Objective: To evaluate the cancer detection rate of whole-body positron emission tomography–computed tomography (PET-CT) in a paraneoplastic neurologic context.

Design: Retrospective medical record review.

Setting: Mayo Clinic, Rochester, Minnesota.

Patients: Fifty-six consecutive patients with clinically suspected paraneoplastic neurologic disorders who underwent PET-CT after negative standard evaluations, including CT.

Main Outcome Measure: Rate of cancer detection.

Results: Abnormalities suggestive of cancer were detected using PET-CT in 22 patients (39%); 10 patients (18%) had cancer confirmed histologically. Cancers detected (limited stage in 9 of 10 patients and extratruncal in 4) were as follows: 2 thyroid papillary cell carcinomas, 3 solitary lymph nodes with unknown primary (2 adenocarcinomas and 1 small cell carcinoma), 1 tonsil squamous cell carcinoma, 3 lung carcinomas (1 adenocarcinoma, 1 small cell, and 1 squamous cell), and 1 colon adenocarcinoma. Detection of a well-characterized neuronal nuclear or cytoplasmic paraneoplastic autoantibody was associated with a successful PET-CT–directed cancer search (P < .001). Detection of limited-stage cancer facilitated early initiation of oncologic treatments and immunotherapy; cancer remission was reported in 7 patients, and sustained improvements in neurologic symptoms were reported in 5 (median follow-up, 11 months; range, 2-48 months). Combined data from 2 previous studies using conventional PET alone (123 patients) revealed that 28% of patients had a PET abnormality suggestive of cancer and that 12% had a cancer diagnosis.

Conclusion: In a paraneoplastic neurologic context, PET-CT improves the detection of cancers when other screening test results are negative, particularly in the setting of seropositivity for a neuronal nuclear or cytoplasmic autoantibody marker of cancer.

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noma) and PCA-Tr (related to Hodgkin disease) are less common. In the setting of seropositivity for one of those antibodies, routine evaluations for cancer may be unrevealing, leading to consideration of exploratory endoscopy or surgery.

Magnetic resonance imaging (MRI) is useful for evaluating the extent (staging) of a known cancer, including breast and rectal adenocarcinomas, and for distinguishing thymoma from thymic carcinoma. In patients with autoantibodies predictive of small cell lung carcinoma, MRI may be useful where CT findings have been equivocal, but MRI is generally not used as a primary oncologic screening tool.

Positron emission tomography (PET) of the whole body (usually orbits to thighs) seems to be useful in localizing otherwise occult cancers. The use of PET permits the detection of radiolabeled fluodeoxyglucose (FDG) preferentially taken up by highly metabolically active cancers. In selected patients known to be seropositive for a paraneoplastic autoantibody, PET has been reported to have greater sensitivity for cancer than does CT. A sensitivity of 90% for PET was reported in patients with ANNA-1, PCA-1, or PCA-Tr, whereas CT had a sensitivity of just 30%. In that series, sequential CT and PET had a sensitivity of 100% for cancer. Also, PET helps direct the cancer search in unselected patients with suspected paraneoplastic neurologic disorders where CT has been unrevealing. The accuracy of PET can be further enhanced by co-registering metabolic PET abnormalities with anatomical CT abnormalities (PET-CT). To our knowledge, PET-CT has not been systematically evaluated in patients with suspected paraneoplastic neurologic disorders.

Factors that might predict the detection of cancer by means of PET in a paraneoplastic context have not been determined. Herein, we describe the neurologic, radiologic, laboratory, and oncologic findings of Mayo Clinic patients in whom a paraneoplastic neurologic disorder was suspected by a staff neurologist and who underwent whole-body PET-CT to detect a primary cancer because standard oncologic evaluations were unrevealing (2005-2008). We also present a review of the literature pertaining to the use of PET in the oncologic evaluation of patients with paraneoplastic neurologic disorders.

