PETCT in management of paraneoplastic syndromes

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**What is a paraneoplastic syndrome?**

On occasion, patients with malignant disease develop symptoms that are not the direct effect of the primary tumour or of metastases, but rather reflect varied systemic effects of the malignancy. The various collections of symptoms that may result from this are termed “paraneoplastic syndromes.” Clinical features are complex and varied, and may affect any system including endocrine, neuromuscular, musculoskeletal, cardiovascular, cutaneous, haematologic, gastrointestinal or renal. Symptoms may be non-specific, in which case they are termed “miscellaneous.”

The exact pathophysiological mechanisms responsible for their production are not clearly understood. They can be triggered by an altered immune system response to a neoplasm, tumour production of hormones and protein-hormone precursors, cytokines or a variety of enzymes and fetal proteins. However, they may be idiopathic. It should also be borne in mind that there are benign disorders that mimic paraneoplastic syndromes.

Paraneoplastic syndromes may occur in patients with active cancer or those in remission after treatment, but they most commonly occur in patients not known to have cancer. It is thus important to thoroughly investigate anyone who presents with clinical features suggestive of a paraneoplastic disorder. This is particularly so because paraneoplastic syndromes are non-metastatic in nature and thus the underlying lesion may be potentially curable.

**Onconeural antibodies**

The diagnosis of a paraneoplastic syndrome and differentiation from non-neoplastic forms may be aided by the presence of autoantibodies in many patients with a true paraneoplastic disorder. These autoantibodies can be against any tissues of the body, but most are directed against the central nervous system. These are termed onconeural antibodies.

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1. Anti-Hu. Previously known as antineuronal nuclear antibody 1 (ANNA-1), this is found in patients with paraneoplastic subacute sensory neuropathy and, less commonly, in non-sensory neuropathies and/or encephalomyelitis. The underlying malignancy in the majority of patients with anti-Hu antibodies is small cell lung cancer.

2. Anti-Ri. Previously known as antineuronal nuclear antibody 2 (ANNA-2) is the least common of the onconeural antibodies. It is found in patients with opsinclonus/myoclonus syndrome, and occasionally in patients with cerebellar ataxia. The majority of the patients are female and the underlying malignancy is usually breast or one of the gynaecological neoplasms.

3. Anti-Yo. Also known as anti-Purkinje cell antibody 1 (APCA-1), this is found in patients with paraneoplastic cerebellar degeneration. Similar to anti-Ri, the vast majority of patients are postmenopausal females with underlying breast or gynaecological malignancies.

4. Antineuronal antibodies Ma1 and Ma2 (also called anti-Ta) are members of a novel but expanding family of brain-specific or testis-specific proteins. Associated neurological symptoms vary, but often include abnormalities in eye movement, short-term memory loss, seizures, personality change or confusion. While Ma1 is not found in association with one particular type of tumour, Ma2 seems to be strongly associated with testicular cancer.

5. Antibodies against amphiphysin (a synaptic vesicle protein) have been detected in the serum of patients with the paraneoplastic form of stiff man syndrome (a rare, idiopathic or paraneoplastic autoimmune neurological disorder characterised by stiffness of skeletal muscles with superimposed spasms). The associated underlying malignancies include breast, small cell lung and ovarian carcinoma.

Non-neuronal antibodies are also frequently found, particularly in patients with anti-Hu and anti-Yo antibodies.

In general, their presence does not appear to correlate with particular clinical characteristics. Examples include antinuclear antibodies and anticytoplasmic antibodies. Antibodies against the voltage-gated potassium channel may be associated with non-paraneoplastic limbic encephalitis.

**Imaging strategy – Role of PETCT**

Once it has been confirmed that a paraneoplastic syndrome is likely to be present, imaging plays an important role in trying to locate the primary tumour. The role of 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography (FDG-PET) with computed tomography (hereafter referred to only as PETCT) in clinical management of paraneoplastic syndromes is still evolving, but it remains the most promising modality. It has emerged as an effective diagnostic tool in the detection and staging of many malignancies. Its main advantage lies in its ability to demonstrate function. It can thus demonstrate abnormally increased metabolic activity in a structure that may otherwise appear anatomically normal, making it more sensitive than conventional imaging modalities. Furthermore, the field of coverage with PETCT is more than that of conventional CT or MRI, allowing the possibility of detection of disease in parts of the body not generally imaged with CT or MRI.

To our knowledge, no validated national guidelines on the imaging of these patients exist. However, the Royal College of Radiologists (RCR) guidelines have a suggested pathway for the investigation of patients with an unknown primary tumour, and the European Federation of Neurological Societies (EFNS) has developed recommendations for imaging of patients with neurological paraneoplastic presentations. Note that these guidelines are for slightly different clinical scenarios (unknown primary versus neurological paraneoplastic disorders), but both include recommendations on the role of PETCT.

