Positron Emission Tomography–Computed Tomography in Paraneoplastic Neurologic Disorders

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NEUROLOGY

ORIGINAL CONTRIBUTION

Positron Emission Tomography–Computed Tomography in Paraneoplastic Neurologic Disorders

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Systematic Analysis and Review

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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.

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

Structure of JC

- Background – who and where study was done
- Brief synopsis of study – how they did it and what they concluded from it
- Methods, Results with *critique*
- Discussion
- Things which can been done differently
- Applicability to our practice of medicine.

Basic info…

- Journal:
  Arch Neurol. 2010, January 11, 2010 (Published online)
  ARCH NEUROL/VOL 67 (NO. 3), MAR 2010 (Published hard copy)
- Authors:
  - Departments of Neurology (Drs McKeon, Lachance, Lennon (*Vanda A. Lennon, M.D., Ph.D.*), Boeve, Mokri, Britton, Drubach, and Pittock),
  - Laboratory Medicine and Pathology (Drs McKeon, Apiwattanakul, Lachance,Lennon, and Pittock),
  - Immunology (Dr Lennon),
  - Biostatistics (Dr Mandrekar),
  - Radiology (Dr Mullan).
- Site: Mayo Clinic, Rochester, Minnesota.
- Study period: 2005 – 2008.
- Sample Size: 56 consecutive patients.
- Design: Retrospective medical record review.
- Main Outcome Measure: Rate of cancer detection.
- Some places PND – Paraneoplastic Neurological Disorders, term has been used.

Study in nut shell

- They took Mayo clinic nuclear medicine/radiology database – search term "paraneoplastic" – finally studied 56 pt's hospital records who were suspected to have paraneoplastic neurological disorder. Tried to decide usefulness of PET/CT in detecting primary tumor in paraneoplastic neurologic disorders.

Paraneoplastic Neurologic Disorders

- Probably, best known paraneoplastic syndrome is –

- Definition: A paraneoplastic syndrome is the consequence of the presence of cancer in the body, but is not due to the local presence or metastasis of cancer cells. These phenomena are mediated by an immune response against the tumor cells. "Onconeuro antigens"
- Limitations of this definition.
- Typical work up of suspected paranoplastic syndrome to look for primary –
  - physical examination;
  - computed tomography (CT) of the chest, abdomen, and pelvis;
  - mammography in women;
  - testicular ultrasonography,
  - prostate-specific antigen testing in men and
  - autopsy.

Paraneoplastic neurological syndromes	Frequency of paraneopl -astic origin	Main associated tumors	Main frequent associated paraneoplastic antibodies
LEMS	60%	SCLC	VGCC-Ab*
Subacute cerebellar ataxia	50%	Ovary, breast SCLC Hodgkin's disease Others	Yo-Ab (PCA1-Ab**) Hu-Ab (ANNA1-Ab**) CV2-Ab (CRMP5-Ab**) Tr-Ab Ma-Ab (Ta-Ab**)
Opsomyoclonus	20%	Neuroblastoma Breast, lung	Hu-Ab (ANNA1-Ab**) Ri-Ab (ANNA2-Ab**)
Sensory neuronopathy	20%	SCLC	Hu-Ab (ANNA1-Ab**) CV2-Ab (CRMP5-Ab**)
Limbic encephalitis	20%	SCLC Testicular SCLC	Hu-Ab (ANNA1-Ab**) CV2-Ab (CRMP5-Ab**) Ma2-Ab (Ta-Ab**) Amphiphysin-Ab
Encephalomyelitis	10%	SCLC Others	Hu-Ab (ANNA1-Ab**) CV2-Ab (CRMP5-Ab**) Amphiphysin-Ab Ma2-Ab (Ta-Ab**)

Orphanet J Rare Dis. 2007; 2: 22.

