Positron Emission Tomography Scanning and the Management of the Unknown Primary and Malignant Melanoma

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Case Presentation
Patient W.W.

- In August 1997, a 66 year old African-American man presented to an otolaryngologist with a right neck mass
- Patient quit smoking 20 yrs prior to presentation
- History of complete heart black s/p pacemaker

Initial Evaluation

- Large 3 cm right jugulodigastric node, present for several years before evaluation
- CT scan did not reveal any other lesions
- Recommended to undergo needle aspiration, but lost to follow-up for 2.5 years

Diagnostic Workup

- Seen again in August 2000
- Mass now 7 cm in size
- Patient otherwise asymptomatic
- FNA consistent with metastatic poorly differentiated squamous cell carcinoma
- Head and neck examination and radiologic studies failed to reveal primary tumor site (Tx N2-3 M0)

Radiology

Management

- PET scan, panendoscopy with biopsies, and neck dissection recommended
- 10/20/00 whole body PET scan revealed intense uptake in right submandibular region.
- No primary site identified, although perhaps obscured by signal from lymph node.

Management

- On 11/13/00, patient underwent panendoscopy with biopsies
- Right tonsil felt to be full; wide excision tonsillectomy performed
- Left tonsil biopsied
- Right modified radical neck dissection performed sparing spinal accessory nerve with removal of mass

Pathology

Postoperative Course

- Patient sent to SICU postoperatively
- Overall, uneventful hospital course
- Hematocrit 36.7 on postop day #1
- Tonsillectomy site, neck sites all healed appropriately
- Drains removed on postop day 5 and 6
- Discharged home on postoperative day 6
- Final path: tonsils normal; true unknown primary

PET scanning detects glucose

- Described for detection of brain tumors in 1986, 1992 for head and neck tumors
- Relies on uptake of 18-F-fluorodeoxyglucose by cells
- Gives tomogram with resolution = 6mm
- 10 min required per bed position, total time up to one hour
- Radiation exposure <10 mSieverts per 370 mBq dosage of glucose (similar to CT scan)
- SPECT scanning is a variant; it detects *Single Photon Emissions* as opposed to *Positron Emissions*

PET scanning not appropriate for initial evaluation of cancer

- Sensitive and specific: in *known* laryngeal tumors, PET scan had sensitivity of 88% for primaries and 81% for cervical metastases at pathologic exam, identical to CT or MRI.
- PET is 82% sensitive for pathologically proven nodal metastatic disease; CT is 84% and manual exam 71%
- Nonetheless, PET does not have anatomic clarity and detail of CT or MRI

Is PET scan appropriate for workup of unknown primary tumors?

- Between 0.5-5% of head and neck tumors present as tumors of unknown primary
- 5% of all cervical LN metastases are cancers of unknown primary
- Diagnostic options include panendoscopy with random biopsy, CT, MRI, and PET scan
- Therapy can include generalized radiation if site of tumor is not found but this carries extra morbidity
- 5-year survival is 6-35%, worse than that of patients whose primary cancer is known

Sensitivity of random biopsies and CT or MRI is poor

- Random biopsies have sensitivity of 10%
- Adding CT or MRI scanning increases sensitivity to 20%
- Can PET scanning improve this rate?

PET scanning has been evaluated as a clinical test for source of unknown primaries

"It is inherent that a statistical view of the diagnostic tools for the detection of an unknown primary is difficult: the diagnostic method being successful excludes the patient from the group of interest because he or she no longer has an occult tumor." (Jungehuelsing et al. 2000)

Some “studies” are personal observations without data

- McGuirt, WF *et al*., 1998: “In our experience, the yield in clinically negative or true unknown primary tumors after a negative thorough otolaryngologic office examination is low.”
- Jungehuelsing et al, 1999: “PET . . . may visualize malignant lesions more specifically.”
- Keyes et al, 1997: “our own experience . . . has been disappointing.”