With reference to the use of PETCT in imaging of the unknown primary, RCR guidelines make a distinction between metastatic squamous cell carcinoma to the neck of unknown origin, and metastatic adenocarcinoma of unknown origin. In the former scenario, PETCT is recommended if no primary neoplasm is detected with routine imaging, panendoscopy and biopsy. In metastatic adenocarcinoma of unknown origin, PETCT is recommended if no primary neoplasm is detected with routine imaging, panendoscopy and biopsy. In metastatic adenocarcinoma of unknown origin, however, there is deemed to be insufficient evidence on the diagnostic value of PETCT to justify its use.

The extrapolation of these recommendations to paraneoplastic syndromes is thus not straightforward, unless the particular presenting paraneoplastic syndrome and onconeural antibody profile give a high probability of a specific primary tumour type. The EFNS Task Force on management of neurological paraneoplastic syndromes, however, was more explicit in recommending PETCT in all patients with neurological paraneoplastic syndromes in whom routine CT and/or MRI was negative.

In general, due to cost considerations, CT of the chest, abdomen/pelvis or mammography should be performed as
the initial investigation (depending on the clues about the likely primary tumour which can be inferred from the type of paraneoplastic presentation and/or serum onconeural autoantibody profile). If these fail to reveal the primary lesion, then it is advised to proceed to PETCT. The EFNS task force recommends serial imaging six monthly for up to four years if no primary is found on the initial round of investigations. It does not specify the recommended modality for this serial imaging. Other researchers have specifically recommended serial PETCT if the initial examination is negative. PETCT may also play a role in imaging the functional disturbances in paraneoplastic CNS manifestations, particular paraneoplastic limbic encephalitis and cerebellar degeneration.

**Case illustration**

We now describe a case report illustrating the sensitivity of PETCT over routine imaging techniques in paraneoplastic syndromes.

A 37-year-old woman, who was previously well other than a history of polycystic ovarian syndrome, presented with cranial nerve palsies (left sixth and bilateral facial nerve palsies). Initial blood tests were normal, including negative immunological tests for onconeural antibodies. An initial CT scan showed enlarged cystic ovaries, which were thought to reflect the patient’s known polycystic ovarian syndrome. No other significant abnormality was identified on CT (figures 1a and 1b). MRI of the brain and skull base showed non-specific high T2W signal abnormality of the sixth and seventh cranial nerves with moderate contrast enhancement, but with no abnormal thickening, or skull base lesion.

As there was no clear explanation for the patient’s cranial nerve palsies, a paraneoplastic cranial neuropathy was suspected. PETCT was recommended, to search for a possible primary lesion. The results of this were very surprising due to the florid nature of the findings (figures 2a, 2b, 2c) given a negative initial CT. PETCT demonstrated that the enlarged ovaries were, in fact, highly metabolically active, making an underlying malignancy highly likely. Furthermore, there was abnormally high metabolic activity in the right adrenal gland (which was not enlarged on CT), in multiple retroperitoneal and mediastinal lymph nodes not appreciated on the diagnostic CT scan, and in vertebral bodies (in retrospect, could be identified on the diagnostic CT). It also demonstrated increased uptake in the cranial nerves, brachial plexus, as well as the roots of the spinal nerves. There was added metabolically active soft tissue at the skull base extending to the cranial nerves. Histological diagnosis turned out to be non-Hodgkin’s lymphoma.

Thus, in retrospect, the patient’s presentation was not with a paraneoplastic syndrome, but with probable small volume metastatic disease to the cranial nerves. However, given the neurological presentation and non-specific findings on initial imaging in comparison with florid PETCT findings, this case demonstrates the potential usefulness of PETCT in paraneoplastic syndromes/the unknown primary.

**References**


**FIGURE 1a** Diagnostic CT scan showing bilateral ovarian enlargement.

**FIGURE 1b** Diagnostic CT scan at level of right adrenal – no adrenal mass or nodule is seen.

**FIGURE 2a** Upper row – registration CT scan and PET image. Lower row – fusion PETCT images, axial and coronal. Note high metabolic activity within ovaries, right adrenal, left femoral head and L1 vertebral body (arrows).
FIGURE 2b
PETCT images; note increased activity in right adrenal and pancreatic head.

FIGURE 2c
PETCT images showing abnormal activity in skull base and spinal nerve roots (ellipse), brachial plexus (thin arrow) and mediastinal nodes (thick arrows).