Med Oncol (2011) 28:258–264
DOI 10.1007/s12032-010-9446-y

ORIGINAL PAPER

The role of PET-CT in the differential diagnosis of thymic mass after treatment of patients with lymphoma

Bala Basak Oven Ustaalioglu · Mesut Seker · Ahmet Bilici · Nesrin Canpolat · Emre Yıldirim · Umut Kefeli · Recep Ustaalioglu · Burçak Erkol Yilmaz · Taflan Salepci · Nagehan Ozdemir · Mahmut Gumus

Received: 23 November 2009 / Accepted: 1 February 2010 / Published online: 13 February 2010

Abstract Thymic hyperplasia is a common phenomenon in both children and young adults after chemotherapy and may explain the finding of a mediastinal mass in patients with malignant lymphoma after complete remission. In the present study, we report 5 cases with malignant lymphoma presenting with a mediastinal mass on CT scan after completion of chemotherapy diagnosed as thymic hyperplasia by PET-CT imaging. We retrospectively analyzed 5 patients who presented with anterior mediastinal masses a median of 4 months (range 3–6) after achieving complete remission following successful treatment for malignant lymphoma. Three patients were diagnosed with Hodgkin's lymphoma (HL) and the others with non-Hodgkin's lymphoma (NHL). The median age of the patients was 23 (range of 18–47). PET-CT was performed on these patients to determine the characteristics of a mass which had been detected on CT. PET-CT was performed for all patients, and the thymic masses demonstrated only mild FDG uptake considered to be consistent with thymic hyperplasia. During a median of 24 months of follow-up, all patients were recurrence-free with a median survival of 15 months (range 10–26 months). It is important to be aware of the possibility of thymic hyperplasia after chemotherapy to avoid misdiagnosis or over-staging of disease, as well as unnecessary biopsies, especially when the presenting anterior mediastinal mass was originally located near the thymus on CT scan. Mild FDG PET uptake was sufficient for the diagnosis of benign disease in the cases in this study.

Keywords PET · Thymic hyperplasia · Lymphoma · Mediastinal mass

B. B. O. Ustaalioglu (✉) · M. Seker · A. Bilici · U. Kefeli · T. Salepci · M. Gumus
Department of Medical Oncology, Dr. Lütfi Kırdar Kartal Education and Research Hospital, Selimiye Mah, Şair Nesimi sok, Kardeşler Apt. No: 1, Daire:4, 34668 Üsküdar, Istanbul, Turkey
e-mail: basakoven@yahoo.com

N. Canpolat
Department of Nuclear Medicine, Kosuyolu Education and Research Hospital, Istanbul, Turkey

R. Ustaalioglu
Department of Thoracic Surgery, Dr.Siyami Ersek Cardiothoracic Surgery Hospital, Istanbul, Turkey

N. Ozdemir
Department of Radiation Oncology, Dr. Lütfi Kırdar Kartal Education and Research Hospital, Istanbul, Turkey

E. Yıldirim · B. E. Yilmaz
Department of Pathology, Dr. Lütfi Kırdar Kartal Education and Research Hospital, Istanbul, Turkey

Introduction

Thymic hyperplasia after chemotherapy is a common phenomenon in children and can be observed in young adults [1–3]. However, this entity has rarely been described in older patients [1]. The occurrence of a mediastinal mass in patients following complete remission (CR) from Hodgkin's lymphoma (HL) frequently indicates relapse but some benign processes like thymic hyperplasia may present with similar features [4, 5]. After CR of testicular carcinoma, thymic hyperplasia has also been reported [6]. It is postulated that thymus regeneration following involution during chemotherapy represents a rebound phenomenon [2, 4]. In this study, we report 5 cases with malignant lymphoma presenting with a mediastinal mass on the CT scan after chemotherapy, initially thought to be

due to relapse of lymphoma. After positron emission tomography (PET-CT) imaging, mild ^{18}F-fluorodeooxyglucose (FDG) uptake indicated only thymic hyperplasia rather than recurrent malignancy. Since all of the reported patients were asymptomatic, they were followed without further investigation, and during the follow-up period, the masses on CT scans remained unchanged, confirming their benign nature.