PET compared to endoscopic “gold standard” with previously negative CT and/or MRI

- Greven et al. studied 13 patients with cervical lymphadenopathy with *negative* initial CT or MRI of head and neck. All given PET scan. Post-scan panendoscopy used as “gold standard”.

		endoscopic biopsy +	endoscopic biopsy -
PET	+	1	6
	-	1	5

BUT this study compared to endoscopy that was in part guided by the results of the test being evaluated!

PET compared to endoscopic “gold standard” with previously negative CT and/or MRI

- Stokkel et al. considered nine patients with cervical SCCA and negative CT. Carried out PET scan followed by endoscopic biopsy.

		endoscopic biopsy +	-
PET	+	5	3
	-	0	1

BUT this study compared to endoscopy that was in part guided by the results of the test being evaluated!

SPECT compared to endoscopic “gold standard” with previously negative CT and/or MRI

- Mukherji et al. Compared CT/MRI and PET to endoscopic biopsy in 12 patients with negative CT scan. Carried out PET scan followed by endoscopic biopsy.

		endoscopic biopsy +	-
PET	+	6	3
	-	1	2

BUT this study compared to endoscopy that was in part guided by the results of the test being evaluated!

PET compared to endoscopic “gold standard” with previously negative CT and/or MRI

- In five patients with negative CT and/or MRI, Mendenhall *et al*. found PET relatively insensitive for picking up lesion.

		endoscopic biopsy	
		+	-
PET	+	1	4
	-	0	0

Summary: PET/SPECT before endoscopy

- PET has a 45% positive predictive value when endoscopy is used as a gold standard. Its sensitivity for identifying unknown primaries is 13/39 (33%).

		endoscopic biopsy	
		+	-
PET	+	13	16
	-	2	8

PET after negative CT/MRI and negative endoscopy

- Jungehuelsing et al. (*OHNS* September 2000) found 27 of 723 head and neck cancer patients to have an unknown primary after CT, MRI, and endoscopy.
- 7 of these 27 had a positive PET scan that was later biopsy confirmed as the primary.
- False negatives *not* reported, so utility of technique difficult to assess from this study.

PET after negative CT/MRI and negative endoscopy

- Safa et al. studied fourteen patients with biopsy-proven SCCA in neck nodes with negative CT, MRI, and endoscopies.
- Three had lesions identified on PET and subsequently biopsy proven. Two putative sites were biopsy negative.

PET versus CT or MRI

- Hanasono et al in a retrospective unblinded study looked at 20 patients with biopsy-proven SCCA cervical mets. PET scan found the source of 7 (35%), CT scan found 2/9 (22%), MRI found 4/11 (36%). Of 7 primaries found by PET, 5 were base of tongue, one tonsil, one epiglottis; of three missed, two were BOT and one a tonsil. Specificity of PET not reported. Of 14 tumors *not* found by CT or MRI, PET only found 2. Of thirteen tumors not found by PET, CT or MRI found one.

Summary: role for PET in unknown primary?

- PET may be most useful to monitor patients postoperatively
- 11-C-methionine or 11-C-tyrosine may give better results than FDG
- Better research needed!

PET in staging melanoma

- Melanoma is clinically staged as follows:
  - I: less than 1.5 mm thickness
  - II: up to subcutaneous invasion without nodal metastasis
  - III: Nodal without distant metastasis
  - IV: Distant metastasis

PET is superior to CT for staging melanoma

- Scintigraphy has not been shown to help in staging.
- In a study by Rinne et al. of 52 high-risk stage II patients (> 1.5mm depth at presentation), PET scan had a sensitivity of 100% and a specificity of 95.5% compared to a gold standard of biopsy-proven lesions. CT had a sensitivity of 84.6% and a specificity of 68.2%. 12/12 cervical LN mets were detected by PET; 8/12 by CT. PET was superior for cervical and abdominal mets, while CT slightly better for small lung metastases.

PET is superior to CT for staging melanoma

- In a study by Holder et al. of 76 patients with stage II-IV melanoma, PET scan showed a sensitivity of 94.2% and specificity of 83.3% versus 55.3% and 84.4% for CT, respectively for metastatic disease
- False positives included carcinoma, Warthin's tumor, wound inflammation, and endometriosis.
- False negatives included small or diffuse metastases.

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