METHODS

PATIENTS

This study was approved by the institutional review board of the Mayo Clinic Rochester, Minnesota. We identified patients with a neurologic syndrome, suspected to be paraneoplastic, who had undergone comprehensive but unrevealing evaluations for cancer before undergoing PET-CT by using the diagnostic term paraneoplastic to search retrospectively in the Mayo Clinic Rochester medical records linkage system (January 1, 2005, to December 31, 2008). By cross-referencing this list with the Mayo Clinic Department of Radiology’s nuclear medicine imaging database, we identified 112 patients for whom whole-body PET-CT was requested to search for cancer. We eliminated from consideration 56 patients who underwent PET-CT for cancer staging. For the included 56 patients, we abstracted from the Mayo Clinic medical record demographic, clinical (neurologic and oncologic), laboratory (serologic and spinal fluid analysis), and radiologic data.

SERA FOR ALL 56 PATIENTS AND CSF FOR 28 PATIENTS WERE EVALUATED IN THE MAYO CLINIC NEUROIMMUNOLOGY LABORATORY USING STANDARDIZED IMMUNOFLUORESCENCE CRITERIA FOR IgG NEURAL NUCLEAR AND CYTOSPASMIC IgG MARKERS OF PARANEOPLASTIC NEUROLOGIC AUTOIMMUNITY (ANNA-1, ANNA-2, ANNA-3, AMPHIPHYSIN ANTIBODY, PCA-1, PCA-2, PCA-Tr, CRMP-5 IgG, AND ANTIGLIAL/NEURAL NUCLEAR AUTOANTIBODY TYPE 1). Rarer neural-specific antibodies identified by means of immunofluorescence but as yet unclassified for antigen specificity or cancer association are also included in these results. Patient sera were tested additionally by using radioimmunoprecipitation assays for neuronal voltage-gated cation channel antibodies (calcium channel [P/Q-type and N-type] and potassium channel [VGKC]), muscle and neuronal ganglioside (α3) nicotinic acetylcholine receptor (AChR) antibodies, and glutamic acid decarboxylase 65-isofrom antibodies; enzyme-linked immunosorbent assay for striatal antibodies; and recombinant Western blot for CRMP-5 IgG.

STATISTICAL METHODS

Associations between PET-CT-directed cancer diagnosis and potential predictors, such as age, sex, smoking status, history of cancer, neurologic presentation, and CSF and serologic findings, were assessed using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables owing to smaller sample sizes (JMP 7.0 software; SAS Institute Inc, Cary, North Carolina). All the tests were 2-sided, and P < .05 was considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS OF PATIENTS UNDERGOING PET-CT

Of 56 included patients, 50% were men. Median age at neurologic symptom onset was 61 years (age range, 22-80 years). Neurologic manifestations were multifocal in 21 patients (38%). The neuroaxis levels affected, in descending frequency, were as follows: cerebral cortex, 36%; cerebellum, 33%; peripheral nerve, 25%; spinal cord, 22%; brainstem, 18%; nerve root, 14%; basal ganglia, 11%; autonomic nervous system, 7%; cranial nerve, 6%; anterior horn cell, 5%; and muscle, 5%.

Twenty-two patients (39%) were current smokers. Ten patients (18%) had a history of cancer (3 breast, 2 tes-
ticular, and 1 each uterine, myeloma, lymphoma, lung, and prostate) that preceded the neurologic presentation by a median of 9 years (range, 2-33 years), and all were in cancer remission clinically and radiologically at neurologic presentation. Ultimately, PET-CT revealed recurrence of a known cancer in 2 of these patients, 1 with prostatic adenocarcinoma and 1 with squamous cell carcinoma of the lung.