Materials and methods

We analyzed 140 CTs of patients who had been diagnosed with HL or NHL. We identified 5 patients with anterior mediastinal masses which developed after successful treatment of malignant lymphoma in our department of medical oncology at Dr. Lutfi Kirdar Education and Research Hospital, between March 2007 and August 2009. Patients underwent PET-CT to determine the characteristics of these masses. Clinicopathological features for each patient were obtained from patient' charts. Four of the 5 patients had HL, the fifth had NHL. Two cases of HL were nodular sclerosing type, and the others were lymphocyte predominant, and classic type HL respectively. The patient with NHL was diffuse large B-cell lymphoma (DLBCL). While 2 patients with HL were stage IIB, the others were stage IIIB and IV, and the NHL patient was stage IIIB. The median age of the patients was 23 in the range of 18–47. All patients were treated with combination chemotherapy such as doxorubicine, bleomycine, vinblastine, dacarbazine (ABVD) for HL and rituximab, cyclophosphamide, doxorubicine, vincristine, prednisolone (R-CHOP) for NHL.

Whole-body imaging was carried out using a combined PET/CT scanner (Biograph Sensation 16 PET/CT system, Siemens Dual, LSO). After the patients had fasted for at least 12 h prior to imaging, their blood glucose levels were obtained and all were below 200 mg/dL prior to tracer injection. 10–15 mCi (370–550 MBq) ^{18}F FDG were injected into a peripheral vein. After tracer injection, patients rested on a comfortable chair during the FDG uptake period. Approximately 60–120 min later, attenuation-corrected images were acquired with a scanner (axial field of view of 10.1 cm and resolution of approximately 5 mm). A CT scan was performed prior to acquisition of PET data in a single step with the patients in a supine position for accurate anatomic localization. The field of view extended from the top of the skull through to the upper thighs in one imaging procedure. During the scan, the patients were asked to maintain shallow respiration. Thereafter, an emission PET scan was acquired in two-dimensional mode over the same anatomic regions. Attenuation-corrected PET images, CT scans and co-registered PET/CT images were interpreted using a dedicated image fusion workstation, and a final consensus was reached for all patients. Interpretation was performed by a nuclear medicine physician. For the determination of SUV, the ROI (region of interest) was identified on transaxial, coronal or sagittal slices. The standardized uptake value (SUV) was calculated by placing a ROI around the structure of interest. The maximum SUV, within a given ROI, was recorded and was accepted as SUVmax. FDG uptake in the anterior mediastinum, in the characteristic diffuse, inverted V shape was considered thymic activity. The SUV area with increased activity in the thymus was recorded. The typical triangular shape of retrosternal accumulation which corresponded to the anatomic bilobed figure of the thymus was interpreted as reactive thymic hyperplasia after chemotherapy [7]. Clinical notes and follow-up imaging of all patients who showed FDG uptake in the anterior mediastinum were reviewed to assess stability.

Statistical analysis

The median age of the patients was defined. The response to therapy was assigned according to the response evaluation criteria in solid tumors (RECIST) criteria as complete, when no tumor was seen radiologically. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or last known contact.

Results

Response to treatment was evaluated by CT for all patients, and PET-CT was carried out in 2 cases. CR for all cases in this report was documented at the end of the chemotherapy. After a median of 4 months (range 3–6 months) following the completion of chemotherapy, anterior mediastinal masses were detected on thoracic CT that had not been seen in the previous studies. None of the patients had lymphoma symptoms at that time. PET-CT was then performed for all of these patients, and thymic masses demonstrated mild FDG uptake, compatible with thymic hyperplasia. During a median of 24 months of follow-up, all patients were recurrence-free with a median survival of 15 months (range 10–26 months), thus the PET-CT diagnosis of benign thymic hyperplasia was confirmed clinically.