Antibodies	Main associated neurological syndromes	Cancer
Hu-Ab (ANNA1-Ab**)	Sensory neuronopathy Encephalomyelitis Chronic gastrointestinal pseudoobstruction Cerebellar ataxia Limbic encephalitis	SCLC
Yo-Ab (PCA1-Ab**)	Subacute cerebellar ataxia	Ovary, breast, uterus
CV2-Ab (CRMP5-Ab**)	Cerebellar ataxia Sensory-motor neuropathy Uveitis, retinopathy Encephalomyelitis	SCLC, thymoma
Ri-Ab (ANNA2-Ab**)	Opsomyoclonus Cerebellar ataxia	Breast, SCLC
Amphiphysin-Ab	Stiff-person syndrome Sensory neuronopathy Encephalomyelitis	Breast, SCLC
Tr-Ab	Cerebellar ataxia	Hodgkin's disease
Ma2-Ab (Ta-Ab**)	Limbic encephalitis	Testicular
CAR-Ab	Retinopathy	Breast, SCLC

Orphanet J Rare Dis. 2007; 2: 22.

Methods - Patients

- Mayo Clinic Rochester medical records linkage system – search term "paranoplastic" looking for … from 1-1'05 to 12-31-'08
- Cross referenced with Department of Radiology's nuclear medicine imaging database – found 112 pts *(Critique – sampling bias – what if CT CAP found primary)*
- 56 – for cancer staging, 56 – for PND

Methods - Paraneoplastic Serological & CSF Evaluation

- 56/56 sera and 28/56 CSF were available
- Tests:
  - Common test: IgG neuronal nuclear and cytoplasmic markers of PND *(Critique: is glia specific Ab are next holy grail?)*
  - Rare neural-specific antibodies were looked for
  - Neuronal voltage-gated cation channel antibodies
  - striational antibodies & CRMP-5 IgG.

Methods – Statistical Methods

- Associations between PET/CT to potential predictors: e.g. age, sex, smoking status, history of cancer, neurologic presentation, and CSF and serologic findings
- Categorical variables - Fisher exact test & Continuous variables - Wilcoxon rank sum test
- Statistical software used: JMP 7.0 software; SAS Institute Inc, Cary, North Carolina.
- All the tests were 2-sided, and $P < .05$ was considered statistically significant.

Methods – Review of the literature

- PubMed search term "*positron emission tomography* + *paraneoplastic.*"
- They included all studies (excluding single case reports) that assessed PET in the oncologic evaluation of suspected PND and similar data. *(Critique: search term PET-CT)*

Results - Clinical Characteristics of patients undergoing PET-CT

- Median age of symptom onset 61 (range 22-80)
- 23/56 (50%) were male
- 22/56 (39%) were current smokers
- 10/56 (18%) had h/o cancer – median cancer free period before neurolgical sympmtoms 9 years (2-33 years) *Critique: higher dignostic yield due to more # of pts with h/o cancer?*
- PET-CT discovered recurrence of cancer in 2/10 (20%) patients

Results - Clinical Characteristics of patients undergoing PET-CT

- Neuraxis level affected:
  - 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%.
  - 21/56 (38%) had multifocal manifestations

Results – Laboratory Findings

Serum and CSF Evaluation for Paraneoplastic Antibodies

- 39/56 (70%) pt. had paraneoplastic Ab with known significance
- 38/39 at Mayo and 1/39 at Athena
- 13/56 (23%) neuronal nuclear or cytoplasmic paraneoplastic autoantibodies
  - 7/13 serum only, 1/13 CSF only, 5/13 serum+CSF
  - 7/13 (54%) were found to have cancer with PET-CT
- 22/56 (39%) neuronal or muscle autoantibodies
- 3/26 (12%) were found to have cancer with PET-CT – Note 2 of these pts were positive for VGKC. *Critique: How they come up with denominator of 26?*

Results – Laboratory Findings
Other CSF Findings

- 16/43 (37%) pt. had 1 or more inflammatory markers
  - elevated leukocyte count,
  - supernumerary oligoclonal bands,
  - elevated IgG index
  - *Critique: no mention of increased protein?*

Results – Radiological Evaluations Before PET-CT

- Pt. underwent median of 3 investigations (1-6)
- 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), and
  - Transvaginal ultrasonography of the pelvis (2 patients).

