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The role of [^{18}F]fluoro-2-deoxyglucose-PET scanning in the diagnosis of paraneoplastic neurological disorders

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Summary

The detection of an occult tumour in a patient with a suspected paraneoplastic neurological disorder (PND) may be difficult because of the limitations of conventional imaging techniques. [^{18}F]fluoro-2-deoxyglucose-PET (FDG-PET) can visualize a small tumour anywhere within the body. We retrospectively reviewed the case notes of 43 unselected patients with suspected PND referred for FDG-PET scanning to determine how useful this technique was when conventional imaging was negative. All patients had undergone standard radiological investigations and bronchoscopy (where appropriate) prior to PET scanning. There were discrete areas of hypermetabolism suggestive of malignancy (positive) in 16 patients (37%). A tissue diagnosis of cancer was subsequently made in seven patients (two at post-mortem), further radiological studies were suggestive of cancer in one patient, one patient subsequently presented with a metastatic deposit which was biopsied, and four patients died shortly afterwards without a post-mortem. In three patients, subsequent investigations were negative for cancer. Serum anti-neuronal antibodies were present in 43% and CSF oligoclonal bands were present in 46% of patients with positive PET scans compared with 16 and 26%, respectively, in PET-negative patients, but this was not significant. Only one patient with a negative scan has been diagnosed subsequently as having malignancy on prolonged follow-up. These findings confirm that FDG-PET scanning is a useful technique in the detection of small tumours in patients with suspected PND. False positives and false negatives do occur, but at a sufficiently low frequency to justify the clinical usefulness of this technique.

Keywords: paraneoplastic neurological disorder; FDG-PET scanning; anti-neuronal antibodies

Abbreviations: FDG-PET = [^{18}F]fluoro-2-deoxyglucose-PET; PND = paraneoplastic neurological disorder

Introduction

Paraneoplastic neurological disorders (PND) are rare non-metastatic manifestations of cancer, which usually present as rapidly progressive subacute neurological dysfunction. Both the CNS and the PNS, including the neuromuscular junction, may be affected either in isolation or as a multifocal process. These conditions are important to recognize as they prompt a detailed search for a potentially treatable underlying tumour, most commonly small cell lung cancer. However, the diagnosis of such disorders is difficult, particularly when serum anti-neuronal antibodies, diagnostic markers of these syndromes, are absent. Even when an underlying malignancy is present, its identification with conventional imaging techniques is frequently limited by the small size of the tumour.

Fluorodeoxyglucose-PET (FDG-PET) scanning permits the detection of metabolically active tumour tissue with a resolution of 6–8 mm. It has recently emerged as a practical and cost-effective imaging modality in patients with a variety of tumours, in particular lung cancer (Coates and Skehan, 1999), colorectal cancer (Akhurst and Larson, 1999) and lymphoma (Moog *et al.*, 1997). However, it has not been applied systematically to the diagnosis of an occult tumour in patients with suspected PND in whom conventional imaging by CT scanning of the thorax, abdomen and pelvis has failed to reveal a primary.

We have combined the experience of two large neurological centres with access to clinical PET scanning in an attempt to define how useful this technique is in the management of

patients with suspected PND. We also wanted to determine whether there were any laboratory criteria that would increase the likelihood of a positive scan.

Methods

Patients

The case records of patients with suspected PND who had been referred for FDG-PET scanning to three centres (Clinical PET Centre, St Thomas' Hospital; Department of Nuclear Medicine, Middlesex Hospital; Mount Vernon Hospital) from 1996 to 2000 were reviewed retrospectively and relevant data extracted. All patients had been investigated previously for an underlying malignancy by conventional radiography, CT scanning, ultrasound, mammography and bronchoscopy (where appropriate).

PET scans

After a 6-h fast, patients were injected with 350 MBq of [^{18}F]FDG and standard half-body studies were performed after a 60-min uptake period. The machine systems used were a Siemens/CTI ECAT 951/31R (Erlangen, Germany) (St Thomas'), GE Advance (Milwaukee, Wis., USA) (Middlesex) and Siemens ECAT EXACT 47 (Mount Vernon) with spatial resolution of 4.75–6 mm. Images were reconstructed independently by at least two nuclear medicine physicians (St Thomas' Hospital, Middlesex Hospital) blinded to the clinical findings and displayed as coronal, transaxial and sagittal sections. All scans were reported blinded to the clinical information and a consensus report was issued. The one Mount Vernon scan was read by one radiologist. Areas of non-physiological increased tracer uptake were reported.

