False-Positive FDG-PET Imaging of the Thymus of a Child with Hodgkin's Disease

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During the evaluation of a child who had completed treatment for Hodgkin's disease, a PET study strongly suggested recurrent disease in the mediastinum. Biopsies were obtained and revealed normal thymic tissue only, with no evidence of recurrent disease. The ongoing difficulty in establishing accurate disease status in patients treated for Hodgkin's disease is discussed, along with recommendations for treating pediatric patient populations.

Key Words: FDG-PET; Hodgkin's disease; thymus; pediatrics

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One of the more difficult clinical challenges in patients with Hodgkin's disease is the determination of a patient's disease status during or after the course of planned treatment. Most subtypes of Hodgkin's lymphoma, particularly nodular sclerosing, are characterized by extensive fibrosis and scar tissue that leave abundant amounts of residual tissue in the original site of the disease. In many patients, particularly younger children, enlargement of the thymus gland will frequently follow completion of chemotherapy, further complicating the evaluation of the patient's disease status. Plain radiography and CT scans demonstrate anatomic residual tissue but do little to help clarify whether there is viable tumor tissue contained within the residual mass. Other diagnostic modalities, including magnetic resonance (MR) imaging and ^{67}Ga scintigraphy (*1*), have yielded mixed results in various studies and have not been found to be universally reliable in determining disease status.

PET scanning is a relatively new technique that has been shown to be an effective means of following selected patients with lymphoma (*2–7*). We report a false-positive PET study performed with ^{18}F-fluorodeoxyglucose (FDG) of the thymus in a patient with Hodgkin's disease, demonstrating the ongoing difficulty in assessing disease status in this patient population.

CASE REPORT

At 9 yr of age, the patient first presented with asymptomatic enlargement of left cervical, axillary and supraclavicular nodes of several weeks duration, low-grade fever, fatigue and sore throat. There was no documented weight loss or night sweats. A biopsy of a left supraclavicular node confirmed the diagnosis of nodular sclerosing Hodgkin's disease. CT scan of the chest revealed a large anterior mediastinal mass and two small pulmonary nodules. There was no abdominal disease found on the CT scan. Bone marrow aspirates and biopsies were negative for metastatic involvement. Gallium-67 scintigraphy, including SPECT of the chest and abdomen, demonstrated abnormal foci in the cervical, mediastinal and axillary regions.

Based on the patient's age and stage, she started chemotherapy using a hybrid COPP-ABV regimen (cyclophosphamide, vincristine, prednisone and procarbazine, alternating with doxorubicin, bleomycin and vinblastine). Initial treatment yielded an excellent therapeutic response with disappearance of all palpable lymph nodes, dramatic shrinkage of the mediastinal mass and resolution of the pulmonary nodules. Adverse effects of the treatment included moderately severe vinca alkaloid neuropathy (manifested by peripheral neuropathy with decreased reflexes, constipation, jaw and abdominal pain) and decreased pulmonary function with a moderate restrictive pattern. She completed all planned six cycles of chemotherapy treatment with no major complications. Diagnostic evaluation that included ^{67}Ga and CT scans performed after the completion of her last course of medication revealed no evidence of residual disease.

Four months after discontinuing therapy, she was found to have an asymptomatic, enlarged anterior mediastinal mass on routine follow-up chest radiograph, measuring 8.8 × 2 × 2 cm on subsequent CT scan. There was no fever, respiratory distress or other systemic complaints. Radiogallium scintigraphy with SPECT revealed a large area of increased uptake in the mediastinum (Fig. 1).