Result – Findings & Outcomes PET-CT Findings

- 22/56 (39%) Whole-body PET-CT was suggestive of cancer.
- 20/22 underwent target evaluation

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

Patient No./Sex/ Age at Neurologic Symptom Onset, y	Neurologic Syndrome	Paraneoplastic Antibodies Detected	Region of Abnormal FDG Uptake on PET-CT	Biopsy Findings
1/F/61	Whole-body tremulousness (myoclonus)	Nil	Left thyroid lobe	Hurthle cell adenoma of the thyroid
2/M/27	Limbic and rhombic encephalitis	Ma1	Left hyoid bone	ENT examination negative
3/M/58	Dementia	Ganglionic AChR, 0.10 nmol/L[a]	Superior right thyroid lobe	Papillary carcinoma of the thyroid
4/M/61	Cognitive decline, spells	VGKC, 0.27 nmol/L[a]	Right thyroid lobe	Papillary carcinoma of the thyroid
5/M/58	Limbic encephalitis	ANNA-1, 3840[b]	Right lung hilum and right anterior lower lung	Non–small cell lung carcinoma
6/M/69	Myelopathy	Unclassified neuronal nuclear antibody	Left palatine tonsil	Squamous cell carcinoma of the tonsil
7/F/59	Cerebellar ataxia	Unclassified neuronal nuclear antibody	Left lower lung subpleural nodule	Adenocarcinoma of the lung

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.

aReference range, 0.03 nmol/L or less (serum).

bReference range, end-point dilution less than 240 (serum).

cReference range, end-point dilution less than 60 (serum).

Patient No./Sex/ Age at Neurologic Symptom Onset, y	Neurologic Syndrome	Paraneoplastic Antibodies Detected	Region of Abnormal FDG Uptake on PET-CT	Biopsy Findings
8/F/80	Myelopathy	Nil	Right thoracic hilar lymph nodes	Normal
9/M/56	Limbic encephalitis	ANNA-1, 122 880[b]	Retroperitoneal lymph nodes	Metastatic adenocarcinoma of the prostate
10/F/51	Multiple cranial neuropathies	ANNA-1, 7680[b]	Left cervical lymph node	Small cell lung carcinoma
11/M/59	Autonomic neuropathy	Striational, 7680[c]	Hepatic flexure of the colon	Tubulovillous adenoma
12/F/52	Lower extremity stiff-limb phenomena	Amphiphysin, 3840[b]	Left axillary lymph node	Adenocarcinoma of the breast
13/M/70	Muscle cramps, limbic encephalitis	VGKC, 4.34 nmol/L[a]; α3 AChR, 0.10 nmol/L[a]	Sigmoid colon	Adenocarcinoma of the colon
14/M/65	Myeloneuropathy	CRMP-5 IgG, 30 720[b]	Right thoracic hilar lymph nodes	Small cell lung carcinoma

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.
aReference range, 0.03 nmol/L or less (serum).
bReference range, end-point dilution less than 240 (serum).
cReference range, end-point dilution less than 60 (serum).

Patient No./Sex/ Age at Neurologic Symptom Onset, y	Neurologic Syndrome	Paraneoplastic Antibodies Detected	Region of Abnormal FDG Uptake on PET-CT	Biopsy Findings
15/F/79	Peripheral neuropathy	Nil	Left upper lobe of the lung	Normal
16/M/60	Cerebellar ataxia	Striational, 61 440[c]	Lower esophagus	Normal
17/F/74	Chorea, dementia, dysautonomia	Nil	Cecum	Normal
18/F/66	Peripheral neuropathy	ANNA-1, 122 880[b]	Right upper lobe nodule	Normal
19/F/71	Myopathy	Nil	Right paratracheal lymph nodes	Noncaseating granulomas
20/M/54	Cerebellar ataxia	Nil	Right axillary lymph node	Normal
21/F/79	Ataxia, dementia, peripheral neuropathy	ANNA-1, 3840[b]	Left lung hilum	Not performed
22/F/56	Myelopathy	Nil	Multiple foci of hypermetabolism	Not performed

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.

aReference range, 0.03 nmol/L or less (serum).