Patients with positive PET scans were subsequently reimaged using fine-cut CT scans and, where appropriate, were biopsied or operated on. The patients with negative PET scans were followed up to determine the final neurological diagnosis. If no definite diagnosis emerged after subsequent investigations, information was specifically requested as to whether they had subsequently developed a malignancy. This was done by writing to the referring consultant or general practitioner.

Immunochemistry

Details of investigations for CSF oligoclonal bands and anti-neuronal antibodies were confirmed with the neuro-immunology laboratory. CSF oligoclonal bands were measured by isoelectric focusing and anti-neuronal antibodies detected using a combination of immunohistochemistry using paraffin-embedded rat cerebellum and brainstem together with Western immunoblotting against a homogenate of human Purkinje cells and cortical neurones. The presence of anti-Hu and anti-Yo antibodies was confirmed by Western immunoblotting against recombinant Hu and Yo antigens (kindly donated by Professor Angela Vincent, Oxford).

Table 1 *Indications for FDG-PET scanning in patients with suspected PND*

Clinical presentation	No. of patients
Cerebellar ± brainstem syndrome	15
Motor neuropathy	6
Sensory neuro(no)pathy	8
Myelo(radiculo)pathy	3
Respiratory failure	2
Lambert–Eaton myasthenic syndrome	3
Other	6
Total	43

Statistical analysis

Fisher's exact test ($\alpha = 0.05$) for differences in proportions between the PET-positive and PET-negative patients was carried out.

Results

A total of 43 patients (24 male, 19 female) was scanned. Indications for scanning are presented in Table 1. Sixteen patients had PET scans consistent with malignancy (positive) and 27 had normal (negative) scans. The clinical details of the 16 positive patients are listed in Table 2. The clinical details, final diagnosis and length of follow-up for the negative patients are listed in Table 3. The mean (standard deviation) duration of follow-up was 18.1 (10.2) months and the median (range) was 16 (2–44) months.

Of the 16 patients with a positive scan, a histological diagnosis was confirmed in seven (two at post-mortem) and dedicated CT imaging suggested malignancy in one patient. One patient (Case 5 in Appendix I) presented with a small-cell lung cancer metastasis 16 months after the PET scan. In two patients, subsequent investigations (including prostatic biopsy and CT scanning of the thorax) were negative for malignancy. In a third patient, with a sensory neuronopathy and anti-Hu antibodies, sequential CT scanning showed slow growth in the hilar lesion, which was considered, but not proven, to be due to a malignant tumour. The other four patients died shortly afterwards and did not undergo autopsy, so the findings on PET could not be confirmed.

All but one of the patients with a negative PET scan have remained free of malignancy on extended follow-up and in many cases alternative diagnoses have been made (Table 3). One patient with a cranial polyneuropathy, whose PET scan was reported initially as normal, subsequently developed a ductal carcinoma of the breast. However, on review, a small area of increased uptake could be discerned in the right breast, which was not initially reported. Her subsequent clinical course led to the diagnosis of neurosarcoidosis as a

Table 2 *Clinical details of patients with positive PET scans*

Patient	Age (years)	Sex	PET location	Malignancy	Neurological syndrome	CSF oligoclonal bands	Anti-neuronal antibodies
1	66	M	Bowel	Presumed caecal carcinoma*	Brainstem encephalitis	Positive	Negative
2	62	M	Right hilum	Small-cell lung cancer	Cerebellar degeneration	Positive	Negative
3	70	M	Retrocardiac area	Lung cancer (at PM)	Ophthalmoplegia, deafness, ataxia	Positive	Negative
4	75	M	Prostate‡	Negative after biopsy	Vasculitic neuropathy	Negative	Negative
5	58	F	Left hilum	Small cell lung cancer†	Cerebellar degeneration	Not done	Positive (Hu)
6	62	M	Right hilum	Never confirmed (died without PM)	Cerebellar degeneration, deafness, cognitive decline	Positive	Positive (Hu)
7	78	M	Bowel	Carcinoma of colon	Multifocal motor neuropathy	Matched	Positive (Hu)
8	62	F	Right hilum	Never confirmed (died without PM)	Encephalopathy	Positive	Positive (Hu)
9	62	M	Lung	Undifferentiated lung cancer	Demyelinating neuropathy	Matched	Not done
10	83	F	Bowel	Caecal carcinoma (at PM)	Myopathy, weight loss	Not done	Negative
11	64	F	Pleura	CT showed fibrosis only	GBS plus membranous GN	Negative	Negative
12	68	F	Left hilum and Mediastinum	Never confirmed (died without PM)	Demyelinating neuropathy	Not known	Not done
13	57	F	Right hilum	Negative after bronchoscopy	Sensory neuronopathy	Negative	Positive (Hu)
14	75	F	Right lung base and pelvis	Adenocarcinoma unknown primary, in pelvis	Sensory neuronopathy	Not done	Positive (Yo)
15	50	M	Right hilum and para-oesophageal region at D7	Never confirmed (died without PM)	Cerebellar degeneration, cognitive decline	Negative	Negative
16	54	M	Left hilum and lung base	Small cell lung cancer	LEMS, autonomic failure, cognitive decline	Positive	Negative