LABORATORY FINDINGS

Serum and CSF Evaluation for Paraneoplastic Antibodies

Antibodies with known paraneoplastic significance were detected in the serum of CSF of 39 patients (70%). One or more neural autoantibodies were detected in 38 of 56 patients (68%) using the standard Mayo Clinic serologic evaluation. In addition, Ma1 antibody was identified serologically in 1 patient tested (Athena Diagnostics, Worcester, Massachusetts). The neuronal nuclear or cytoplasmic paraneoplastic autoantibodies detected by means of immunofluorescence in 13 patients (23%) were ANNA-1, 6 patients; PCA-1, 1; PCA-2, 1; CRMP-5 IgG, 1; amphiphysin antibody, 1; and unclassified neuronal nuclear or cytoplasmic antibodies, 3. All except the unclassified antibodies were confirmed by means of Western blot analysis. Seven of these 13 antibodies were identified in serum only, 5 were identified in serum and CSF (ANNA-1, 4; and CRMP-5 IgG, 1), and 1 was identified in CSF only (PCA-1). Seven of these 13 seropositive patients (54%) were ultimately found to have cancer via PET-CT.

One or more additional neuronal or muscle autoantibodies were detected in 22 patients (39%), in descending frequency: α3 AChR, 8; voltage-gated calcium channel, 7 (P/Q-type, 4; and N-type, 3); striational, 6; VGKC, 2; muscle AChR, 1; and Ma1, 1. Also, CRMP-5 IgG was identified using Western blot alone in 7 patients in which findings from immunofluorescence were negative. Three of these 26 patients (12%) were ultimately found to have cancer via PET-CT; both patients seropositive for VGKC antibody had a cancer detected.

Other CSF Findings

Results of standard CSF analyses were available for 43 patients. The CSF was determined to have 1 or more inflammatory markers (elevated leukocyte count, supernumerary oligoclonal bands, and an elevated IgG index, consistent with a paraneoplastic neurologic disorder) in 16 patients (37%).

RADIOLOGIC EVALUATIONS BEFORE PET-CT

Before PET-CT, included patients underwent a median of 3 (range, 1-6) radiologic or endoscopic investigations at Mayo Clinic to look for a primary site of cancer. Investigations included chest CT (54 patients; 52 had negative and 2 had indeterminate findings), abdomen and pelvis CT (49 patients), mammography (15 patients), upper gastrointestinal endoscopy (14 patients), colonoscopy or colonography (14 patients), abdominal ultrasound (6 patients), neck ultrasonography (3 patients), transvaginal ultrasonography of the pelvis (2 patients).

FINDINGS AND OUTCOMES

PET-CT Findings

Whole-body PET-CT was suggestive of cancer in 22 patients (39%) (Table 1); 20 of those patients underwent targeted evaluations (tissue biopsy in 19 and laryngoscopy in 1).

Biopsy Findings

Cancer was confirmed histologically in 10 patients (18%), representing half of all patients with a PET finding suggestive of cancer (Figure). All 10 patients were also seropositive for a paraneoplastic autoantibody (Table 2): 7 had neuronal nuclear or cytoplasmic antibodies identified by means of immunofluorescence and 3 had ion channel antibodies (VGKC, 2; and α3 ganglionic AChR, 1).

Of the 10 identified cancers were limited in stage (Table 2). These cancers included 3 lung carcinomas (1 adenocarcinoma, 1 small cell carcinoma, and 1 squamous cell carcinoma), 3 lymph node carcinoma metastases (2 adenocarcinomas and 1 small cell carcinoma), 2 thyroid carcinomas (both papillary), 1 colon adenocarcinoma, and 1 palpate tonsil squamous cell carcinoma. Of the 3 patients in whom carcinoma was found in lymph nodes, 1 had metastatic prostatic adenocarcinoma, 1 had breast adenocarcinoma discovered after axillary lymph node biopsy, and 1 had small cell carcinoma with no primary identified (despite surveillance for 4 more years). Patients 5 and 7 had indeterminate pulmonary abnormalities that were suggestive of cancer (>1 cm in size) detected by means of CT. These abnormalities were highly suggestive of cancer using the PET-CT criteria and were subsequently confirmed histologically to be carcinoma.