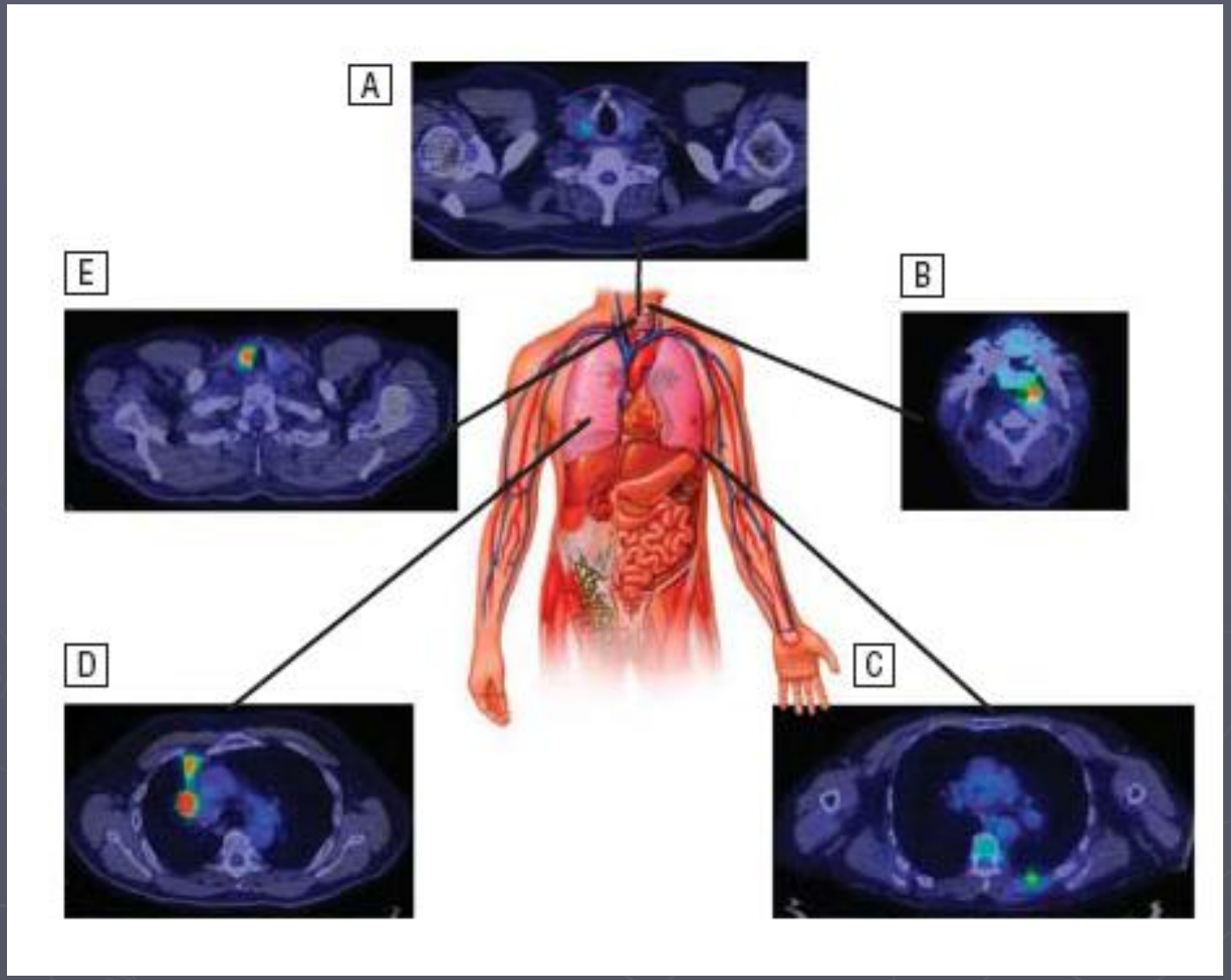
bReference range, end-point dilution less than 240 (serum).

cReference range, end-point dilution less than 60 (serum).

