A Case of Diffuse Large B-Cell Lymphoma in Association With Paraesophageal Leiomyoma: Highlighting False-Positivity of PET Scan and Importance of Tissue Diagnosis

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Abstract
PET scan and PET/CT scans are being widely used for staging of diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma. They are sensitive and specific imaging techniques available for lymphoma. However, practicing hematologists must be aware of false-positive tests, which can upgrade the stage of the lymphoma significantly and may alter the treatment paradigm for an individual patient. This report describes a case of DLBCL that was upgraded with PET/CT scan to stage IVA from stage IA. Pursuit of tissue biopsy with minimally invasive surgery eventually confirmed it to be stage IA DLBCL and paraesophageal leiomyoma. This case highlights the potential pitfalls of modern imaging techniques and the need for histologic diagnosis. (JNCCN 2012;10:577–581)

Overview
The treatment of aggressive non–Hodgkin’s lymphoma (NHL) includes systemic chemo-immunotherapy sometimes followed by radiation therapy. Treatment is determined by the lymphoma subtype and stage. CT scans and bone marrow biopsies are standard of care for initial staging. More recently, FDG-PET is often used to further delineate staging and assess subsequent response to therapy. The International Prognostic Index (IPI), which takes into account anatomic stage, number of extranodal sites, lactate dehydrogenase level, performance status, and age, has improved the ability to predict outcome in diffuse large B-cell lymphoma (DLBCL). In a patient with localized nonbulky early-stage disease (stage I–II) and no adverse prognostic factors, chemotherapy can be abbreviated to 3 cycles followed by involved-field radiation therapy. However, patients with advanced-stage disease (Ann Arbor stage III–IV) or high IPI scores are treated with 6 to 8 cycles of chemotherapy. With the widespread use of FDG-PET scans, practicing hematologists must be aware of the potential pitfalls of false-positive PET scans in upstaging patients and always bear in mind that histologic diagnosis is imperative to determine the extent of disease.

Case Report
A 56-year-old woman noted a slowly enlarging right parotid mass for approximately 2 months. She denied any fever, night sweats, decreased salivation, dry eyes, pain, or facial paresthesias. She had an intentional weight loss of about 19 pounds over the preceding months. She had no history of autoimmune diseases. On examination, the parotid mass was 1.5 cm, firm, immobile, and nontender, and no evidence was seen of facial nerve palsy. She had no palpable peripheral adenopathy. Abdominal examination revealed no organomegaly. Fine-needle
aspiration biopsy was performed, which showed an atypical lymphoid proliferation with CD20, CD19, CD10, and lambda restriction on flow cytometry. This was consistent with a non-Hodgkin’s B-cell lymphoma. CT of the face, neck, and torso revealed a 1.6-cm enhancing nodule in the right parotid and a 6 × 3-cm posterior mediastinal mass engulfing the distal esophagus (Figure 1A, C). PET fused with CT images (PET/CT) showed intense FDG uptake within the right parotid mass with a standardized uptake value (SUV) of 20.7 (Figure 1D), and heterogeneous uptake in the distal esophageal mass with a maximum SUV of 5.4 (Figure 1B). Bone marrow biopsy showed active trilineage hematopoiesis with no evidence of lymphomatous involvement. Lactate dehydrogenase level was normal. The remainder of her chemistry profile revealed normal electrolyte levels and renal and liver function tests. The patient was scheduled for superficial parotidectomy. Because FDG uptake was seen in the paraesophageal mass, the decision was made to pursue histologic diagnosis first. The patient underwent endoscopic ultrasound (EUS)—guided core biopsy of the paraesophageal mass and subsequently thoracoscopic incisional biopsy; which were both nondiagnostic on final pathology.

