CT imaging was performed 60 minutes after 370 megabequerel ^{18}F-FDG injection using an integrated PET/CT scanner (Siemens, Biograph mCT, Germany). ^{18}F-FDG PET/CT imaging showed multiple nodular skin lesions with increased FDG uptake on both legs (SUV_{max}: 6.1). In addition, there were hypermetabolic bilateral inguinal and popliteal lymph nodes (SUV_{max}: 3.6-5.6) (Figure 3).

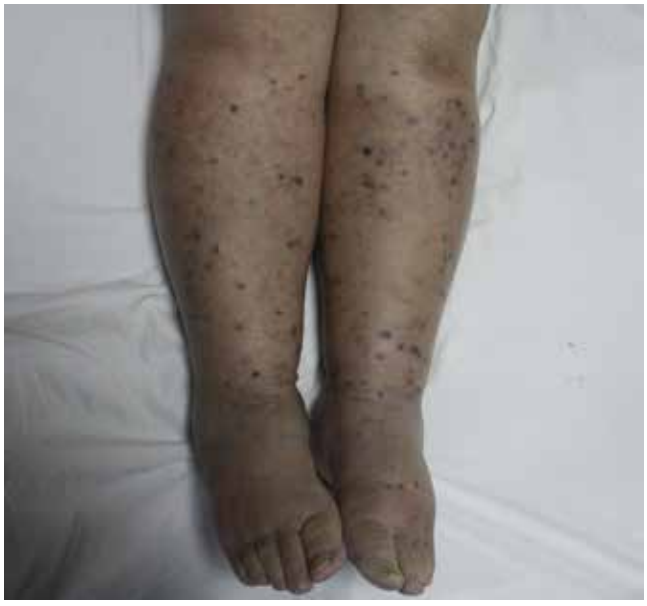

Figure 1. Dark blue-purplish macular and nodular skin lesions on the legs

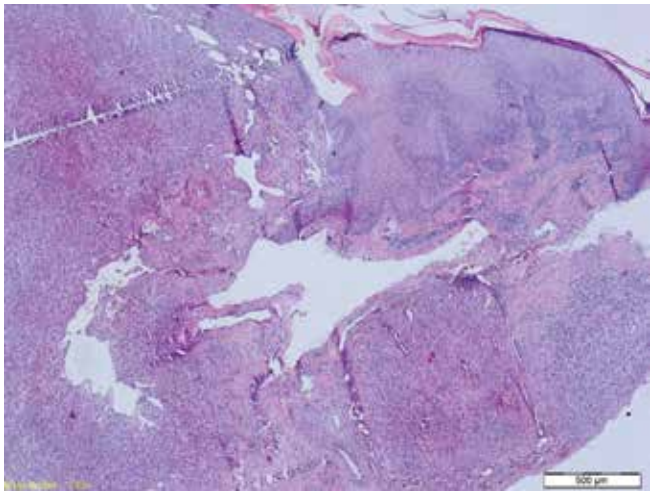

Figure 2. The underlying epidermis spindled cells showing lobular growth pattern (hematoxylin and eosin x40)

Literature Review and Discussion

KS is a common tumor in AIDS patients. Most patients present with a single or few lesions, however multiple lesions have also been reported (4). In most cases, the lesions are asymptomatic. Four variants of KS have been recognized clinically: classical KS, endemic (African) KS, iatrogenic (organ transplant-related) KS, and AIDS-related (epidemic) KS (5). Disease stage, clinical type and immune status are important in determining treatment options including surgery, radiotherapy, chemotherapy and immunotherapy. Various imaging modalities including gastrointestinal endoscopy, conventional radiography, CT, magnetic resonance imaging (MRI), and radionuclide imaging are used for staging. Imaging findings depend on the organ systems that are affected. CT and MRI are generally more useful in the assessment of visceral and lymphatic KS. Thoracic disease, which is a common visceral involvement, bilateral hilar lymphadenopathy and bilateral involvement in the mid and lower lung zones with