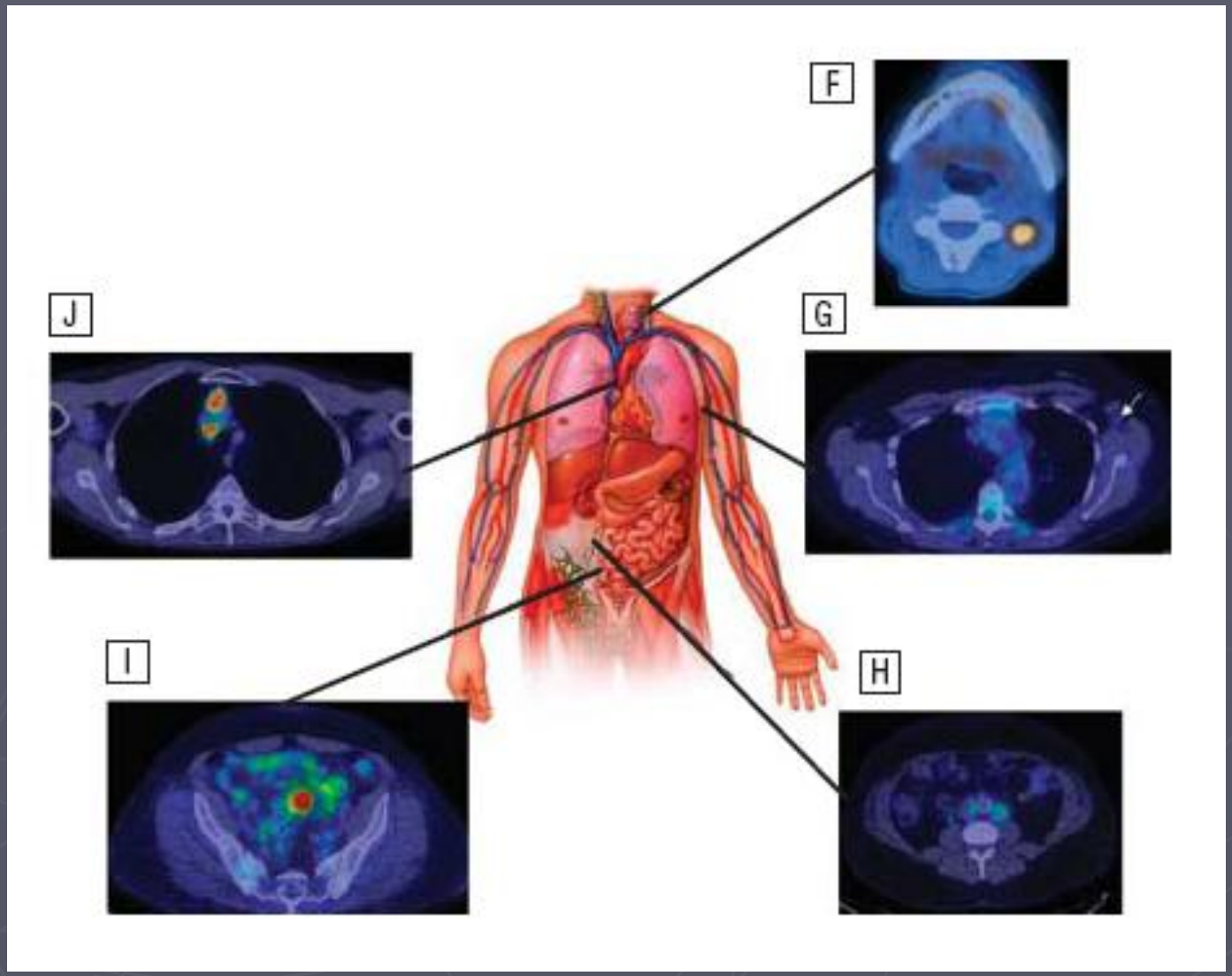
Result – Biopsy Findings

- 10/56 (18%) cancer confirmed histologically {10/20 whoes PET-CT was positive}
- All 10 were seropositive for paraneoplastic Ab