Case 1

A 23-year-old woman diagnosed as DLBCL stage IIB was treated with 6 cycles of R-CHOP and radiotherapy (RT). Before diagnosis, PET-CT revealed high FDG uptake on the left hemithorax with the invasion of pleural surface (SUV max 22.2). At the completion of therapy, CR was

confirmed by PET-CT. Four months after achieving CR, a thorax CT revealed a new mass measuring 4 cm located on the anterior mediastinum. The patient had no symptoms, and complete blood counts and biochemical tests including liver and renal function tests, LDH, $\beta 2$ microglobulin levels were within the normal range. A repeat PET-CT was performed, and FDG uptake in the anterior mediastinum (SUVmax = 4) corresponding to the 4-cm soft tissue nodule was detected. It was consistent with an enlarged thymus by morphological criteria, including the typical inverted V shape. She did not give consent for biopsy from the mass. A follow-up CT showed no change in the size of the nodule 3 months later, and no evidence of disease recurrence has been detected after more than 10 months of follow-up.

Case 2

The patient is a 22-year-old man who presented with stage IIB classic type HL and a bulky mediastinal mass. Eight course of ABVD resulted in a CR on PET-CT. Three months later, the planned CT revealed an enlarging mass in anterior mediastinum, measuring 2.5 cm in greatest diameter. There were no other sign of lymphoma progression. Due to mental retardation of the patient, his parents did not give consent for an invasive procedure. A PET-CT was performed to evaluate this mass, and no abnormal FDG uptake was detected, consistent with thymic hyperplasia. The patient has remained in CR during a follow-up period of 15 months.

Case 3

A 47-year-old woman presented with nodular sclerosing HL, stage IIB. Mediastinal and cervical lymph node enlargement was documented by thorax CT. CR was documented with a PET-CT after a total of 6 cycles of ABVD followed by RT. Three months later, a thorax CT revealed an enlarging mass (6 cm in largest diameter) in the anterior mediastinum. This mass was larger than the pre-treatment size of the tumor before treatment. PET-CT showed mild FDG accumulation in the thymus and anterior mediastinum, which was persistent but stable 11 months after treatment.

Case 4

The patient was an 18-year-old woman presented with a stage IV HL lymphocyte predominant type. A pre-treatment PET-CT showed increased FDG uptake in the cervical, paraaortic, mesenteric lymph nodes, liver and bone marrow indicating the known sites of her disease but without involvement of mediastinum. CR was achieved after 6 courses of ABVD as confirmed with PET-CT. Three months after completing therapy, a thorax CT scan showed an isolated thymic mass measuring 7 × 5 × 4 cm in size. A PET-CT demonstrated the typical inverted V-shaped FDG uptake with new activity in the thymic mass and superior mediastinum (SUVmax 5.5; Fig. 1,2). She had no symptoms of lymphoma. CT-guided transthoracic fine needle aspiration biopsy (TTNAB) was performed of the mass. Thymic cells were obtained from the biopsy specimen. By light microscopy, thymic epithelial-like cells and small lymphocytes were seen. Hassall corpuscles, which are more specific for thymus, were not seen. The patient was followed with serial thorax CT and PET-CT scans after 3 and 6 months, respectively. On the PET-CT, a diagnosis of thymic hyperplasia was made by virtue of the fact that the FDG uptake declined compared to previous PET-CT scan. She was well and in continued CR for 17 months.

Case 5

A 23-year-old woman presented with bulky mediastinal disease and cervical lymph node swelling. Immuno-histochemical studies demonstrated nodular sclerosing HL, stage IIIB. She received 6 cycles of ABVD chemotherapy, and a CR was achieved. Three months after completing chemotherapy, a thorax CT scan revealed a mediastinal tumor mass with a maximum diameter 6 cm. The patient was asymptomatic, and she decided to follow this mediastinal mass. After 4 months, a PET-CT was performed, and typical inverted V-shaped diffuse FDG uptake in the anterior mediastinum was seen (SUVmax 4.1; Figs. 3, 4).