No cancer was detected in 12 patients (55%) who had PET-CT abnormalities suggestive of cancer (Table 1). Two had premalignant lesions: a Hurttle cell adenoma of the thyroid (patient 1) and a tubulovillous adenoma of the colon (patient 11). Biopsy of the paratracheal node revealed noncaseating granulomas suspected to be sarcoidosis (patient 19). Biopsy results were negative in 5 patients, and other PET-directed evaluations without biopsy were negative in 2. No further evaluations were undertaken in 2 patients, 1 of whom died soon after PET-CT.

TREATMENTS AND OUTCOMES

Of the 10 patients who had a histologically confirmed cancer, 7 received cancer-directed therapy and immunotherapy, 2 received cancer-directed therapy alone, and 1 received only immunotherapy (Table 2). Seven of these 10 patients had remission from cancer in the posttreatment surveillance period (median, 11 months; range, 2-48 months). Improvements in neurologic symptoms were reported by their physicians for 5 patients (attributed to combined cancer-directed therapy and immunotherapy).
in 4 patients and to cancer-directed therapy alone in 1). Sustained stabilization of neurologic symptoms after immunotherapy was documented in another 3 patients.

**FACTORS ASSOCIATED WITH PET-CT–DIRECTED CANCER DIAGNOSIS**

The median time from neurologic symptom onset to PET-CT was not different for patients in whom cancer was found (8.5 months; range, 3-12 months) and in whom cancer was not found (9 months; range, 1-168 months). The association of a neuronal nuclear or cytoplasmic paraneoplastic autoantibody detected by means of immunofluorescence and a successful cancer search using PET-CT was significant (P = .001); 7 of 10 patients with cancer (70%) and 6 of 44 patients without cancer (14%) were seropositive. No other statistically significant associations with cancer detection by PET-CT were identified.

**LITERATURE REVIEW**

We identified 4 other studies that evaluated the utility of PET for cancer diagnosis in patients with paraneoplastic neurologic disorders who met the inclusion criteria of the present study (Table 3). Detection of a paraneoplastic autoantibody was an inclusion criterion in 2 of the studies, and clinical suspicion of a paraneoplastic neurologic disorder was an inclusion criterion in 2 studies. The design of both of the latter studies was similar to that of the present study. The combined data for 123 patients from those 2 studies revealed a PET abnormality suggestive of cancer in 34 patients (28%), and a cancer diagnosis was confirmed in 15 of these patients (12%). Of 16 patients in whom 1 or more paraneoplastic antibodies were found, 6 (38%) had a PET-directed cancer diagnosis. The present study is the only study for which PET-CT data are available.

### Table 1. Demographic, Neurologic, Serologic, Radiologic, and Histologic Findings for 22 Patients With Abnormalities Suggestive of Cancer Detected Using PET-CT