To further delineate the nature of the recurrent mass, a PET study was performed. Images of the body from the thyroid area to the groins were obtained between 66 and 96 min after the injection of 151.7 MBq (4.1 mCi) of FDG; FDG was prepared on-site (*8*). Attenuation correction was performed with three previously obtained transmission scans of the same regions. Visual analysis was performed on the reconstructed transaxial, coronal and sagittal images. Semiquantitative measurements of FDG uptake in suspicious and control areas was performed by the method of standardized uptake values (SUV). This technique has been used frequently in several medical centers, including North Shore University Hospital, to assess the metabolic activity in tumors (*9,10*). The images disclosed a large focus in the anterior mediastinum extending to the right hilum (Fig. 2), corresponding in localization and shape to the abnormality shown on the CT scan and radiogallium scintigraphy. No abnormal foci were observed in the abdomen. In our patient, the SUV in the thymic mass was 2.12, which may be considered slightly elevated. By comparison, SUVs in normal liver, normal lung and abdominal wall were 1.26, 0.35 and 0.60, respectively. Based on the PET findings, in the context of this patient and in our experience, a lymphomatous recurrence could not be ruled out.

The patient was taken to the operating room where on mediastinoscopy an enlarged thymus was found, and no adenopathy or masses were evident. Multiple biopsies of the thymus and surrounding tissue revealed no evidence of lymphoma or other malignant tissue. No treatment was administered. During the ensuing few months, the thymic enlargement underwent a spontaneous complete resolution, with negative follow-up chest radiographs. She remains well with no sign of recurrent disease 18 mo after the completion of her therapy.

DISCUSSION

Most pediatric malignancies will usually respond well to modern multidisciplinary treatment regimens with a rapid disappearance or shrinkage of bulk disease as the malignant

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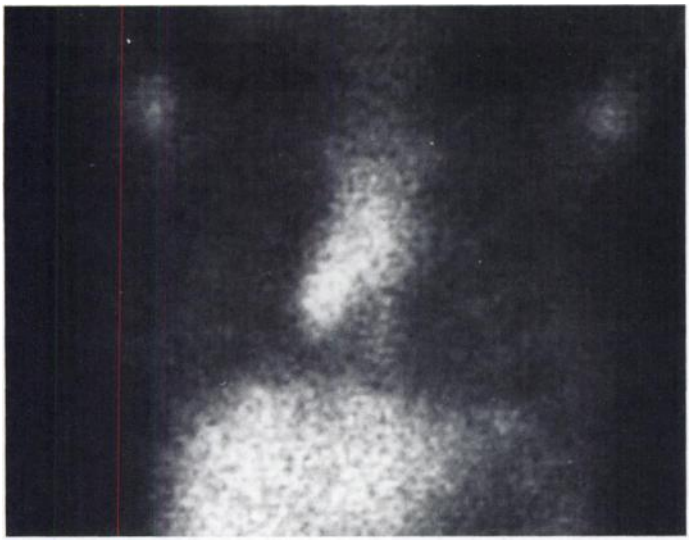

FIGURE 1. Anterior planar image of the chest and upper abdomen obtained 72 hr after the injection of 255 MBq (6.9 mCi) ^{67}Ga citrate. A large area of abnormally increased tracer activity is seen in the mediastinum similar to that seen in the FDG/PET image obtained 16 days after the ^{67}Ga study.

cells are destroyed. However, some tumors, most commonly Hodgkin's disease, other lymphomas and neuroblastomas, often elicit an intense sclerotic reaction leaving behind extensive fibrous tissue (or benign ganglioneuroma in the case of neuroblastoma) as the malignant tissue regresses (*11,12*). A major diagnostic challenge has been the determination of persistent or recurrent disease in the midst of the residual tissue, which will affect all subsequent therapeutic decisions. While routine radiography and CT scanning accurately depict the location and extent of residual tissue, it cannot differentiate between active disease and scar tissue. Likewise, MR images can yield accurate representations of mass disease but have not been effective in demonstrating differences between metabolically active malignant tissue and fibrous remnants.