BORING
We need a break



A, Patient 4: right thyroid lobe (papillary cell carcinoma).
B, Patient 6: left palatine tonsil (squamous cell carcinoma).
C, Patient 7: lower left subpleural nodule (adenocarcinoma).
D, Patient 5: right lung hilum and anterior right lower lung (non–small cell carcinoma).
E, Patient 3: superior right thyroid lobe (papillary carcinoma).



F, Patient 10: left cervical node (small cell carcinoma).
G, Patient 12: left axillary node (arrow, adenocarcinoma of the breast).
H, Patient 9: retroperitoneal nodes (prostatic adenocarcinoma).
I, Patient 13: sigmoid colon (adenocarcinoma of the colon).
J, Patient 14: right thoracic hilar nodes (small cell carcinoma).

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

Patient No.	Syndrome	Paraneoplastic Autoantibody	Neoplasm	Surgical Resection	Radiotherapy	Chemotherapy	Immunotherapy	Change in Disability With Treatment	Follow-up, mo	Cancer in Remission at Last Follow-up
3	Cognitive decline	α3 AChR	Papillary carcinoma of the thyroid	Yes	No	No	Nil	No further deterioration	10	Yes
4	Cognitive problems, spells	VGKC	Papillary carcinoma of the thyroid	Yes	No	No	Nil	Cognitive problems and spells resolved	7	Yes
5	Limbic encephalitis, dysautonomia	ANNA-1	Squamous cell carcinoma of the lung	No	Yes	Yes	PLEX, corticosteroids, Cyc	Limbic encephalitis resolved, mild dysautonomia persisted	40	Yes
6	Myelopathy	Unclassified	Squamous cell carcinoma of the palatine tonsil	Yes	No	No	Corticosteroids	From walking with a walker to walking with a cane	6	Yes
7	Cerebellar ataxia	Unclassified	Adenocarcinoma of the lung	Yes	Yes	No	IVIg	Continued to deteriorate	2	No

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.

			of the lung					deteriorate		
9	Limbic encephalitis	ANNA-1	Metastatic adenocarcinoma of the prostate to retroperitoneal lymph nodes	No	No	Yes	IVIg, corticosteroids, Cyc	No further deterioration	3	No
10	Dystonia, brainstem encephalitis, cranial neuropathies	ANNA-1	Small cell carcinoma (cervical node only)	No	No	Yes	Azathioprine	No further deterioration	48	Yes
12	Stiff-man phenomena	Amphiphysin	Adenocarcinoma of the breast, with axillary lymph node invasion	Yes	No	Yes	Corticosteroids, Cyc	From wheelchair bound to walking with a cane	12	Yes
13	Limbic encephalitis	VGKC	Adenocarcinoma of the colon	Yes	No	No	Corticosteroids, mycophenolate	Cognitive problems resolved	12	Yes
14	Myelopathy	CRMP-5 IgG	Small cell carcinoma of the lung	No	No	No	Corticosteroids, mycophenolate	No further deterioration	24	Unknown

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.