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Neurologic Symptom Onset, y</th>
<th>Neurologic Syndrome</th>
<th>Paraneoplastic Antibodies Detected</th>
<th>Region of Abnormal FDG Uptake on PET-CT</th>
<th>Biopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/61</td>
<td>Whole-body tremulousness (myoclonus)</td>
<td>Ma1 Ganglionic AChR, 0.10 nmol/L</td>
<td>Left thyroid lobe</td>
<td>Hurthle cell adenoma of the thyroid</td>
</tr>
<tr>
<td>2/M/27</td>
<td>Limbic and thornbic encephalitis Dementia</td>
<td>VGKC, 0.27 nmol/L</td>
<td>Right thyroid lobe</td>
<td>Papillary carcinoma of the thyroid</td>
</tr>
<tr>
<td>3/M/58</td>
<td>Limbic encephalitis</td>
<td>ANNA-1, 3840^b</td>
<td>Right lung hilum and right anterior lower lung</td>
<td>Non–small cell lung carcinoma</td>
</tr>
<tr>
<td>4/M/61</td>
<td>Cognitive decline, spells</td>
<td>VGKC, 0.27 nmol/L</td>
<td>Right thyroid lobe</td>
<td>Papillary carcinoma of the thyroid</td>
</tr>
<tr>
<td>5/M/58</td>
<td>Limbic encephalitis</td>
<td>ANNA-1, 3840^b</td>
<td>Right lung hilum and right anterior lower lung</td>
<td>Non–small cell lung carcinoma</td>
</tr>
<tr>
<td>6/M/69</td>
<td>Myelopathy</td>
<td>Unclassified neuronal nuclear antibody</td>
<td>Left palatine tonsil</td>
<td>Squamous cell carcinoma of the tonsil</td>
</tr>
<tr>
<td>7/F/59</td>
<td>Cerebellar ataxia</td>
<td>Unclassified neuronal nuclear antibody</td>
<td>Left lower lung subpleural nodule</td>
<td>Adenocarcinoma of the lung</td>
</tr>
<tr>
<td>8/F/80</td>
<td>Myelopathy</td>
<td>Nil</td>
<td>Left thoracic hilar lymph nodes</td>
<td>Normal</td>
</tr>
<tr>
<td>9/M/56</td>
<td>Limbic encephalitis</td>
<td>ANNA-1, 122 880^b</td>
<td>Retropertioneal lymph nodes</td>
<td>Metastatic adenocarcinoma of the prostate</td>
</tr>
<tr>
<td>10/F/51</td>
<td>Multiple cranial neuropathies</td>
<td>ANNA-1, 7680^b</td>
<td>Left cervical lymph node</td>
<td>Small cell lung carcinoma</td>
</tr>
<tr>
<td>11/M/59</td>
<td>Autonomic neuropathy</td>
<td>Striational, 7680^c</td>
<td>Hepatic flexure of the colon</td>
<td>Tubulovillous adenoma</td>
</tr>
<tr>
<td>12/F/52</td>
<td>Lower extremity stiff-limb phenomena</td>
<td>Amphiphysin, 3840^b</td>
<td>Left axillary lymph node</td>
<td>Adenocarcinoma of the breast</td>
</tr>
<tr>
<td>13/M/70</td>
<td>Muscle cramps, limbic encephalitis</td>
<td>VGKC, 4.34 nmol/L^c; α3 AChR, 0.10 nmol/L^d</td>
<td>Sigmoid colon</td>
<td>Adenocarcinoma of the colon</td>
</tr>
<tr>
<td>14/M/65</td>
<td>Myeloneuropathy</td>
<td>CRMP-5 IgG, 30 720^b</td>
<td>Right thoracic hilar lymph nodes</td>
<td>Normal</td>
</tr>
<tr>
<td>15/F/79</td>
<td>Peripheral neuropathy</td>
<td>Nil</td>
<td>Left upper lobe of the lung</td>
<td>Normal</td>
</tr>
<tr>
<td>16/M/60</td>
<td>Cerebellar ataxia</td>
<td>Striational, 61 440^c</td>
<td>Lower esophagus</td>
<td>Normal</td>
</tr>
<tr>
<td>17/M/4</td>
<td>Chorea, dementia, dysautonomia</td>
<td>Nil</td>
<td>Cecum</td>
<td>Normal</td>
</tr>
<tr>
<td>18/F/66</td>
<td>Peripheral neuropathy</td>
<td>ANNA-1, 122 880^b</td>
<td>Right upper lobe nodule</td>
<td>Normal</td>
</tr>
<tr>
<td>19/F/71</td>
<td>Myopathy</td>
<td>Nil</td>
<td>Right paratracheal lymph nodes</td>
<td>Noncaseating granulomas</td>
</tr>
<tr>
<td>20/M/54</td>
<td>Cerebellar ataxia</td>
<td>Nil</td>
<td>Right axillary lymph node</td>
<td>Normal</td>
</tr>
<tr>
<td>21/F/79</td>
<td>Ataxia, dementia, peripheral neuropathy</td>
<td>ANNA-1, 3840^b</td>
<td>Left lung hilum</td>
<td>Not performed</td>
</tr>
<tr>
<td>22/F/56</td>
<td>Myelopathy</td>
<td>Nil</td>
<td>Multiple foci of hypermetabolism</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

Abbreviations: AChR, acetylcholine receptor; ANNA-1, antineuronal nuclear autoantibody type 1; CRMP-5, collapsin response-mediator protein 5; ENT, ears, nose, throat; FDG, fludeoxyglucose; PET-CT, positron emission tomography–computed tomography; VGKC, voltage-gated potassium channel.