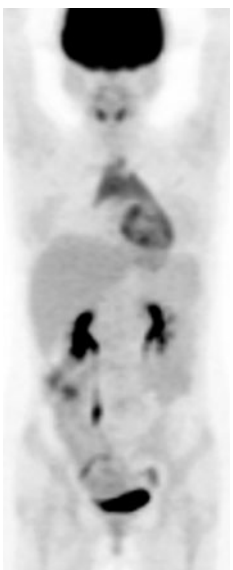

Fig. 1 Coronal ^{18}F-FDG PET scan obtained from an 18-year-old girl with Hodgkin's lymphoma demonstrates an inverted V-shaped area of anterior mediastinal uptake on the transaxial view with a SUVmax 5.5

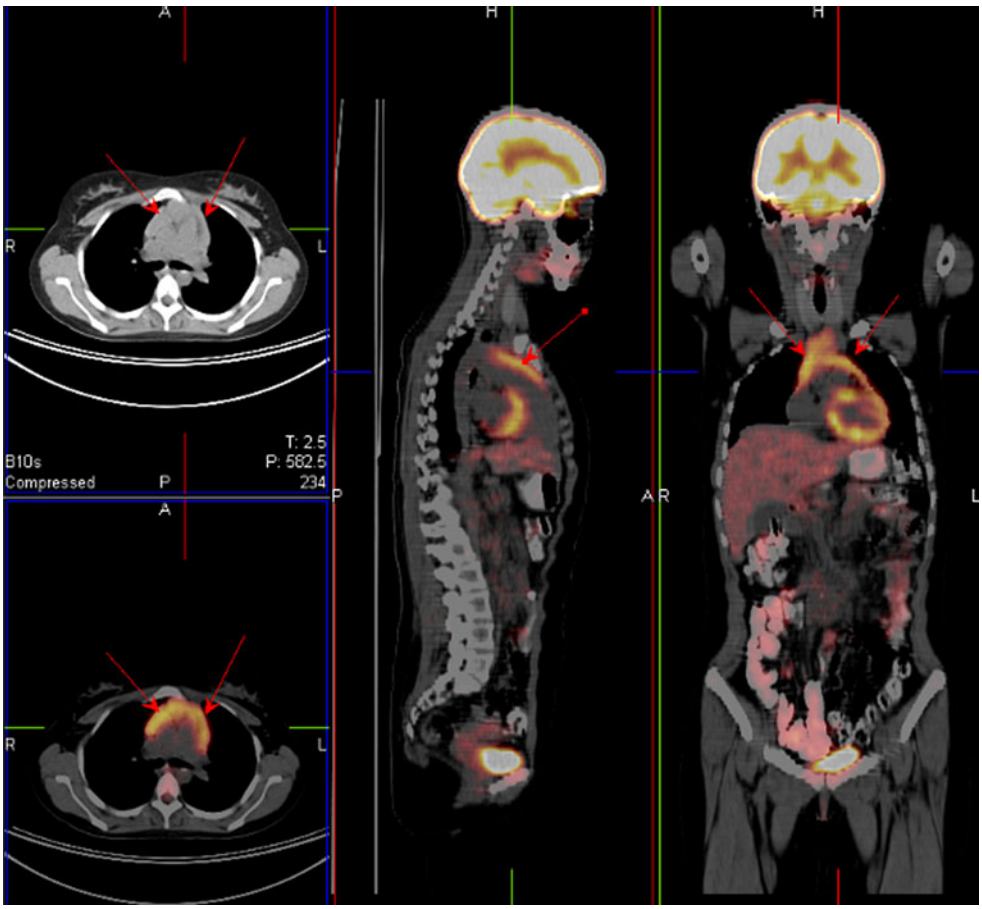

Fig. 2 The anterior mediastinal mass on the CT and PET-CT (transaxial, vertical and coronal sections) scan of patient after 3 months from the chemotherapy that indicates thymic hyperplasia

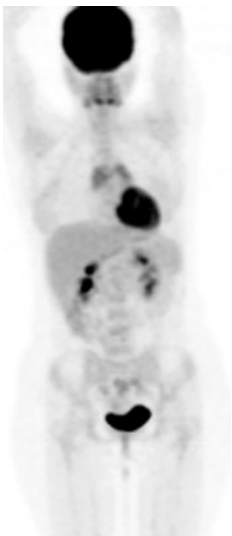

Fig. 3 Coronal ^{18}F-FDG PET scan obtained from a 23-year-old girl with Hodgkin's lymphoma demonstrates an inverted V-shaped area of anterior mediastinal uptake on the transaxial view with a SUVmax 4.1

A diagnosis of thymic hyperplasia was made. She was well and in continuous CR for 26 months. The characteristics of all patients are shown in Table 1.