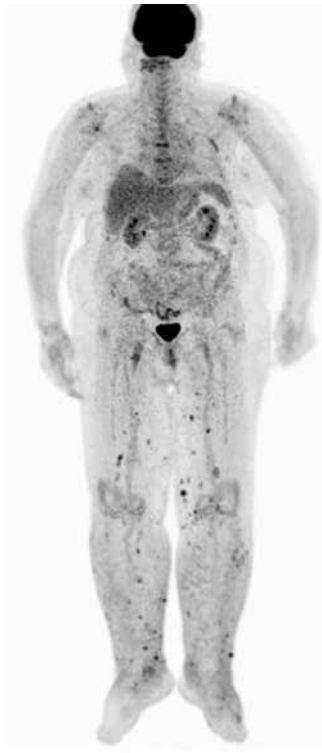

Figure 3. Maximum intensity projection images show multiple nodular lesions with increased fluorodeoxyglucose uptake on the skin and subcutaneous tissues of the legs (SUV_{max}: 6.1), and hypermetabolic lymph nodes at bilateral inguinal and popliteal sites

peribronchial and perivascular opacities is characteristic on high resolution CT. MRI has higher sensitivity in detecting cardiac lesions and bone involvement (6,7).

Thallium-201 (^{201}Tl) and gallium-67 (^{67}Ga) scintigraphy had been previously used for differential diagnosis. ^{67}Ga negative and ^{201}Tl positive lesions were most likely accepted as KS, whereas both ^{67}Ga and ^{201}Tl positive lesions were considered as lymphoma (8). ^{99m}Tc tetrofosmin had also been once used in patients with KS as a tumor screening agent (9).

Recently, ^{18}F-FDG PET/CT imaging is being used for the evaluation of visceral and lymphatic involvement, and staging of KS. It has a role in both staging and the evaluation of response to therapy (10,11). In addition, PET/CT is an effective method in detecting clinically occult KS lesions that were not detected with other imaging methods (12). KS may demonstrate heterogeneous FDG avidity. In some previous studies, lymph node and visceral involvement such as the bone and lungs were detected by ^{18}F-FDG PET/CT imaging (10,11,13,14). Diffuse and focal FDG uptake in the skin have also been reported (14,15). In our patient, an increased FDG uptake was detected in nodular skin lesions on the lower extremities, and the highest SUV_{max} value of these lesions was 6.1. ^{18}F-FDG PET/CT imaging detected lymph node involvement in addition to widespread cutaneous involvement in our patient.

In conclusion, whole body ^{18}F-FDG PET/CT imaging can detect the extent of visceral and lymphatic involvement, and makes a significant contribution in both staging and clinical management of KS.

Ethics

Informed Consent: Consent form was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ekin Şavk, Concept: Arzu Cengiz, Yakup Yürekli, Design: Arzu Cengiz, Ekin Şavk, Canten Tataroğlu, Data Collection or Processing: Arzu Cengiz, Ekin Şavk, Canten Tataroğlu, Yakup Yürekli, Analysis or Interpretation: Arzu Cengiz, Ekin Şavk, Canten Tataroğlu, Yakup Yürekli, Literature Search: Arzu Cengiz, Writing: Arzu Cengiz, Yakup Yürekli.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report
Mol Imaging Radionucl Ther 2016;25:143-146 DOI:10.4274/mirt.97759

Fasciola Hepatica Mimicking Malignancy on ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography

^{18}F-Florodeoksiglukoz-Pozitron Emisyon Tomografi/Bilgisayarlı Tomografide Maligniteyi Taklit Eden Fasciola Hepatica

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Abstract

A 48-year-old female with complaints of gastrointestinal symptoms such as abdominal pain, fatigue, vomiting, nausea, and weight loss was diagnosed with neuroendocrine tumor after removal of a 2 mm lesion from the stomach with endoscopic biopsy. Her magnetic resonance imaging that was performed due to on-going symptoms showed multiple linear hypointense lesions in the liver. Positron emission tomography/computed tomography (PET/CT) scan was performed for differential diagnosis, which showed high fluorodeoxyglucose (FDG) uptake in these lesions. Clinical and laboratory findings revealed the final diagnosis as Fasciola hepatica. The imaging features of this case is presented to aid in differentiating this infectious disease from malignancy and avoid misdiagnosis on FDG-PET/CT.
Keywords: Fasciola hepatica, ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography, infection