^a Reference range, 0.03 nmol/L or less (serum).

^b Reference range, end-point dilution less than 240 (serum).

^c Reference range, end-point dilution less than 60 (serum).
The use of PET-CT increased the diagnostic yield for cancer by 18% in patients with suspected paraneoplastic neurologic disorders for whom results of standard oncologic tests were negative. Data from other reported studies using similar methods revealed that 15 of 123 patients (12%) with a suspected paraneoplastic neurologic disorder had a PET-directed cancer diagnosis. The difference in diagnostic yield for cancer between the present study and previously reported studies may be explained by the larger number of patients available for follow-up in the present study or possibly by the enhanced sensitivity of PET-CT over PET alone.

Detection of a well-characterized neuronal nuclear or cytoplasmic antibody in paraneoplastic serologic or CSF evaluation was strongly associated with a PET-directed cancer diagnosis; 56% of seropositive patients had cancer (3 had ANNA-1; 2 had unclassified neuronal nuclear or cytoplasmic antibodies; 1 had CRMP-5 IgG, and 1 had amphiphysin antibody). Cation channel autoantibodies do not have as strong an association with cancer but are instructive in some patients. Cancer was found in both patients in whom VGKC antibodies were detected (1 thyroid papillary and 1 colon adenocarcinoma). Tan et al recently reported a 33% frequency of cancer detection in patients with VGKC antibodies, with notable inclusion of colon and thyroid cancers. It is instructive that patient 3 had a cancer associated with ganglionic AChR antibody seropositivity (papillary carcinoma of thyroid).

The cancer screening investigation most commonly acquired before PET-CT was CT of the chest, abdomen, and pelvis. However, 4 of the 10 detected cancers using PET-CT were outside the anatomical scope of CT of the chest, abdomen, and pelvis (thyroid, 2; cervical lymph node, 1; and palatine tonsil, 1). The other 6 detected cancers were too small to be detected by appropriate regional CT (lung, 4; axillary lymph node, 1; and colon, 1). Clearly, CT alone is not sufficient to exclude cancer in cases with a high index of suspicion for cancer. Lucchinetti et al reported that initial screening with CT is unrevealing in 60% of patients with ANNA-1, but cancer is detected in 90% of those patients when evaluation is more extensive or is repeated. In the present study, PET-CT enabled the detection and precise anatomical localization of metabolic abnormalities suggesting cancer in 22 patients, for whom further evaluations led to cancer diagnoses in 10 (45%).

In patient 7, PET-CT was critical in determining the oncologic significance of a subpleural pulmonary nodule initially detected using CT. Veronesi et al reported that PET-CT had 88% sensitivity and 93% specificity for cancer in patients with progressive pulmonary nodules exceeding 8 mm. In patient 9, who was seropositive for ANNA-1, recurrent metastatic prostatic adenocarcinoma was detected, although a coexisting occult small cell carcinoma was suspected before biopsy. A previous diagnosis of prostatic adenocarcinoma is obtained in 39% of patients with small cell carcinoma of the prostate, which is a rare entity.

Follow-up of neurologic symptoms and cancers in the 10 patients herein was short (median, 11 months). Oncologic treatment initiated by the detection of cancer at an early stage using PET-CT was associated with remission in 7 of the 10 patients. Nine of 10 patients improved or stabilized neurologically after oncologic treatment or immunotherapy. Neurologic symptoms resolved in both patients with VGKC antibodies after surgical resection of a thyroid cancer (patient 4) or a colon cancer (plus immunotherapy in patient 13).