Discussion

Thymic hyperplasia is well known to be in the differential diagnosis of mediastinal mass lesions and to occur in patients cured of HL [8]. Reactive thymic hyperplasia following chemotherapy for malignant tumors can be misdiagnosed as residual tumor or disease relapse, leading to unnecessary diagnostic procedures and treatment [9].

FDG PET has become a widespread tool in the staging of cancers, including lymphomas. FDG uptake in the normal thymus can be seen in children and in young adults [10]. FDG uptake has also been shown to be increased in the thymus in adults after chemotherapy [1, 11]. Kumar et al. [12] analyzed 23 patients with anterior mediastinal masses suspicious of thymic origin on CT scan and then all patients underwent PET-CT. According to the level of FDG uptake, the pattern of uptake, the presence of invasion to surrounding structures or metastases, thymic hyperplasia, thymoma and thymic carcinoma were considered in the differential diagnosis, and these diagnoses were supported histopathologically. Zhen and et al. [9] evaluated clinical

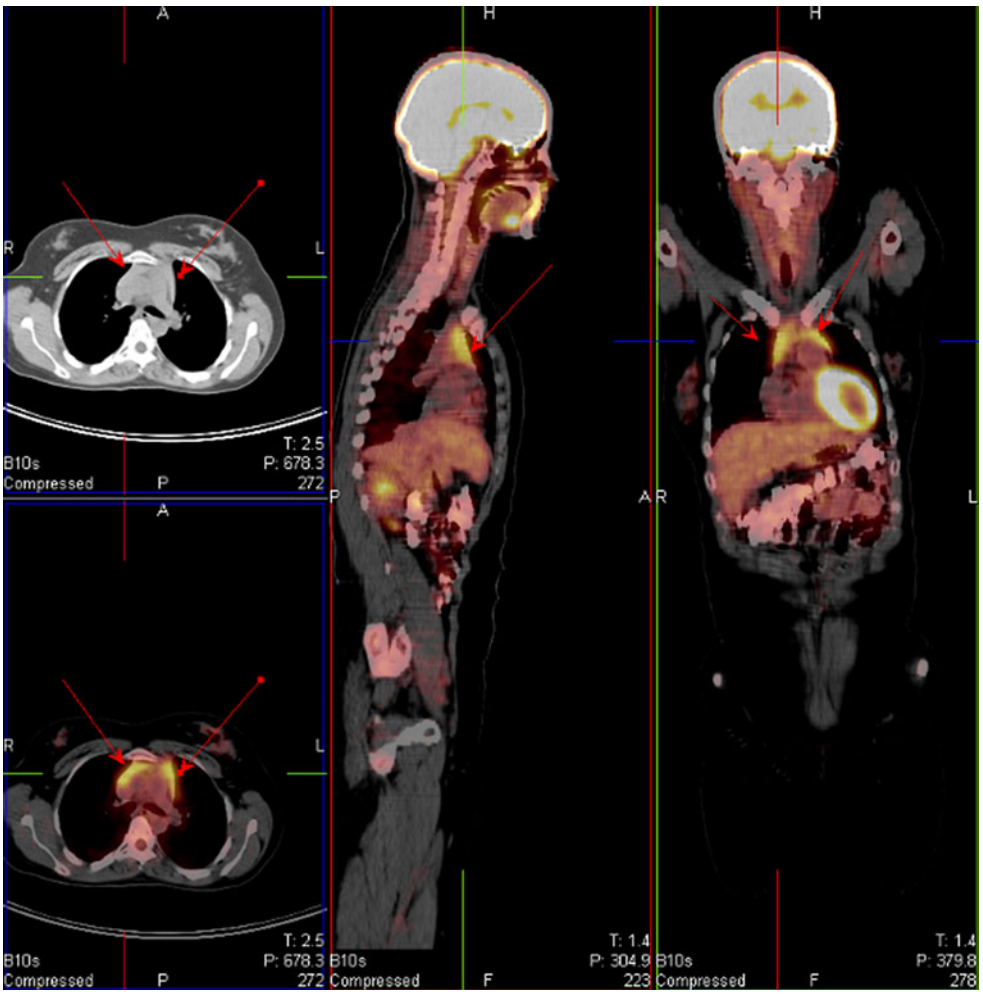

Fig. 4 The anterior mediastinal mass on the CT and PET-CT scan (transaxial, vertical and coronal sections) of a patient with Hodgkin's lymphoma 4 months after chemotherapy indicating thymic hyperplasia

Table 1 The characteristics of all our patients

Patient	Age	Subtype	Stage	Treatment	Duration after completion of chemotherapy to thymic hyperplasia (mo)	Size of the tumor (cm)	SUVmax	OS (mo)
1	23	DLBCL	IIB	R-CHOP	4	4	NA	10
2	22	Classic type HL	IIB	ABVD	6	2.5	NA	15
3	47	Nodular sclerosing HL	IIB	ABVD+RT	3	6	NA	11
4	18	Lymphocyte rich HL	IV	ABVD	6	7	5.5	17
5	23	Nodular sclerosing HL	IIIB	ABVD	4	6	4.1	26

DLBCL diffuse large B-cell lymphoma; *HL* Hodgkin's lymphoma, *R-CHOP* rituximab, cyclophosphamide, doxorubicine, vincristine, prednisolone; *ABVD* doxorubicine, bleomycine, vinblastine, dacarbazine; *RT* radiotherapy; *mo* month

data from 13 children with thymic hyperplasia following chemotherapy for malignant lymphoma. When a new thymic mass was detected with CT during follow-up, PET-CT evaluation was performed in 5 cases and no vital tumor was seen.