However, despite the negative EUS-guided biopsy, given the positive uptake on PET scan and possibility of sampling error, the authors proceeded with robotic resection of the paraesophageal tumor. The patient was discharged home on the second postoperative day. The morphologic and immunohistochemical findings were consistent with a leiomyoma, and no evidence was seen of lymphoma (Figure 2). Hematoxylin and eosin (H&E) staining under high power (Figure 2A) revealed a spindle cell neoplasm. The tumor exhibited positive immunoreactivity for smooth muscle actin (Figure 2C), desmin, and actin. The tumor was negative for c-kit (Figure 2B) and DOG1 (Figure 2D), thus excluding a gastrointestinal stromal tumor. The tumor was also negative for keratin (epithelial marker), CD34 (vascular marker), and S-100 (neural marker).

![Figure 1](image1.png)  
**Figure 1** CT of the face, neck, and torso, and PET/CT showing FDG uptake. CT of the chest with contrast (A) reveals a large mass surrounding the distal esophagus measuring 6.0 x 3.7 cm and extending to the gastroesophageal junction. Heterogeneous FDG uptake is seen on PET/CT (B). CT of the face with contrast (C) revealed a 1.6-cm mass in the superficial lobe of the right parotid gland. Intense uptake occurred in this mass (D).
Subsequently, the patient underwent superficial parotidectomy. The patient tolerated the procedure well and final pathology showed DLBCL (Figure 3). Immunohistochemical studies were consistent with a DLBCL with strongly positive immunoreactivity for CD20 (Figure 3C), CD10 (Figure 3B), CD43, bcl-6, and MUM1. The B cells were negative for CD5 and bcl-2. The Ki-67 proliferative index was approximately 80% (Figure 3D).

Therefore, the patient had stage I DLBCL and was started on R-CHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone). She refused involved-field radiation therapy after 3 cycles of systemic immunochemotherapy, and therefore received a total of 6 cycles of systemic immunochemotherapy. She is still experiencing complete remission at 2 years of follow-up.

Discussion
FDG-PET is a noninvasive imaging technique that is based on the glucose metabolic pathway. FDG is transported into the cells using glucose transporters. However, after initial phosphorylation, it cannot be metabolized further and is trapped inside the cells. As the 18F isotope decays, it releases positrons that undergo annihilation reaction after colliding with electrons and releases photons, which are detected by the PET scanners. Malignant cells have high proliferative capacity and thus high glycolytic metabolism, and hence these areas are detected as “hot” on PET. Results can be semiquantitatively expressed as SUV, which is the radiotracer activity in the lesions compared with the background activity.

Use of functional scans, such as PET, in patients with lymphoma was recently reviewed. In a meta-analysis of 20 different retrospective and prospective studies evaluating FDG-PET in Hodgkin lymphoma and NHL, the median sensitivity was 87% (range, 81%–97%), median specificity was 94% (range, 80%–100%), and the false-positivity rate was 11.4% (range, 6%–20%). However, no data on prevalence were reported to allow calculations of positive or negative predictive values. High false-positivity rates can have many causes. Any physiologic or pathologic processes that lead to a high rate of activation of glycolytic pathway can potentially cause abnormal FDG uptake. Variable amounts of FDG uptake are seen in normal tissues, such as brown fat, thyroid, ovaries, premenopausal uterus, testes, prepubertal thymus, gastrointestinal tract, brain, and urinary system. Inflammatory cells, such as activated granulocytes, macrophages, and lymphocytes, also have a high rate of glucose metabolism, and consequently high FDG uptake is seen in inflammatory conditions or infections. Postoperative and postradiation changes also fall in this category. Approximately 75% of all false-positive FDG-avid lesions are secondary to inflammatory or physiological processes, but approximately 25% are from benign tumors or tumor-like conditions. These benign conditions have wide varieties, including papillomas, adenomas, Gaucher disease, pheochromocytomas, leiomyoma, uterine fibroids, hemorrhagic ovarian cysts, Paget disease,
and avascular necrosis. PET/CT images may help in better characterization and morphologic evaluation of the abnormal FDG-avid lesions, and thus help differentiate benign causes, such as inflammation, from those that are malignant. However, some benign tumors, such as the leiomyoma seen in this patient, are difficult to differentiate from malignant processes and may require histologic confirmation.

