

Spontaneous Regression of Follicular, Mantle Cell, and Diffuse Large B-Cell Non-Hodgkin's Lymphomas Detected by FDG-PET Imaging

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Abstract: Spontaneous regression of non-Hodgkin lymphoma (NHL) has been reported in low-grade tumors but is an extremely rare event in intermediate- and high-grade disease. Documentation of spontaneous regression by serial fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging has not been reported in the literature. We present 3 cases of spontaneous regression, 1 each of follicular lymphoma (FL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL), which showed spontaneous regression on serial FDG-PET imaging. All patients underwent serial whole-body FDG-PET scans 60 minutes after intravenous injection of 9–11 mCi of this radiotracer. None of them had any chemotherapy, radiotherapy, or surgery after the baseline PET scan. Spontaneous regression of disease in all 3 cases was correlated with conventional imaging and clinical course. All 3 patients had positive FDG-PET results on their baseline scan. There was complete disappearance of FDG uptake on a follow-up PET scan for the patient with follicular lymphoma. These results suggest complete regression. The patients with MCL and DLBCL both showed a significant reduction in FDG uptake on serial whole-body PET scans, suggesting partial regression in both cases. Although spontaneous regression of lymphoma is uncommon, this phenomenon can be successfully demonstrated by FDG-PET imaging. Therefore, serial PET imaging may play an important role in detecting this unusual event and may further enhance our understanding of the biologic behavior of this malignancy.

Key Words: spontaneous cancer regression, FDG-PET, non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma

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Non-Hodgkin lymphomas (NHL) comprise a heterogeneous group of entities based on pathologic definition of the disease with variable clinical courses. Uncommonly, this malignant disease can regress spontaneously as noted in the literature.¹ Spontaneous regression has been reported to occur primarily in low-grade lymphomas with incidences varying from 10% to 23%.^{1–3} Although spontaneous regression of intermediate- and high-grade lymphomas has been reported in patients with extranodal disease, this phenomenon is extremely rare in high-grade disease with nodal involvement.^{1,5–7} Structural and functional imaging studies are commonly used to assess disease activity and to guide management of these patients. Assessment of response to treatment and detection of residual and recurrent disease is traditionally accomplished by computed tomography (CT) and positron emission tomography (PET) imaging. The critical drawback of CT and other anatomic imaging techniques is that size is the only major criterion for detecting disease activity. Therefore, these methods are unable to distinguish between involved and uninvolved nodes, and cannot distinguish residual/recurrent disease from residual scar tissue.^{8–11} Fluorodeoxyglucose (FDG) PET can overcome these difficulties and is therefore frequently applied in the management of patients with lymphoma.^{9–12}

We present 3 cases of spontaneous regression as detected by serial FDG-PET imaging: 1 of follicular lymphoma (FL), which showed complete regression, and 1 each of mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL), which revealed partial regression

CASE REPORTS

Case No. 1

A 59-year-old woman presented with left parotid swelling which, on biopsy, was determined to be a low-grade follicular NHL. The patient underwent surgical excision of the parotid tumor in 1998. A bone marrow biopsy performed in March 2000 showed marrow involvement. A CT scan performed in March 2002 revealed no abnormality. An FDG-

PET scan was performed for staging and detection of residual disease in April 2000. The whole-body FDG-PET scan showed areas of focal increased radiotracer uptake in the inguinal lymph nodes bilaterally with a standardized uptake value (SUV) of 2.6. This was interpreted to be consistent with active disease at these sites (Fig. 1A). There was also mild, diffuse increased FDG uptake in the spleen and bone marrow. Considering the low grade of malignancy, a decision was made not to treat the patient with either radiation or chemotherapy at that time. A follow-up FDG-PET scan was performed in July 2003 to rule out progression of disease. The patient remained asymptomatic during the interim period between scans. These later PET images demonstrated normal FDG distribution in the entire body (Fig. 1B). The previously noted abnormal FDG uptake in the inguinal regions bilaterally had resolved completely. The mild, diffuse increased FDG uptake in the spleen appeared to be unchanged from the previous PET study.

Case No. 2

A 75-year-old man presented with a lump in the left neck in September 2002. A CT scan obtained at that time showed posterior cervical lymphadenopathy measuring up to 1.4 cm. Fine needle aspiration of the lymph node revealed a monoclonal B-cell population that expressed CD19, CD20, and CD5. A CT scan of the chest, abdomen, and pelvis was performed for further evaluation but showed no evidence of adenopathy. A bone marrow examination performed at that time showed no evidence of bone marrow involvement by lymphoma. An FDG-PET scan performed in November 2002 revealed abnormal FDG uptake in the left neck (SUV of 3.6) and upper abdomen in the periaortic region (SUV of 2.8). A follow-up CT scan of the abdomen was performed within 1 week of the FDG-PET scan and showed a 1-cm lymph node in the retroperitoneum, corresponding in location to the positive PET scan (Fig. 2A). A subsequent excision biopsy of this lymph node confirmed the diagnosis of mantle cell lymphoma. The impression at this point was clinical stage IIIA mantle cell lymphoma. Because the patient was entirely asymptomatic, he was kept under an initial period of active