Öz

Kırk-sekiz yaşında karın ağrısı, yorgunluk, bulantı, kusma ve kilo kaybı şikayetleri ile başvuran kadın hastada midede nöroendokrin tümör saptandı. Şikayetlerinin devam etmesi üzerine yapılan manyetik rezonans görüntülemede karaciğerde multipl odakta lineer hipointens alanlar saptandı. Ayırıcı tanı amacıyla pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) çekimi için kliniğimize refere edilen hastanın PET/BT görüntülerinde multipl odakta yüksek florodeoksiglukoz tutulumu gözlendi. Hastaya klinik ve laboratuvar tetkikleri ile Fasciola hepatica tanısı kondu. Bu olgu, enfeksiyöz hastalıkların maligniteden ayrımı ve PET/BT'de yanlış değerlendirmenin önlenmesi amacıyla bildirilmektedir.
Anahtar kelimeler: Fasciola hepatica, ^{18}F-florodeoksiglukoz-pozitron emisyon tomografi/bilgisayarlı tomografi, enfeksiyon

Introduction

Fasciola hepatica is a helminth that causes the liver fluke disease called fascioliasis. The disease can lead to liver cirrhosis, liver failure and biliary tract obstruction (1). Fascioliasis is mostly seen in England and Ireland in Europe, northern Iran, northern Africa, Egypt, Cuba, especially the Peruvian and Bolivian Andes in South America (2).

^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is a frequently used imaging tool for the management of oncologic patient and has lead to significant changes (3). In recent

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years, applications of ^{18}F-FDG-PET/CT have become popular in non-oncological conditions such as infection and inflammation, central nervous system disorders, and cardiovascular disease (4,5,6). It can be used both for diagnosis and evaluation of therapy response.

Active granulomatous and infectious disease such as tuberculosis and sarcoidosis, infection or recent instrumentation can cause high FDG uptake in involved areas and lead to confounding results (7,8,9). So, the differential diagnosis of malignancy and infection-inflammations in PET/CT is very important for patient management and for avoiding unnecessary invasive procedures. Knowledge on the laboratory findings, clinical and imaging signs of infectious diseases can preclude the interpreter from misdiagnosis, and the patients can be evaluated more effectively. In this case, we aimed to report the PET/CT images of Fasciola hepatica in a patient with neuroendocrine gastric cancer.

Case Report

A 48-year-old female with complaints of gastrointestinal symptoms such as abdominal pain, fatigue, vomiting, nausea, and weight loss was admitted to the gastroenterology clinic in order to perform an endoscopy. The endoscopy revealed multiple polypoid lesions with a diameter of 1-2 mm. The histopathology examination showed grade 1 neuroendocrine tumor and incomplete metaplasia. After polypectomy, since the symptoms of the patient did not relieve completely, she was referred to magnetic resonance imaging (MRI) for detection of possible metastasis or any other etiology. MRI showed multiple linear hypointense lesions in the liver (Figure 1). A PET/CT scan was performed for differential diagnosis, which showed high FDG uptake in these lesions (Figure 2). However, the findings in FDG-PET/CT were not thought to be related to metastasis since it is known that grade 1 neuroendocrine tumor does not have FDG avidity. Thus, this uptake was thought to be associated with either a