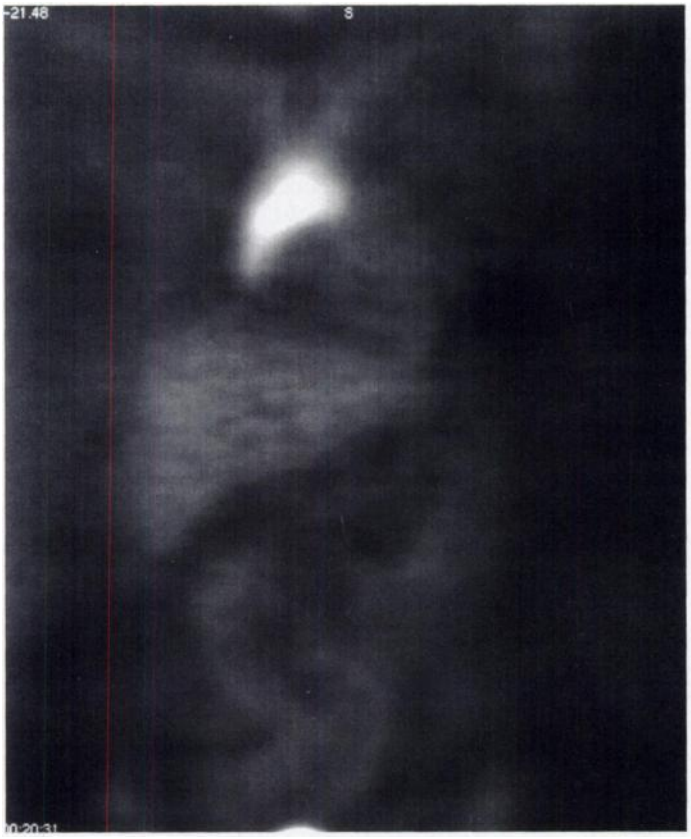

FIGURE 2. Coronal PET image of thorax, corrected for attenuation obtained from 66–96 min post-FDG injection. There is a large focus of moderate accumulation of FDG in the mediastinum extending to the region of the pulmonary hilum.

Radionuclide scanning using ^{67}Ga citrate has shown to be helpful in demonstrating metabolically active tissue, thus serving as an adjunct to CT scans and MR images in identifying likely areas of active malignant tissue in sites of residual bulk disease (*13–15*). While often a useful tool, false-positive scans in areas of active thymic activity have limited its role, particularly in younger children who frequently experience "rebound" thymic hyperplasia after treatment (*16–18*). A few investigators have reported uptake in normal tissue (including the pulmonary hila) and nontumoral lesions, thus suggesting a limited specificity of gallium scanning. These scans have also been less reliable in identifying active malignant disease below the diaphragm (*19*), underscoring the need for staging laparotomy in the patient who is to receive radiation therapy only.

PET studies with FDG have recently shown to be useful in identifying lymphomatous tissue and other malignant neoplasms. Most of the PET studies in oncology patients have been performed with the positron-emitter ^{18}F-2-FDG. This approach is based on the early work of Warburg in the 1930s, demonstrating that malignant tissue has a higher rate of glucose metabolism (glycolysis) than normal tissue. The early PET studies were performed in cerebral tumors where measurement of cerebral glucose metabolism with FDG revealed a correlation between peak metabolic activity in the tumor (rate of glycolysis) and the histologic grade of the tumor (*20*). Several studies have reported good sensitivity in locating a variety of malignant thoracic lesions, including bronchogenic carcinoma, metastatic carcinoma, metastatic Wilms tumor and lymphoma (*4*). PET scanning has also demonstrated greater reliability in detecting abdominal sites of lymphoma (*2*). It has been suggested that PET scans might be the best reflection of disease status in the patient with residual mass. The experience with our patient demonstrates the difficulty in establishing reliable evidence of viable tumor. In our patient, the strong uptake in the enlarged, but histologically normal thymic tissue points to the continued problem of differentiating mediastinal disease in pediatric patients with lymphoma who are prone to thymic rebound. Increased FDG accumulation has been seen in reactive nodes, as well as in patients with inflammatory lung disease (*21*). The results of our patient demonstrate the need for a more reliable diagnostic method of evaluating disease status. Recent reports suggesting the efficacy of a somatostatin receptor (*22,23*) and ^{201}Tl (*24*) scintigraphic studies in differentiating tumor from other metabolically active, nonmalignant thoracic tissues will require further analysis and confirmation with larger numbers of patients before being generally accepted as reliable indicators of recurrent or persistent disease. This is a particularly critical issue in pediatric patients with lymphoma who have a high salvage rate, and therefore, a need for early detection of recurrent disease.

