PETCT in the evaluation of paraneoplastic syndromes

by Daniel J Bell, FRCR
and Adil AL-Nahhas, FRCP
Hammersmith Hospital, Imperial College Healthcare NHS Trust, London

Guichard and Vignon originally coined the term paraneoplastic in 1949 when they discussed the differential diagnosis of a case of a metastatic uterine cervical malignancy with central and peripheral neuropathies.1 After autopsies on an additional three patients with similar neuropathies to that of the first, no malignant cells were found in the spinal cord or nerve roots of any of them.2 Therefore, these researchers felt paraneoplastic was more appropriate than neoplastic to describe these presentations.

A paraneoplastic syndrome (PS) is now defined as a clinical syndrome characterised by non-metastatic systemic effects associated with a malignancy. These syndromes seem to stem from chemical agents secreted by the neoplasm, may occur remotely from the malignancy per se, and may be metachronous or synchronous with the clinical presentation of the primary tumour itself. The substances produced by the tumour may mimic normal hormones or may antagonise normal circulating chemical mediators, although in many cases the responsible biochemical intermediary remains to be discovered.3

A panoply of PS presentations are seen, the majority emulating more common benign conditions. The full array of body systems are affected including neurologic, musculoskeletal, cardiovascular, haematologic, gastrointestinal, renal, dermatologic, endocrine, psychiatric and miscellaneous.4

Small cell lung carcinoma appears to be the most common aetiology, however, a diversity of other malignancies are seen to present in this way including lymphoma, ovarian, testicular, bladder, thymoma, myeloma, rectal, head and neck and gastric.

Helping to hone the diagnostic process further is the knowledge that certain paraneoplastic syndromes have strong associations with specific malignancies. For instance, paraneoplastic pemphigus has a distinctive clinical presentation and histology to that of classical pemphigus, and is strongly associated with lymphoproliferative conditions, most commonly non-Hodgkin's lymphoma.5 Unfortunately, many paraneoplastic syndromes, especially non-specific systemic presentations, for example cachexia and loss of appetite, have been related to a wide array of carcinomas.

Paraneoplastic syndromes may be the first or most prominent manifestation of malignancy. As the underlying neoplasm may be otherwise occult they can manifest a testing diagnostic conundrum as standard diagnostic tests serially fail to identify the offending malignancy. Conventional anatomic imaging, encompassing ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI), can be frustratingly unremarkable in the detection of occult carcinomas and in distinguishing between benign and malignant disease.6,7

Conversely, functional imaging may have some measure of success in these clinical scenarios. Metabolic imaging, for example whole-body [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET), is very sensitive in depicting the greater glucose uptake of tumours. In a small cohort of patients chosen for their propensity for paraneoplastic tumoural neuronal autoantibody, standalone FDG-PET was found to have a higher sensitivity for malignancy than conventional CT.8,9

In one study FDG-PET was found to have a sensitivity of 90% in 10 patients with anti-Hu, anti-Yo and anti-Tr antibodies (autoantibodies found in paraneoplastic neurological syndromes). By contradistinction the detection rate by conventional CT was a mere 30%. The combination of the two modalities improved the sensitivity for demonstrating a carcinoma to 100%. Similarly, other series have also shown the usefulness of FDG-PET in cases of clinically suspected PS where non-functional imaging has drawn a blank.10,11

Since the introduction of the first commercial hybrid PETCT scanner in 2000, several studies have demonstrated the value of co-registered FDG-PET and CT images in the investigation of paraneoplastic syndromes. The PET and CT images provide complementary information within a single study; the presence of a viable tumour and its accurate location. Most of these studies were of relatively small cohorts, generally those with a suspected paraneoplastic neurological syndrome (PNS).12,13,14

Rigorous evidence based guidelines for the imaging of paraneoplastic syndromes are lacking. The EFNS (European Federation of Neurological Societies) Task Force has designated FDG-PETCT (henceforth known as PETCT) as an integral element in the work-up of an individual with a conjectured PNS, especially those in whom small cell bronchogenic carcinoma, thymoma, breast and ovarian carcinomas are suspected.15

Royal College of Radiologists guidelines advocate the use of PETCT in paraneoplastic syndromes in "selected patients with non-metastatic manifestations of neoplastic disease such as neurological signs or raised antibodies to exclude or confirm an occult primary tumour when conventional imaging is negative or equivocal." The guidelines also suggest PETCT to be of value in excluding pyrexia of unknown origin “in highly selected patients where conventional imaging is negative or equivocal.”16

For our own retrospective series of 126 patients with prior negative conventional morphological imaging and a suspected paraneoplastic syndrome, PET and PETCT conclusively demonstrated evidence of malignancy in an additional 10 patients, equating to a positive detection rate of 8% (submitted for publication).