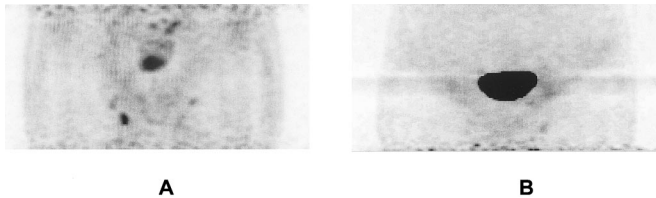


FIGURE 1. F-18-FDG PET scan showed increased radiotracer uptake in bilateral inguinal lymph nodes more on the right side (A). Follow-up PET scan showed normal FDG uptake in the entire body and complete resolution of inguinal lymph node uptake (B).

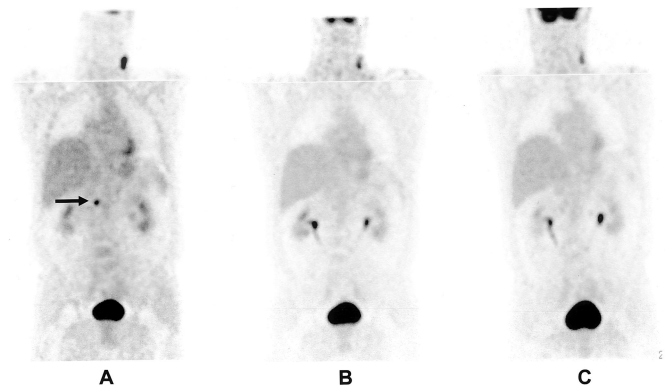


FIGURE 2. F-18-FDG whole-body PET scan showing multiple foci of intense FDG uptake in the left neck and periaortic region (black arrow). These findings were suggestive of active disease involvement (A). Follow-up PET scan showing increased FDG uptake in the left neck, but appear to be decreased in number and intensity of FDG uptake as compared with the prior study (B). Second follow-up PET scan showing less intense FDG uptake in the left neck as compared with the first study, suggestive of significant regression (C).

observation. A follow-up FDG-PET scan was performed in March 2003 and again revealed abnormal FDG uptake in the left neck (SUV of 2.2). However, this region of uptake was less intense as compared with the previous study (Fig. 2B). The previously noted abnormal FDG uptake in the periaortic region showed no FDG uptake in this second scan (postexcision biopsy). A follow-up CT scan at that time also showed a decrease in size of the cervical lymph node. The patient underwent a third PET scan in November 2003, which revealed mild to moderately increased FDG uptake (SUV of 1.3) in the cervical region. The FDG uptake in this region was less intense uptake than that of both previous scans in the cervical region. No other discrete foci were suggestive of active disease (Fig. 2C). The patient is still asymptomatic. These findings have enhanced the impression of a spontaneous regression of previously active disease.

Case No. 3

A 45-year-old man was diagnosed with DLBCL in 1998. The patient was treated with radiation and chemotherapy in 1998–1999 and remained in complete remission until December 2002. A chest CT scan was performed in December 2002 and revealed disease in the left axillary lymph nodes. An FDG-PET scan was advised to confirm the findings of the CT scan. An FDG-PET scan was performed 1 week later and confirmed the CT findings. The PET scan revealed at least 6 abnormal foci of intense uptake of varying size and intensity in the left axillary region, which suggested active disease at this site. Two other sites of FDG uptake were also noted, 1 each in the right mediastinum and the

paraortic region. These sites were also thought to represent involvement by the disease (Fig. 3A). The patient underwent a left axillary lymph node biopsy and results were consistent with active DLBCL. A follow-up FDG-PET scan was performed in April 2003, which revealed 4 foci of increased uptake in the left axilla that appeared to be less intense compared with the previous study (Fig. 3B). This observation suggested either a mild spontaneous improvement or a mere representation of the lymph node excision. The sites previously detected in the right mediastinum and the paraortic regions were still present but appeared to be less intense as compared with the initial scan. The patient did not receive any radiation, chemotherapy, or surgery after the second FDG-PET scan. A follow-up CT scan performed in June 2003 revealed no abnormalities. The patient underwent a third PET scan in July 2003, which revealed mild to moderately increased uptake in the left axilla. This uptake was less intense than that noted on the previous scan. SUV were not calculated in this patient. No other discrete foci were suggestive of active disease (Fig. 3C). These findings were interpreted to represent inflammatory changes, but the possibility of residual tumor could not be excluded. The previously detected uptakes in the mediastinum and paraortic region were no longer visualized on the third PET scan. This further enhanced the impression of spontaneous regression of the previously active disease.

