Lack of FDG Uptake in Small Cell Carcinoma Associated with ANNA-1 Positive Paraneoplastic Autonomic Neuropathy

Matthew S. Block, MD, PhD, and Robert Vassallo, MD*†‡*

A 76-year-old smoker presented with profound weight loss due to gastrointestinal dysmotility associated with high levels of the paraneoplastic antibody ANNA-1. Serial computed tomography scans showed regressing subcarinal adenopathy, and positron emission tomography imaging showed mild fluorodeoxy-D-glucose uptake in subcarinal nodes, suggestive of benign disease. Diagnosis of small cell carcinoma was established by biopsy of mediastinal nodes. This case highlights the importance of a thorough search for malignancy in patients with high levels of circulating autoantibodies and suggests that benign-appearing imaging studies be interpreted with caution in patients with paraneoplastic autoimmune syndromes.

Key Words: Small cell cancer, PET, ANNA-1, Paraneoplastic, Autoimmune.

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The diagnosis of small cell carcinoma can only be established by tissue biopsy; however, the decision to proceed to biopsy is generally guided by imaging findings. Small cell carcinoma is an aggressive tumor that characteristically causes avid fluorodeoxy-D-glucose (FDG) uptake on positron emission tomography (PET) scanning. As a result, FDG-PET and PET-computed tomography (CT) are commonly used in the diagnostic workup of lung nodules suspected to be small cell cancer, or in diagnostic staging. In a subgroup of patients with small cell and other cancers, an autoimmune paraneoplastic syndrome may occur, resulting in neurologic manifestations associated with circulating antibodies directed to a variety of host antigens.[1]

Herein, we report a patient who presented with an autonomic gastrointestinal motor neuropathy associated with high levels of circulating type 1 antineuronal nuclear autoantibodies (ANNA-1). Unexpectedly, the chest CT showed subcarinal and mediastinal adenopathy, which partially regressed upon longitudinal follow-up and demonstrated only minimal uptake of FDG on PET scanning, suggesting benign disease rather than malignancy. Definitive diagnosis was established by direct biopsy of subcarinal adenopathy, which demonstrated small cell carcinoma.

*Department of Medicine, Mayo Clinic, †Thoracic Diseases Research Unit, Division of Pulmonary and Critical Care Medicine, and ‡Clinical Immunology and Immunotherapeutics Program, Mayo Clinic, Rochester, Minnesota.

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Address for correspondence: Robert Vassallo, MD, Division of Pulmonary and Critical Care Medicine, Stabile 8-54, 200 First ST SW, Rochester, MN 55905. E-mail: Vassallo.robert@mayo.edu

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CASE REPORT

A 76-year-old man with a 120 pack-year smoking history presented for evaluation of a 55 pound unintentional weight loss over the preceding 13 months. Associated symptoms included dysphagia, diarrhea with fecal incontinence, ataxia, and symptoms of a peripheral neuropathy. Prior workup had included routine laboratory testing, indicative only of mild microcytic anemia; a bone marrow biopsy, an abdominal ultrasound, and a head MRI, each of which were unremarkable. A chest CT obtained 9 months before presentation showed a 9 mm pulmonary nodule and a 2-cm subcarinal (station 7) lymph node. A decision was made to follow up these findings rather than biopsy, and a follow-up scan 6 months before presentation showed stability of the lung nodule and adenopathy.

On arrival at our institution, the patient underwent a body CT scan, which revealed the prominent station-7 lymph node had regressed significantly in size to 1 cm (Figure 1) whereas the previously noted 9-mm pulmonary nodule was unchanged. Further evaluation of the chest CT findings was undertaken with PET-CT, which showed mild FDG uptake in both the pulmonary nodule and at station 7 [maximum SUV 1.4], and was radiographically considered as distinctly unlikely to be malignant (Figure 2). No other foci of high FDG uptake were found. Because of the patient's neurologic symptoms suggestive of autonomic and peripheral neuropathy, testing for paraneoplastic antibodies was done, revealing an ANNA-1 titer of 1:7680 (normal $<$1:240). Based on this finding, mediastinoscopy with biopsy of station-7 lymph nodes was performed, yielding the diagnosis of limited stage small cell carcinoma.

The patient subsequently underwent comprehensive neurologic evaluation, which indicated the presence of autoimmune gastrointestinal dysmotility and peripheral neuropathy. He was treated with multiple courses of intra-

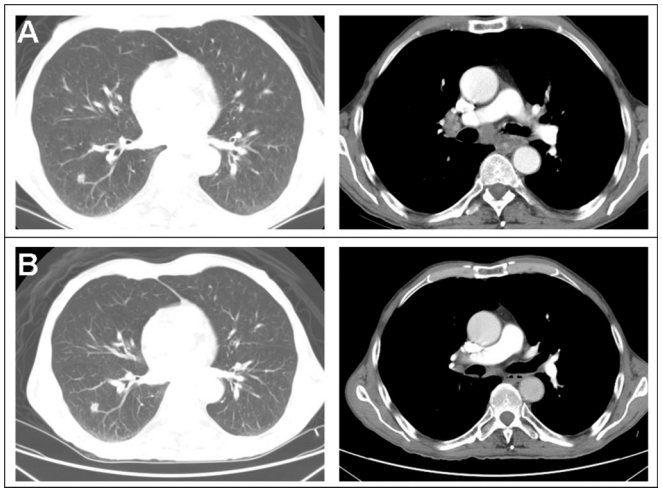

FIGURE 1. *A,* Representative images from the chest computed tomography (CT) performed at the onset of symptoms showing a 9-mm right lower lobe pulmonary nodule and lymphadenopathy in the subcarinal lymph nodes with a maximal diameter of 2 cm. *B,* Chest CT obtained approximately 6 months after the initial CT, demonstrating stability in the right lower lobe nodule and regression of the subcarinal adenopathy.