CONCLUSION

As with other radionuclide imaging, FDG-PET scanning may not be specific for identifying residual or recurrent disease in children with Hodgkin's disease. At this time, the best choices for accurately determining disease status in the asymptomatic patient are either a less practical approach using multiple biopsies of suspected lesions or a close clinical follow-up with frequent radiographic studies looking for changes in the size of residual tissue with enlarging masses suggestive of recurrent disease.

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Scintigraphic Monitoring of Reticuloendothelial System in Patients with Type 1 Gaucher Disease on Enzyme Replacement Therapy

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The purpose of this study was to define the scintigraphic pattern of marrow replacement and changes in reticuloendothelial activity after enzyme replacement therapy in patients with Gaucher disease. **Methods:** Forty patients underwent baseline whole-body imaging with ^{99m}Tc-sulfur colloid and evaluation of liver and spleen volume with CT or magnetic resonance imaging. Thirty-seven of the 40 patients were treated with enzyme replacement. Therapeutic responses of central and peripheral bone marrow and the changes in pulmonary uptake of ^{99m}Tc-sulfur colloid were assessed visually at 1–4 yr after the start of therapy. Changes in liver and spleen volumes were analyzed quantitatively. The initial pattern of marrow involvement was correlated with disease severity (based on baseline blood counts and liver and spleen volumes). **Results:** Baseline studies revealed that 38 of 40 (95%) and 28 of 40 (70%) of the patients in this study had abnormal peripheral and central marrow activity, respectively. Twenty of 24 evaluable patients (83.3%) on therapy showed regression of peripheral bone marrow activity to a more proximal location in the lower extremities, increased ratio of pelvic/proximal femoral activity to distal activity or both. Fourteen of 19 treated patients (73.7%) with abnormal initial central marrow activity showed detectable improvement in central bone marrow activity as a result of therapy. In patients with initial lung uptake of ^{99m}Tc-sulfur colloid, 91% showed complete resolution of the uptake after therapy. These changes in colloid uptake and distribution were associated with significant reductions in liver and spleen volumes and improvements in blood counts. **Conclusion:** Most patients with Gaucher disease demonstrate increased central bone marrow activity and regression of activity in peripheral bone marrow with enzyme replacement therapy. Additionally, the abnormal phagocytic pulmonary activity observed before therapy in many of the patients resolves.

Key Words: Gaucher disease; enzyme therapy; technetium-99m-sulfur colloid

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Gaucher disease (GD) is an inborn error of glycosphingolipid metabolism due to deficiency of the lysosomal hydrolase, glucocerebrosidase. Clinically, three subtypes are delineated on the basis of the absence (Type 1) or presence and severity (acute Type 2 and subacute Type 3) of neurologic involvement. The primary features include progressive hepatosplenomegaly, skeletal disease and anemia and thrombocytopenia as a result of replacement of the bone marrow with lipid-laden macrophages ("Gaucher cells") (*1,2*). The peripheral spread of the Gaucher cell infiltrate is accompanied by progressive replacement of marrow adipocytes in the axial and appendicular skeleton. Enzyme replacement therapy using placenta-derived (alglucerase) or recombinant (imiglucerase) glucocerebrosidase eliminates most of the clinical manifestations (*3,4*).

We report our experience with reticuloendothelial system (RES) scintigraphy using ^{99m}Tc-sulfur colloid (sulfur chloride)

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