We recognize several limitations of this study: the retrospective design, the relatively small sample size, the exclusion of patients who had negative findings on standard evaluations but did not undergo PET-CT at Mayo Clinic, and selection bias for patients with detectable neural autoantibodies. Some patients may have had PET-CT after leaving Mayo Clinic, and others may have been de-
nied the test on financial grounds. Also, patients were systematically tested only for autoantibodies routinely available in the Mayo Clinic paraneoplastic evaluation, which does not include testing for Ma/Ta and N-methyl-D-aspartate receptor autoantibodies. Because seropositivity for a paraneoplastic autoantibody and clinical suspicion for a paraneoplastic neurologic disorder (and, hence, ordering a PET-CT) are inextricably linked, not

Table 2. Neurologic, Serologic, Oncologic, Treatment, and Outcome Data for 10 Patients With Cancer Detected Using PET-CT

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Syndrome</th>
<th>Paraneoplastic Autoantibody</th>
<th>Neoplasm</th>
<th>Surgical Resection</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Immunotherapy</th>
<th>Change in Disability With Treatment</th>
<th>Cancer in Remission at Last Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Cognitive decline</td>
<td>α3 AChR</td>
<td>Papillary carcinoma of the thyroid</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Nil</td>
<td>No further deterioration</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Cognitive problems, spells</td>
<td>VGKC</td>
<td>Papillary carcinoma of the thyroid</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Nil</td>
<td>Cognitive problems and spells resolved</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Limbic encephalitis, dysautonomia</td>
<td>ANNA-1</td>
<td>Squamous cell carcinoma of the lung</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>PLEX, corticosteroids, Cyc</td>
<td>From walking with a walker to walking with a cane</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Myelopathy</td>
<td>Unclassified</td>
<td>Squamous cell carcinoma of the palate tonsil</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Corticosteroids</td>
<td>Continued to deteriorate</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Cerebellar ataxia</td>
<td>Unclassified</td>
<td>Adenocarcinoma of the lung</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>IVIg</td>
<td>No further deterioration</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Limbic encephalitis</td>
<td>ANNA-1</td>
<td>Metastatic adenocarcinoma of the prostate to retroperitoneal lymph nodes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Azathioprine</td>
<td>No further deterioration</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>Dystonia, brainstem encephalitis, cranial neuropathies</td>
<td>ANNA-1</td>
<td>Small cell carcinoma (cervical node only)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Corticosteroids, Cyc</td>
<td>From wheelchair bound to walking with a cane</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>Stiff-man phenomena</td>
<td>Amphiphysin</td>
<td>Adenocarcinoma of the breast, with axillary lymph node invasion</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Cognitive problems resolved</td>
<td>No further deterioration</td>
<td>24</td>
</tr>
<tr>
<td>11</td>
<td>Limbic encephalitis</td>
<td>VGKC</td>
<td>Adenocarcinoma of the colon</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Cognitive problems resolved</td>
<td>No further deterioration</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>Myelopathy</td>
<td>CRMP-5 IgG</td>
<td>Small cell carcinoma of the lung</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Cognitive problems resolved</td>
<td>No further deterioration</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: AChR, acetylcholine receptor; ANNA-1, antineuronal nuclear autoantibody type 1; CRMP-5, collapsin response-mediator protein 5; Cyc, cyclophosphamide; IVIg, intravenous pooled human immunoglobulin; PET-CT, positron emission tomography–computed tomography; PLEX, plasma exchange; VGKC, voltage-gated potassium channel.

Table 3. Studies Examining the Utility of PET in the Detection of Cancer in Patients With Suspected Paraneoplastic Neurologic Disorders