DISCUSSION

FL and DLBCL are the 2 most common types of lymphoma and account for approximately 50% of all cases of

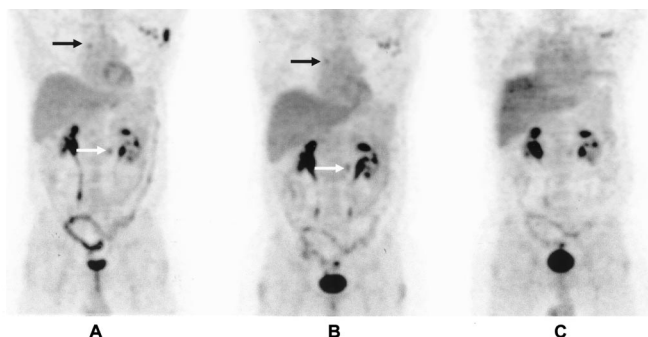


FIGURE 3. F-18-FDG whole-body PET scan showing multiple foci of intense FDG uptake in the left axilla, right mediastinum (black arrow), and pancreatic regions (white arrow). These findings were suggestive of active disease involvement (A). Follow-up PET scan showing increased FDG uptake in all regions mentioned here but appear to be decreased in number and intensity of FDG uptake as compared with the prior study (B). Second follow-up PET scan showing less intense FDG uptake in the left axilla and disappearance of previously described uptake in the mediastinum and pancreatic regions, suggestive of significant regression (C).

lymphoma.^{13,14} FL may transform into DLBCL, but even nontransformed tumors show some overlap with DLBCL in terms of immune phenotype, as well as molecular and cytogenetic abnormalities.^{14,15} Based on current criteria, there may be variants of FL that are clinically related to DLBCL.¹⁶ However, MCL is a biologically more heterogeneous disease and accounts for 5% to 10% of all lymphoma cases.¹⁷ The clinical outcome of FL, DLBCL, and MCL non-Hodgkin lymphomas is highly variable.

Gattiker et al. retrospectively reviewed 209 cases of NHL and noted spontaneous regression in 18 of 140 cases of follicular lymphoma (6 cases with complete remission) and 2 of 69 cases of diffuse lymphomas (both with partial regression).¹ A study by Krikorian et al. showed spontaneous regression in 9 of 44 cases of low-grade advanced lymphomas.² Horning and Rosenberg found 19 of 83 cases of spontaneous regression in low-grade NHL.³ However, the incidence of spontaneous regression is much lower in high-grade lymphomas and has been reported mostly in extranodal disease sites.^{5,6,18,19} Spontaneous regression of nodal high-grade NHL is extremely rare, and only a few cases have been reported in the literature.^{1,7,20,21} However, no case of spontaneous regression of MCL has been reported in the literature.

Modulation of the host immune system, possibly by concurrent bacterial or viral infection or by traumatic effects including reduction of tumor burden by biopsy, could possibly cause spontaneous regression.^{4,22} An immunomodulatory effect has also been suggested as a possible mechanism for regression of gastric lymphomas after treatment with cimetidine and anti *Helicobacter pylori* therapy and for HIV associated T-cell NHL after antiretroviral therapy.^{2,19} An association between spontaneous regression and acute inflammation has also been shown.⁴

It must be noted that to confirm this phenomenon, patients with suspected regression should be monitored over a prolonged period of time because the disease is known to have an unpredictable course. The period of spontaneous regression usually varies from 6 months to 13 years with an average duration of 13 months.^{3,21,22} Conventional imaging techniques such as CT and magnetic resonance imaging suffer from major shortcomings, which include poor sensitivity and specificity in distinguishing between active and inactive disease sites.^{10,11} Until recently, gallium-67 scanning was advocated for the assessment of treatment response and for the prediction of outcome in patients with lymphoma.²³ There are 2 case reports in the literature describing spontaneous regression using gallium.^{7,24} However, in recent years, FDG-PET has replaced the Ga-67 scan as the modality of choice for the management of patients with lymphomas.^{11,25} PET has been shown to have high sensitivity and specificity in predicting therapy-induced complete or partial remissions.⁹ Based on earlier reports, PET was considered less sensitive in low-grade than in high-grade lymphomas.²⁶

However, recent studies revealed a sensitivity of 98% in patients with indolent NHL, possibly as a result of the advancement and superior resolution of modern PET machines.²⁷ The study published by Elstrom et al. from our center showed a sensitivity of 100% and 98% in patients with DLBCL and FL, respectively.¹² De Witt et al. were able to demonstrate that FDG-PET was highly specific for detecting recurrent lymphoma in patients with residual mass disease as detected by CT.²⁶ In the study reported by Jerusalem et al., patients with residual tumor masses as detected by CT and positive FDG-PET results had a tumor recurrence rate of 100%, whereas patients with residual lesions detected by radiologic techniques and negative FDG-PET findings had a recurrence rate of only 26%.¹¹

The present report is unique in documenting spontaneous regression of follicular (low-grade) MCL and DLBCL (intermediate-grade) lymphomas by serial FDG-PET studies. To the best of our knowledge, this is the first report of observations showing spontaneous regression of lymphomas by serial FDG-PET imaging. In conclusion, spontaneous regression is an uncommon phenomenon in patients with low-grade lymphomas and is quite rare in patients with intermediate- and high-grade NHL. These results indicate that FDG-PET may play an important role in following the course of disease activity in patients with NHL.

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