Patel et al retrospectively reviewed the notes of 107 patients who underwent PET, with suspected PNS. Seventy-three patients were positive for paraneoplastic antibodies. Malignancy was histologically proven in 10 patients, of whom eight were PET positive. Two cases of malignancy were negative on PET. This study showed that PET was more sensitive than CT for detecting occult malignancy, with high negative predictive value, of 88% according to this study.17

Younnes-Mhenni et al included 20 patients with PNS and positive paraneoplastic antibodies, who underwent PET examination. In 18 of them, there was abnormal FDG uptake, and in 14 patients tumour diagnosis was histologically proven. With the sensitivity of FDG-PET in tumour detection over 83%, they came to the conclusion that there is a significant role of PET in identifying malignancy.18

McKeon et al presented results of a study showing that PETCT improved cancer diagnosis in 56 patients with PNS. Identification of cancer by PETCT was significantly corre-
lated with detection of a well-characterised paraneoplastic antibodies, when other screening tests were negative.21 Similarily, Linke et al reported that the combination of PET and CT showed very high sensitivity in tumour detecting in patients with paraneoplastic antibodies.22

However, other studies showed different results. Bannas et al have reported FDG abnormal uptake in 10 of 46 retrospectively reviewed patients on PETCT. Paraneoplastic syndrome was proven in only four patients, and in another two there was vasculitic and local metastatic disease. They concluded that PETCT should be reserved for patients in whom other imaging methods failed to identify underlying disease.

The majority of experience at our centre and others around the world deals with paraneoplastic neurological syndromes. However, PETCT can also be selectively useful in the evaluation of some cases of non-neurological paraneoplastic syndromes.

In one study of 55 patients with a diagnosis of dermatomyositis or myositis, the strengths of PETCT for identifying occult malignancy were compared with conventional oncologic imaging. Results highlighted the high negative (86%) and positive predictive values (94%) of PETCT as a single imaging method, comparable to that of broad conventional multiple tests screening.23

Cushing’s syndrome due to ectopic ACTH secretion is an uncommon paraneoplastic phenomenon associated usually with neoplasms derived from neuroendocrine cell-line. The tumours most commonly responsible are carcinoids, either of lung or thymus origin. Less frequently pancreatic islet cell tumours, medullary thyroid cancer, pheochromocytomas and small cell lung carcinomas manifest in this way. FDG-PETCT has only demonstrated variable success in detecting these lesions as many of them are not especially metabolically active.24

However, [18F]-FDG is not the only tracer employed for PETCT imaging of PS. Novel tracers, such as [11C]-5-hydroxytryptophan- and [18F]-DOPA-labelled peptides (eg DOTANOC, etc) radiopharmaceuticals have been used successfully to localise a wide variety of neuroendocrine tumours including bronchial, thymic and gastropancreatic carcinoids, and pancreatic islet cell tumours.25

Tumour-induced osteomalacia (TIO) is a rare condition characterised by a hypophosphataemic state related to renal phosphate wasting. The aetiology appears to be related to the secretion of phosphatonin, proteins that promote tubular phosphate loss. The offending neoplasm is often very small and has been historically very difficult to locate with conventional imaging. However, a couple of recent case reports suggest some success with a functional imaging approach.26

One group was able to detect a neuroendocrine tumour in the right femoral head with 111In-octreotide scintigraphy, confirmed with [18F]-DOTANOC PETCT imaging. CT had previously failed to demonstrate any abnormality.27 Another case report clinicians localised a scapular haemangiopericytoma causing TIO with FDG-PETCT, that whole body MRI had overlooked.28

Pyrexia of unknown origin (PUO) is, of course, often due to occult infection. However, it is well-recognised that a PUO may represent a paraneoplastic syndrome. PETCT is a useful investigative tool in the evaluation of a PUO and, at times, may demonstrate the presence of an underlying cancer.

In a retrospective review of 68 patients with PUO, PETCT exhibited high positive and negative predictive values in detecting the cause of the fever.29 One group found that PETCT provided added value in children when investigating the aetiology of inflammation and fever.30

The recent introduction by vendors of hybrid PET/MRI scanners opens up new, exciting vistas for the evaluation of malignancy. There is no published data as yet but it seems likely that this new hybrid modality will be similarly useful in the detection of occult neoplasms in those presenting with a paraneoplastic condition.

The bottom line from many of the imaging studies, whether CT, MRI, or PETCT, is the importance of a selected population and avoiding the use of imaging as part of a ‘fishing trip’ approach when other investigations have drawn a blank. Another important conclusion is that PETCT is not the panacea that some might assume. Studies demonstrate time and again false-negative results on PETCT.

In conclusion, although not all cases of suspected paraneoplastic syndrome will eventually turn out to be malignant disease, a small proportion will do. Hybrid PETCT imaging of the whole body provides clear added value in the localisation of otherwise occult cancer in those with paraneoplastic syndromes, despite the negative results of other studies.

References

FIGURE 1
PETCT study in a 47-year-old female patient with a history of a progressive cerebellar syndrome with a presumed paraneoplastic aetiology. There is increased metabolic uptake in the left breast (a) and a left axillary node (b) which was biopsy-proven invasive ductal carcinoma of the breast.

FIGURE 2
PET examination in a 33-year-old male patient presenting with limbic encephalitis that is commonly paraneoplastic in origin. There is an FDG-avid prevascular mediastinal soft tissue lesion that was demonstrated at surgery to be a thymic germ cell tumour. (a) Coronal view. (b) Axial view.

FIGURE 3
PETCT in a 52-year-old female patient with a demyelinating neuropathy with multiple FDG-avid nodal lesions throughout the chest, abdomen and pelvis which were all low grade. Lymphoma was suspected but biopsy demonstrated Castleman disease. Castleman disease is associated with paraneoplastic syndromes and subsequent progression to full-blown lymphoma is well recognised. (a) Axial fusion view with low-grade uptake into left axillary nodes. (b) Axial fusion view with low-grade uptake into multiple confluent abdominal retroperitoneal nodes. (c) Axial fusion view with low-grade uptake into left inguinal nodes.