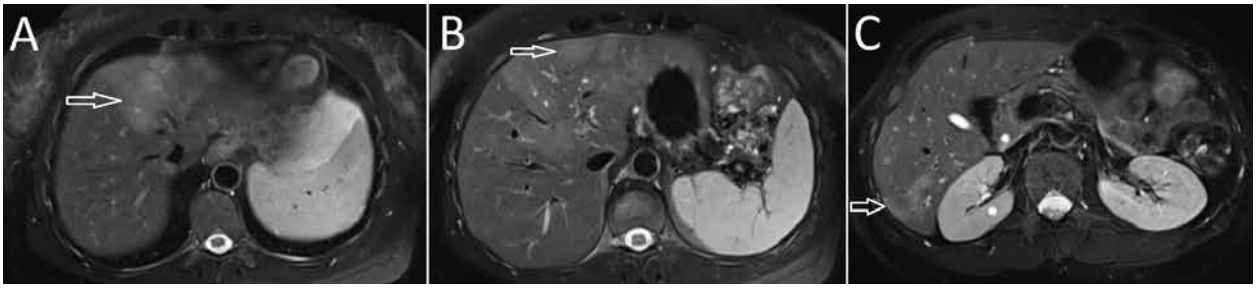

Figure 1. A) Axial T2W magnetic resonance image showing extensive hyper-intense lesions along the portal triads on the left lobe of the liver (arrows), B) A contrast-enhanced T1W magnetic resonance image showing multiple, round, clustered hypo-intense lesions with peripheral contrast enhancement (arrows) in the liver, C) Axial T2W magnetic resonance image showing residual parenchymal hyper-intensity after treatment (arrows)

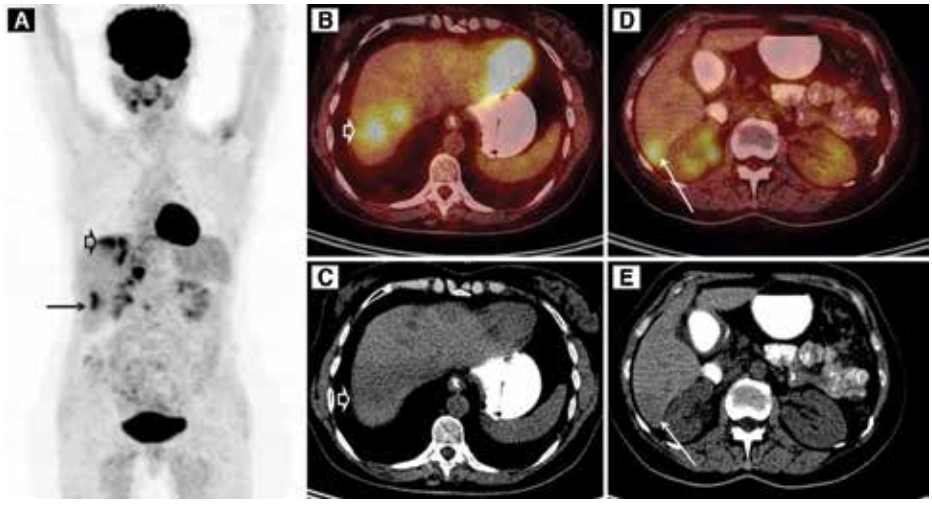

Figure 2. Positron emission tomography/computed tomography (PET/CT) findings of Fasciola hepatica. PET/CT scan was performed 60 min after i.v. injection of 256 MBq of ^{18}F-fluorodeoxyglucose (FDG), using a lutetium oxyorthosilicate crystal equipped PET/CT (mCT20 Siemens, Germany). Maximum intensity projection images (A) show high FDG uptakes in different areas of the liver. Axial CT (C, E) images demonstrate hypodense lesions. FDG uptake (SUV_{max}: 5.8) in the 7th (arrow heads) and (SUV_{max}: 5.2) 6th liver segments (arrows) on axial PET/CT fusion images (B, D)

primary liver malignancy or infectious process. The patient was evaluated in detail with clinical and laboratory analysis. Indirect hemagglutination test for Fasciola hepatica was positive at 1/320. The eosinophil count has elevated to $3x10^3$ (normal range: 0-$0.4x10^3$) and the EO% was 34.6% (normal range: 0-5%). All other laboratory test results were within normal range. Laboratory analysis indicated Fasciola hepatica. The imaging features of this case is presented to aid in differentiating this infectious disease from malignancy and avoid misdiagnosis on FDG-PET/CT.