The reappearance of mediastinal masses in our patients was initially suspected to indicate relapse of lymphoma as each of these patients had previously been demonstrated to be in CR. In one of these 5 patients, the new thymic mass was confirmed as thymic hyperplasia by CT-guided

TTNAB. The others were followed clinically, and PET-CT imaging revealed thymic hyperplasia morphologically. All of these patients were monitored with close clinical follow-up for a median 15 months without evidence of recurrence. The differential diagnosis of mediastinal masses after successful treatment of lymphoma consists of residual fibrosis and necrosis of the primary tumor, recurrence of disease, thymic cyst, thymic hyperplasia, pulmonary fibrosis or granulocytic sarcoma [2, 4]. In the literature, CT, magnetic resonance imaging, ^{67}Gallium scintigraphy and ^{18}F-FDG PET-CT have been reported to be useful methods for the differential diagnosis of these mediastinal masses but there are limitations to each of these imaging techniques [2, 5]. Thymic malignancy can be differentiated from thymoma on the basis of biologic behavior such as local invasiveness and distant metastasis (3). Although histopathologic confirmation is historically needed to make an unequivocal diagnosis and to avoid unnecessary and potentially harmful treatment, we did not perform biopsy initially because we did not suspect relapse of HL on clinical grounds, and secondly, we performed PET-CT to evaluate the FDG uptake of these anterior mediastinal masses identified on the thoracic CT. None of our patients wanted to undergo biopsy, so we performed PET-CT after the thorax CT to aid in the distinction of thymic hyperplasia from lymphoma relapse. The absence of concurrent lymph node enlargement, the timing of thymic enlargement and FDG uptake, morphological features such as a triangular shape which corresponds to the anatomic bilobed figure of the thymus are all significant clues favoring the diagnosis of thymic hyperplasia [3]. In addition, mild and diffuse FDG uptake in the mediastinal mass and stability in the size of the mass itself during follow-up also indicated a benign nature. Thus, in these cases, we did not suspect relapse and instead followed them with the presumptive diagnosis of thymic hyperplasia.