This case report illustrates a false-positive PET/CT and its evaluation. Medical decision-making is confronted with uncertainty.8 Practitioners must thoroughly understand the imaging technology and consider all of the clinical information when making treatment decisions. If misdirected by a single piece of data, the ramifications can be potentially disastrous. Based on heuristic reasoning, the pretest probability of this bulky paraesophageal mass being lymphoma in an asymptomatic lady, with no bone marrow or other nodal involvement and low lactate dehydrogenase, was considered very low. Therefore, if the PET scan had been negative, it would have been helpful in reducing the probability of lymphoma.9 However, with positive FDG uptake and the inconsistency of the additional staging information, further confirmation of histologic diagnosis was pursued. Treatment recommendations were critically dependent on that information.

The availability of minimally invasive diagnostic and surgical procedures has improved the ability to pursue accurate pathologic diagnosis, the gold standard in oncology. EUS provides an accurate view of the esophageal layers and the periesophageal structures and lymph nodes.10 EUS-guided biopsy can be performed using fine needle aspiration and core needles.11,12 This modality is considered safe and highly accurate. The characteristic findings of homogeneity, sharp margins, and hypoechoic arising from the muscularis propria would indicate a leiomyoma.13 When a leiomyoma is suspected, biopsy or breach of the esophageal mucosa is avoided to reduce the likelihood of mucosal injury if resection is required later. In this case, the biopsy afforded by this technique provided insufficient tissue for diagnosis.14

Minimally invasive techniques have provided the ability to perform complex intrathoracic procedures with minimal perturbation of the chest wall and the intrathoracic structures. Robotic technology provides operator-directed 3-dimensional vision with multiple degrees of articulation close to the area of interest, minimizing chest wall trauma. Even complex structures, such as the horseshoe leiomyoma wrapping around the esophagus by more than 180° in this case, can be excised with a high degree of precision, thereby avoiding injury to the thin and delicate esophageal mucosa. In this patient, the benefits of the low morbidity of the minimally invasive procedure were the brief hospitalization, rapid postoperative recovery to normal performance status, and quick wound healing, which allowed her to receive chemotherapy within 4 weeks of the esophageal surgery.

In an alternate scenario, if this patient had only undergone superficial parotidectomy, she would have been treated as stage IV DLBCL (with 2 extranodal...
sites) based on PET imaging. After 6 to 8 cycles of systemic chemotherapy (R-CHOP), the paraesophageal mass would still be FDG-avid on PET scan. According to the NCCN Guidelines for Non-Hodgkin’s Lymphomas, a tissue biopsy would be indicated before changing the course of treatment (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org). This was also underscored by a study looking at interim PET scan after 4 cycles of R-CHOP in the treatment of DLBCL. If a diligent effort for obtaining biopsy is not made, then the risk exists of declaring these patients as having primary refractory disease based solely on a false-positive PET scan. Primary refractory DLBCL is treated with either radiation or salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation. This high-dose therapy is associated with significant morbidity. In the past, transplant-related mortality ranged from 6.5% to 9%, but with better supportive care it has declined to approximately 1%. The cost of high-dose chemotherapy with autologous stem cell transplant is estimated to be $290K to $700K. Hence, clinical reasoning and an understanding of the pathophysiology of disease must not be superseded by modern imaging studies.

Conclusions

The integration of modern imaging techniques such as PET and PET/CT has improved the ability to accurately assess the initial stage of lymphoma, and to assess the response to therapy. However, radiologists and clinicians must be aware of the potential shortcomings of the technology. Accepting a positive PET scan as confirmation of metastatic disease could lead to unnecessary, risky, and costly therapy.

References