Discussion

The gold standard for the diagnosis of Fasciola hepatica is serologic studies. In this case, final diagnosis was confirmed with serologic findings.

There are no pathognomonic imaging findings for fascioliasis. Ultrasound cannot detect fascioliasis. In the acute stage of the disease, CT is the golden standard for imaging. Iron oxide enhanced MR imaging may also be used (10). On CT, the disease usually appears as multiple, small, round, oval, hypodense hepatic lesions with peripheral contrast uptake. On T2-weighted MRI, a capsular hyperintensity is detected in the area where the parasite has penetrated (11). It has been reported that fascioliasis may simulate cholangiocarcinoma on MRI (12).

Firstly, it has been thought that the FDG uptake was related to a malignancy (i.e. hepatocellular cancer?). In this case, the clinician could not decide on the nature of the liver disease (whether metastatic or not) based on the MRI. Thus, he wanted to evaluate the liver further with PET/CT. However, when all the patient's findings were evaluated together, malignancy was excluded based on the final serologic finding.

These misinterpretations have significant impact on patient management. That's why lesions mimicking malignancy, especially on imaging modalities, must be well-known. Clinical suspicion for fascioliasis should be raised in patients who present with non-specific symptoms in endemic areas (13). Imaging modalities prevent patients from unnecessary invasive diagnostic procedures. The interpretation of artifacts, benign causes, and physiologic variants of ^{18}F-FDG imaging is important for tumor staging. It has been reported that several entities mimic malignancy on PET/CT (7,14,15). Infectious diseases can also be evaluated with PET/CT, with a high clinical impact by providing additional diagnostic information (16). A few cases with mild FDG uptake in small Fasciola lesions have been reported in the literature (10,11). In this case, fascioliasis was detected in large areas. To the best of our knowledge, this is the first case in the literature showing extensive fascioliasis of the liver. Since FDG-PET/CT evaluates metabolic characteristics of the lesions, it also helps to detect treatment response. Currently, serial serologic testing is being used for evaluating treatment response in our patient along with radiologic evidence. The metabolic characteristics of the lesions on PET/CT can be more helpful in deciding response to therapy in comparison to CT and MRI.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Erdem Sürücü, Yusuf Demir, Design: Erdem Sürücü, Yusuf Demir, Data Collection or Processing: Ahmet C. Dülger, Şehmus Ölmez, Analysis or Interpretation: Mehmet T. Kitapçı, Erdem Sürücü, Yusuf Demir, Abdüssamed Batur, Literature Search: Erdem Sürücü, Writing: Erdem Sürücü, Yusuf Demir.

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Case Report
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An Incidental Solitary Plasmacytoma of Bone Mimicking Neuroendocrine Tumor Metastasis on ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography

^{68}Ga-DOTATATE Pozitron Emisyon Tomografi/Bilgisayarlı Tomografi Görüntülemede Nöroendokrin Tümör Metastazını Taklit Eden İnsidental Soliter Kemik Plazmasitomu

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Abstract

A 54-year-old woman with suspicion of neuroendocrine tumor (NET) was referred for ^{68}Ga-DOTATATE positron emission tomography/computed tomography (CT) imaging due to clinical findings. A well-defined osteolytic lesion on the corpus of the third lumbar vertebra was evident on CT images with mild uptake of ^{68}Ga-DOTATATE, which led to suspicion of NET metastasis. Histopathologic examination revealed solitary plasmacytoma of the bone. The patient received local external radiotherapy for plasmacytoma. This case indicatesthat other diseases expressing somatostatin receptors may be inaccurately reported as tumor recurrence and highlights the importance of meticulous evaluation of positive findings.
Keywords: ^{68}Ga-octreotide, DOTA(0)-Tyr(3)-, positron emission tomography/computed tomography, plasmacytoma, neuroendocrine tumors