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Characteristic</th>
<th>Underwent PET</th>
<th>With Paraneoplastic Antibody</th>
<th>With Previous Negative Oncologic Evaluations</th>
<th>With PET Abnormality</th>
<th>With Cancer Detected</th>
<th>With Cancer and Paraneoplastic Antibody</th>
<th>With PET Abnormality Without Follow-up</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rees et al,21 2001</td>
<td>Clinically suspected</td>
<td>43</td>
<td>9 (21)</td>
<td>43 (100)</td>
<td>16 (37)</td>
<td>7 (16)</td>
<td>3 (33)</td>
<td>4 (25)</td>
<td>48</td>
</tr>
<tr>
<td>Linke et al,19 2004</td>
<td>Paraneoplastic antibody positive</td>
<td>13</td>
<td>13 (100)</td>
<td>0</td>
<td>10 (77)</td>
<td>9 (69)</td>
<td>9 (69)</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Younes-Mhenni et al,18 2004</td>
<td>Paraneoplastic antibody positive</td>
<td>20</td>
<td>20 (100)</td>
<td>18 (90)</td>
<td>14 (70)</td>
<td>14 (70)</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hadjivassiliou et al,24 2009</td>
<td>Clinically suspected</td>
<td>56</td>
<td>39 (70)</td>
<td>56 (100)</td>
<td>22 (39)</td>
<td>10 (18)</td>
<td>10 (26)</td>
<td>2 (9)</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviation: PET, positron emission tomography.

a Studies with similar methods included in the analysis.

b Study with PET–computed tomography data available.
testing for 1 or more known autoantibodies inevitably leads to ascertainment bias. The inclusion of 2 patients with indeterminate findings on chest CT, both of whom were later determined to have cancer after PET-CT and biopsy, contributed to the 18% diagnostic yield.

To our knowledge, PET-CT has not been evaluated as a primary oncologic screening modality in a paraneoplastic context. The latter approach has potential advantages and limitations. It is acknowledged that PET is more sensitive than CT for many neoplasms, including cancers of the head and neck, lung, breast, pancreas, bile duct, stomach, colon, and uterus. However, endoscopy remains the optimal screening test for esophageal, stomach, and colon cancers; for pancreatic carcinomas, PET and endoscopic ultrasonography are equally sensitive. Other imaging modalities are superior to PET for detecting primary prostate carcinoma (MRI and transrectal ultrasonography) and testicular cancers (CT and ultrasonography). Alone, PET is suboptimal for the detection of bladder and kidney cancers owing to high levels of physiologic FDG uptake by those organs. Testes and ovaries may also have physiologically elevated FDG uptake on PET-CT in this series; other causes of increased FDG uptake seen on PET is not specific for cancer in all cases, as observed in 10 of 20 patients further evaluated after PET-CT in this series; other causes of increased FDG uptake by tissues include premalignant lesions and inflammatory and infectious disorders.

Recognizing the limitations of PET-CT, we favor this modality for initial oncologic evaluation of patients in whom a paraneoplastic neurologic disorder is strongly suspected. Serum autoantibody profiles and familial risk factors for cancer help guide tests for cancers for which there is poor resolution on PET-CT (eg, pelvic ultrasound for ovarian teratomas). Elimination of whole-body imaging with CT alone before further imaging with PET-CT could reduce radiation exposure and the total financial burden of testing.

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Analysis and interpretation of data: McKeon, Lennon, Mandrekar, Mullan, Mokri, and Pittcock.

Drafting of the manuscript: McKeon.

Critical revision of the manuscript for important intellectual content: Apiwattanakul, Lachance, Lennon, Mandrekar, Boeve, Mullan, Mokri, Britton, Drubach, and Pittcock.

Statistical analysis: Mandrekar.

Administrative, technical, and material support: Lennon.

Study supervision: Pittcock.

Financial Disclosure: Dr Lennon stands to receive royalties for commercial assays to detect aquaporin-4–specific autoantibodies. The intellectual property is licensed to a commercial entity for the development of a single, antigen-specific assay, to be made available worldwide for patient care. The test will not be exclusive to the Mayo Clinic. Until now, Dr Lennon has received less than $10,000 in royalties. None of the authors receive royalties from the sale of antibody testing performed in the Mayo Clinic. However, Mayo Collaborative Services Inc does receive revenue for conducting these tests.

Previous Presentation: This study was presented in part at the American Academy of Neurology Annual Meeting, April 29, 2009, Seattle, Washington.

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