Thymic hyperplasia after chemotherapy for HL was first described in 1983, and it probably represents an immunologic rebound phenomenon and in fact may be a good sign of immune recovery [4]. Lin and et al. [4] reviewed 10 cases with thymic hyperplasia after successful treatment of HL. In their study, diagnoses were made by histopathologic examination. The age of these patients was in the range of 2–31 years, and the mediastinal mass was detected 6-12 months after treatment. Wittram et al. [13] showed thymic enlargement by CT in 3 patients with histologically normal thymic tissue which had physiologic FDG uptake on PET-CT. One of these patients had thymic hyperplasia in response to chemotherapy. Langer et al. [14] found 21 cases following treatment for HL with a median age of 23 years (range; 8–40). Anchisi et al. [2] reported 3 cases of thymic hyperplasia 2–8 months after chemotherapy for HL (1 case) and NHL (2 cases). Their ages were 26, 30 and 32 years, respectively. Although in the literature thymic hyperplasia after chemotherapy has been generally seen in younger age individuals, one of our cases was 47 years old. We detected thymic hyperplasia in 4 patients after 3–4 months of chemotherapy, but in the last case, thymic hyperplasia was detected 11 months after the last chemotherapy, and these are all compatible with the literature.

Smith et al. [15] examined 93 PET-CT images which had been performed for staging or restaging of various malignancies. Of 11 patients treated with chemotherapy, the median time interval from completion of chemotherapy to PET-CT was 12 months (range; 2–24 months). All 11 patients had thymic hyperplasia with increased FDG uptake (SUV mean 2.8 $\pm$ 1.38) on PET-CT images. FDG uptake with the characteristic inverted V shape in the anterior mediastinum was considered to be thymic activity. Ten of the 11 patients with increased FDG uptake in mediastinal nodules had follow-up imaging between 6 and 12 months afterward. All of the patients had stable or decreased FDG uptake in the mediastinum and were disease free for 1 year of follow-up. Biopsy of the superior mediastinal nodule was not performed in any of the 11 cases because of the pathognomic FDG activity within the superior mediastinal thymic enlargement revealed by PET-CT. In our study, all patients were asymptomatic for lymphoma. After detection of the anterior mediastinal nodule with thoracic CT, PET-CT was performed, and typical findings suggestive of thymic hyperplasia were observed. SUV alone may have a limited role in differentiation of normal thymus from thymic neoplasia [3]. Brink et al. [16] showed that the highest average of SUV occured in the adults with lymphoma following chemotherapy and was 2.74 $\pm$ 0.66. In the literature, it is suggested that an SUV above 4 may not be considered as physiologic thymic uptake [3, 16]. The FDG uptake in 2 of our patients was 4.1 and 5.5, both above 4, though all of our patients' nodules showed stability in size on follow-up imaging without recurrence of lymphoma there or elsewhere.

On CT, appearance of normal thymus in the anterior mediastinal space is described as a triangular or bilobed structure, with soft tissue density, and whose size varies according to age [2, 3]. Thymic enlargement is usually suspected if the thickness of at least one lobe is greater than two standard deviations above the age-related control [2]. Mackall et al. [17] defined thymic hyperplasia as a twofold or greater increase in thymic volume during the first year after chemotherapy over thymic volume at presentation [2].

Conclusion

Thymic hyperplasia following chemotherapy for lymphoma is rare in the adult population [2]. Thymic

hyperplasia can be suspected when a growing anterior mediastinal mass is observed after the completion of treatment. There are some useful additional diagnostic criteria such as isolated radiologic mass retaining the characteristic shape and density of a normal thymus, without mediastinal lymphadenopathy or other symptoms related to lymphoma, and mild, diffuse FDG uptake on PET-CT. It is important to be aware of this phenomenon to avoid misdiagnosis or over-staging of disease. It may also lead to unnecessary invasive biopsies, especially when there are anterior mediastinal mass is located in the area of the thymus on CT scan. During clinical and radiographic follow-up, FDG PET scan is generally sufficient for diagnosis. However, if new chemotherapy is considered for suspicion of relapse, a definitive, invasive diagnostic procedure should be performed in order to document lymphoma relapse before initiation of therapy.

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