Results – Treatments & Outcomes

- 10 pt with histologically confirmed cancer
  - 7 cancer-directed therapy and immunotherapy
  - 2 cancer-directed therapy
  - 1 immunotherapy
- 7/10 had remission from cancer in the post treatment surveillance period (median, 11 months; range, 2-48 months)
- Neurological symptoms
  - 5/10 improved
  - 3/10 stabilized

Literature Review

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

Source	Patient Characteristic	Patients, No. (%)						
		Underwent PET	With Paraneoplastic Antibody	With Previous Negative Oncologic Evaluations	With PET Abnormality	With Cancer Detected	With Cancer and Paraneoplastic Antibody	With PET Abnormality Without Follow-up
Rees et al,[21] 2001[a]	Clinically suspected	43	9 (21)	43 (100)	16 (37)	7 (16)	3 (33)	4 (25)
Linke et al,[19] 2004	Paraneoplastic antibody positive	13	13 (100)	0	10 (77)	9 (69)	9 (69)	0
Younes-Mhenni et al,[18] 2004	Paraneoplastic antibody positive	20	20 (100)	20 (100)	18 (90)	14 (70)	14 (70)	0
Hadjivassiliou et al,[20] 2009[a]	Clinically suspected	80	7 (9)	80 (100)	18 (23)	8 (10)	3 (43)	7 (39)
Present study, 2009[a,b]	Clinically suspected	56	39 (70)	56 (100)	22 (39)	10 (18)	10 (26)	2 (9)

The combined data for 123 patients from those 2 studies revealed

- 34/123 (28%) PET abnormality suggestive of cancer
- 15/123 (12%) cancer diagnosis was confirmed

Critique: why they chose study 1 and 4

Conclusions

- PET-CT Vs CT – Chest, Abdoman, Pelvis:
  - 4/10 cancers were out side the limits of CT CAP
  - 6/10 cancers were too small to be detected by CT CAP
- Diagnostic yield:
  - PET-CT – 10/56 (18%)
  - PET – 15/123 (12%)

  Critique: authors attributed this to PET-CT being more sensitive imaging modality over PET alone.
- Neuronal nuclear or cytoplasmic antibody - strongly associated with a PET-directed cancer diagnosis
- Cation channel autoantibodies (except VGKC) do not have as strong an association with cancer

Limitations

- Retrospective design,
- Relatively small sample size,
- Exclusion of patients who had negative findings on standard evaluations but did not undergo PET-CT at Mayo Clinic,
- Selection bias for patients with detectable neural autoantibodies.
- Some patients may have had PET-CT after leaving Mayo Clinic, and others may have been denied the test on financial grounds.
- At Mayo Clinic paraneoplastic evaluation does not include testing for Ma/Ta and *N*-methyl-D-aspartate receptor autoantibodies.
- Ascertainment bias, Caveman effect
- 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 increase diagnostic yield from 14 to 18%
- Increased FDG uptake is also seen in premalignant lesions and inflammatory and infectious disorders.

Things which can been done differently

- Radiologist can give out 2 reports
  - PET – findings and conclusions
  - PET/CT – findings and conclusion
- MCG needs medical record system with "advanced search" feature. E.g. …
- Journals should require authors to provide master table as supplement.

Applicability in our practice?

- Whom to refer my patient with confusing neurological problem? – good general neurologist Vs super subspecialized (Paraneoplasticologist/Otoneurologist)
- Paraneoplastic Antibody Evaluation: Mayo Clinic, Athena Diagnostics
  - Serum – 4 ml refrigerated, time 10 days – negative test, 17 days – positive test, cost around $ 1000
  - CSF – 4 ml refrigerated, time 3 days – negative test, 5 days – positive test, cost around $ 1000
- PET-CT (Philips – 64 slice, wt. limit 300-350 lb) is available at MCG nuclear medicine section, Phone # 1-2867. Note pt. needs to be NPO 4 hrs before study. Cost > $ 3000
- Fill out this form for PET/CT at MCG.
- ALWAYS SEND CLINICAL INFORMATION, contact info – mailing address and e-mail address.

References:

- Like all disease there is a "International Paraneoplastic Association" : www.paraneoplastic.org
- *Continuum*, Paraneoplastic Disorders, December 1999, Volume 5, Issue 6
- Mayo Clinic Lab website: http://www.mayomedicallaboratories.com/test-catalog/Overview/80013