Öz

Nöroendokrin tümör (NET) şüphesi bulunan 54 yaşındaki kadın hastaya ^{68}Ga-DOTATATE pozitron emisyon tomografisi/bilgisayarlı tomografi (BT) görüntüleme yapıldı. Lomber 3. vertebrada BT görüntülerinde tanımlanan osteolitik lezyonda düşük düzeyde ^{68}Ga-DOTATATE tutulumu izlenmesi nedeniyle NET metastazı açısından şüpheli bulundu. Histopatolojik örnekleme soliter kemik plazmasitomu olarak sonuçlandı. Hasta plazmasitoma nedeniyle lokal eksternal radyoterapiye yönlendirildi. Bu olgu somatostatin reseptörlerini eksprese eden diğer hastalıkların tümör nüksü olarak yanlış raporlanabileceğini ve pozitif bulguların dikkatli değerlendirilmesinin önemini vurgulamaktadır.
Anahtar kelimeler: ^{68}Ga-oktreotid, DOTA(0)-Tyr(3)-, pozitron emisyon tomografi/bilgisayarlı tomografi, plazmasitom, nöroendokrin tümörler

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Introduction

The primary indication of ^{68}Ga-DOTA-conjugated peptide positron emission tomography/computed tomography (PET/CT) is neuroendocrine tumor (NET) imaging (1). However, tumors that express somatostatin (SST) receptors other than NETs can also be visualized by ^{68}Ga-DOTA-conjugated peptide PET/CT (2). In vitro studies with plasma cell lines have shown that the SST is expressed on malignant plasma cells (3). In our case, a solitary bone plasmacytoma (SBP) in the lumbar spine showed increased ^{68}Ga-DOTATATE uptake mimicking bone metastasis in a patient with suspected NET recurrence.

SBP is characterized by a solitary bone lesion that shows infiltration by plasma cells without evidence of anemia, hypercalcemia, or renal involvement suggesting systemic myeloma (4). SBP may involve any bone but most often affects the axial skeleton, particularly the vertebra, pelvis, ribs and pectoral girdle (4).

Case Report

A 54-year-old woman with suspicion of NET was referred for ^{68}Ga-DOTATATE PET/CT due to clinical findings. A well-defined osteolytic lesion on the corpus of the third lumbar vertebra extending to the right pedicle was evident on CT images (Figure 1a, b; arrows). The corresponding PET images (Figure 1c, d; arrows) demonstrated mild uptake of ^{68}Ga-DOTATATE, which led to suspicion of NET metastasis.

Histopathologic evaluation of the lesion was recommended in order to differentiate bone metastasis of NET from other SST expressing pathologies. Histopathologic examination demonstrated diffuse neoplastic plasma cell infiltration in the bone marrow (Figure 1e). Immunohistochemical staining revealed immunoglobulin λ-light chain antibodies in the tumor, and CD38 antibody positivity on the cell membrane (Figure 1f). All findings indicated SBP with supporting clinical data. The patient received local external radiotherapy for plasmacytoma.

Literature Review and Discussion

^{68}Ga-DOTA-conjugated peptide PET/CT is the imaging modality of choice for NETs for the detection of metastatic disease or local relapse, and it affects therapeutic approach in more than 40% of patients (5,6,7). The most common sites of NET metastasis are the liver, lymph nodes and bone (8). The presence of bone metastasis has vital clinical importance on treatment management, since it has been shown that bone metastasis is associated with poor overall survival (6).

Although results of ^{68}Ga-DOTA-conjugated peptide PET/CT in NETs are remarkable other tumors that express SST (predominantly SST2, SST3 and SST5), such as lymphomas, breast and lung cancers, thyroid cancers, gastrointestinal stromal tumors, prostate cancers and plasmacytoma/multiple myelomas, can also be avid for ^{68}Ga-DOTA-conjugated peptide PET/CT, thus misleading the physician (2).

It is not unusual that SBP has avidity of ^{68}Ga-DOTATATE. Previous studies have shown that ^{111}In-pentetreotide SST scintigraphy is an alternative method to displayin vivo multiple myeloma/SBP activity, especially in patients with relapsing disease and a more aggressive type of myeloma (9). In our case, a solitary osteolytic vertebral lesion with mild ^{68}Ga-DOTATATE uptake is less likely to be a metastasis because skeletal lesions of NETs are mostly osteosclerotic. The metastasis due to NETs are osteolytic only in 10% of the cases (10). A histopathologic evaluation was required for the definite diagnosis of the bone lesion and the patient was diagnosed with SBP, not relapse.