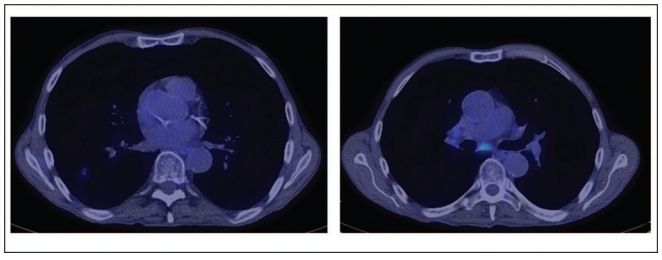

FIGURE 2. Fluorodeoxy-D-glucose-positron emission tomography (FDG-PET) images at the level of the right lower lobe pulmonary nodule (left panel) and the subcarinal region (right panel) demonstrating minimal fluorodeoxy-D-glucose (FDG) accumulation in the subcarinal adenopathy and the nodule (maximal SUV uptake 1.4).

venous immune globulin, chemotherapy consisting of four cycles of carboplatin and etoposide, radiation therapy, and low-dose prednisone. He experienced significant improvement in appetite and diarrhea. His weight increased from 50 to 67 kg. Therapy was also associated with significant improvement in his ataxic gait and peripheral neuropathy. At the most recent follow-up, 2 years since the onset of symptoms, he has no evidence of local small cell cancer progression or metastases.

DISCUSSION

PET scanning in small cell carcinoma is associated with avid FDG uptake,[2] and is considered a very sensitive imaging test in excluding small cell cancer in patients with indeterminate pulmonary nodules greater than 7 mm in size, and/or mediastinal lymphadenopathy. The current case illustrates a potential pitfall with the use of PET imaging in thoracic small cell cancer associated with paraneoplastic syndromes, and illustrates the diagnostic challenge in this unusual subgroup of small cell cancer patients in whom the imaging characteristics may be different from those expected in other cancers, which is not associated with autoimmune phenomena.

Paraneoplastic antibodies are associated with multiple types of cancers. Most paraneoplastic disorders are thought to be mediated by antibodies to "onconeural" antigens—antigens shared by tumors and neural tissues.[3] Although multiple antibodies can coexist and produce varied neurologic syndromes, the antibody ANNA-1 is highly associated with small cell cancer.[1] Type 1 antineuronal nuclear autoantibodies are classically associated with a sensory neuropathy, but various other neuropathic symptoms, including GI dysmotility, are well described.[1,4]

Although most patients with small cell carcinoma present with extensive-stage disease and have an aggressive disease course, our patient presented with limited-stage disease and, to date, has had a relatively indolent clinical course. This is consistent with a previous report that patients with small cell cancer and accompanying paraneoplastic syndromes frequently present with disease confined to the mediastinum.[1] Similarly, no detectable malignancy was found in a significant minority of patients (33 of 200) with anti-ANNA-1 (also known as anti-Hu) autoantibodies.[5] This suggests that paraneoplastic antibodies may exert a beneficial antitumor effect. Consistent with this, a patient with squamous cell lung carcinoma and a paraneoplastic syndrome associated with anti-ANNA-1 autoantibodies experienced a spontaneous complete regression of her cancer.[6] These reports support the hypothesis that in small cell cancer associated with autoimmune phenomena, the production of autoantibodies directed against tumor-associated antigens may result in a beneficial host immune antitumor response.

The diagnosis of small cell carcinoma must be made by tissue biopsy; however, the decision to biopsy is usually guided by chest imaging findings. In the diagnostic evaluation of suspected lung cancer, chest CT and PET provide distinct and complimentary information to the clinician. Experience with the use of PET in lung cancer diagnosis and staging is substantial; however, most studies describing imaging characteristics in lung cancer have focused on non-small cell lung cancer and the imaging characteristics of small cell lung cancer, particularly the subset associated with autoimmune syndromes, is not as well-defined. In one study evaluating PET for primary staging of small cell lung carcinoma, marked accumulation of FDG was detected in the primary tumors of 120 of 120 serial patients (sensitivity 100%).[7] Nevertheless, it does not appear that any of the patients with small cell cancer in that series had paraneoplastic complications. A recent study reported the use of PET and CT as imaging modalities in patients with known paraneoplastic syndromes but unknown primary malignancy.[8] In that case series of 13 patients, FDG-PET alone had a sensitivity of 90% in tumor detection, and the combined sensitivity of PET and CT imaging was 100%. There are some patients with autoimmune paraneoplastic syndromes associated with small

cancer whose imaging studies with body CT and PET will not reveal a potential primary tumor for months and even years after the onset of the paraneoplastic syndrome (unpublished observations). Careful follow-up with serial CT and PET seem to be pertinent in patients with paraneoplastic autoimmune syndromes without evident primary cancer.

Although unique, this case report suggests that the natural biology and radiographic characteristics of small cell lung cancer associated with paraneoplastic autoimmune phenomena is different from other lung carcinomas. Radiographic studies should be interpreted with caution in this specific subgroup of lung cancer, and radiographic characteristics reported to occur in the nonimmunologically active type of lung cancer may not necessarily be extrapolated to patients with paraneoplastic immune small cell cancers. This case was surprising in that neither CT nor PET imaging was suggestive of small cell cancer and diagnosis was only possible by biopsy. In patients with autoimmune paraneoplastic syndromes that are thought to be associated with occult malignancy, imaging studies need to be interpreted with caution.

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