Degenerative diseases in the spine can also lead to increased ^{68}Ga-DOTATATE uptake. Klinaki et al. (11) reported a case with Modic changes in L4-5 vertebras that have caused ^{68}Ga-DOTATATE uptake probably due to increased blood supply or infiltration with activated lymphocytes. Putzer et al. (12) reported a false positive lesion caused by extensive vertebral osteophytes with an inflammatory component.

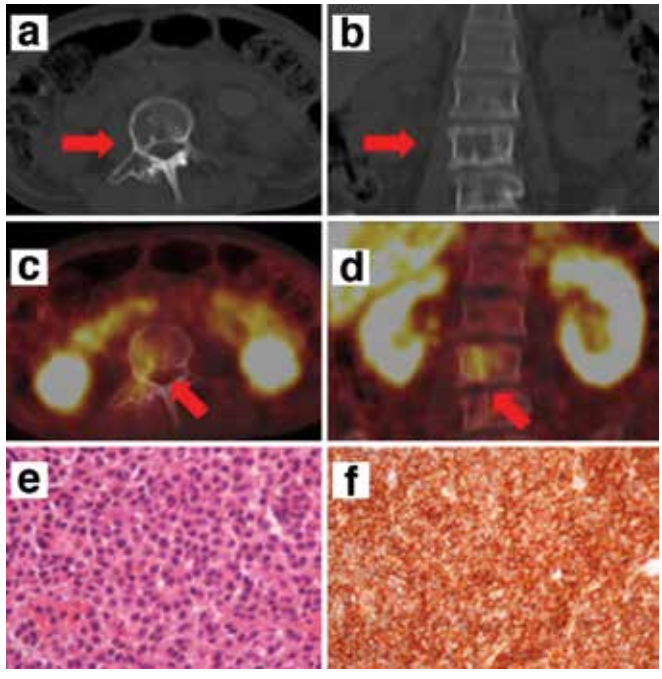

Figure 1. Transaxial (a)-coronal (b) computed tomography images; transaxial (c)- coronal (d) positron emission tomography/computed tomography fusion images; diffuse neoplastic plasma cell infiltration in the bone marrow (e) and CD38 antibody positivity on the cell membrane (f) in immunohistochemical and histopathologic examinations. A well- defined osteolytic lesion on the corpus of the third lumbar vertebra extending to the right pedicle (a, b arrows) showing mild ^{68}Ga-DOTATATE uptake (c, d arrows)

In the literature, there aretwo case reports describing ^{68}Ga-DOTATATE avid vertebral hemangiomas (13,14). The characteristic pattern in CT may help in distinguishing vertebral hemangioma and bone metastasis. A fibrous dysplasia of the bone also demonstrated significant ^{68}Ga-DOTATATE uptake as reported by Kuyumcu et al. (15).

^{68}Ga-DOTATATE has significant clinical impact that direct patients either to surgery or to systemic/palliative therapy. Thus, physicians should be careful when evaluating any lesion. Multiple bone lesions may be mistaken as metastases, and solitary lesions may reveal other diagnoses.

This case indicates that other diseases expressing SST receptors may be inaccurately reported as tumor metastasis and highlights the importance of meticulous evaluation of positive findings.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Duygu Has Şimşek, Cüneyt Türkmen, Concept: Duygu Has Şimşek, Design: Duygu Has Şimşek, Data Collection or Processing: Duygu Has Şimşek, Bilge Bilgiç, Analysis or Interpretation: Duygu Has Şimşek, Serkan Kuyumcu, Işık Adalet, Literature Search: Duygu Has Şimşek, Emine Göknur Işık, Writing: Duygu Has Şimşek.

Conflict of Interest: No conflict of interest was declared by the authors.

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