PM = post-mortem; GBS = Guillain–Barré syndrome; GN = glomerulonephritis; LEMS = Lambert–Eaton myasthenic syndrome; M = male; F = female. *On the basis of subsequent CT pneumocaecogram; †on the basis of subsequent development of skin metastasis; ‡negative on review by one of the authors (S.F.H.) but included on the basis of original report.

cause of the original cranial nerve palsies and therefore the detection of a tumour was probably coincidental. A further two patients with severe sensory neuronopathy and anti-Hu antibodies had negative PET scans and to date no malignancy has been diagnosed.

Six patients (out of 14 tested) with positive PET scans were positive for serum anti-neuronal antibodies compared with three out of 19 PET-negative patients tested ($P = 0.09$, Fisher's exact test). Similarly, six (out of 13 tested) had CSF oligoclonal bands in the PET-positive group compared with five out of 19 in the PET-negative group ($P = 0.09$, Fisher's exact test). Specific case histories illustrating the diagnostic difficulties and the usefulness of the PET scan are reported in Appendix I.

Discussion

FDG-PET scanning is now used routinely in oncology and has been shown to be helpful in the assessment of patients with recurrent or residual disease in colorectal cancer and lymphoma, the preoperative staging of non-small-cell lung cancer and the investigation of single pulmonary nodules (for review, see Bomanji *et al.*, 2001). The sensitivity and specificity of this technique in the detection of mediastinal lymphadenopathy for the preoperative staging of lung cancer are 91 and 86%, respectively, compared with 75 and 66% for CT (Pieterman *et al.*, 2000).

This is the first report of an unselected series of patients with suspected PND who have had FDG-PET scanning as part of their clinical diagnostic work-up. The main limitation of this study is the fact that it was retrospective and so data are incomplete. We accept that this is a preliminary study and therefore it is impossible to give an accurate indication of the sensitivity or specificity of this test. In order to do this, a study would require a large number of patients and a prolonged follow-up, both of which are difficult in practice. In addition, a definite diagnosis of malignancy would have to be made in all cases, which we have found to be

Table 3 *Clinical details, anti-neuronal antibodies, final diagnoses and duration of follow-up of patients with negative PET scans*

Patient	Age (years)	Sex	Clinical details	Anti-neuronal antibodies	Final diagnosis	Malignancy at follow-up	Length of follow-up (months)
1	44	M	Autonomic failure, proximal wasting, weight loss	ND	Diabetic neuropathy/ amyotrophy	No	9
2	61	F	Sensory neuropathy	P (Hu)	Paraneoplastic sensory neuropathy	No	18
3	61	M	Brainstem syndrome, myoclonus, central apnoea	N	Not known	No	12
4	49	M	Cerebellar syndrome	N	Multiple systems atrophy	No	11
5	73	M	Visual failure; previous bladder cancer	N	Leber's hereditary optic neuropathy	No	6
6	68	F	Headaches, cranial polyneuropathy, raised ESR	N	Neurosarcoidosis	Yes (breast)	21
7	60	F	Sensory neuropathy	P (Hu)	Paraneoplastic sensory neuropathy	No	2
8	67	M	Sensory neuropathy	N	Idiopathic sensory axonal neuropathy	No	15
9	62	F	Respiratory failure; previous melanoma	N	Central respiratory failure	No	15
10	79	F	Cerebellar syndrome; weight loss	N	Idiopathic late-onset cerebellar ataxia	No	40
11	47	F	Recurrent sinus vein thrombosis	ND	No underlying cause found	No	26
12	41	F	Jerky stiff person	N	Jerky stiff person	No	24
13	50	M	Cerebellar syndrome, cognitive decline, pyramidal signs	N	Possible cerebral Whipple disease	No	21
14	48	M	Cerebellar syndrome; finger-clubbing	ND	Somatization disorder	No	14
15	74	F	Cerebellar syndrome, neuropathy; previous breast cancer	N	Idiopathic late onset cerebellar ataxia	No	25
16	60	F	LEMS	N	LEMS	No	19
17	51	F	Dementia, supranuclear gaze palsy, respiratory failure	ND	Not known	No	14
18	51	M	Cerebellar syndrome, bladder disturbance	N	Primary progressive multiple sclerosis	No	6
19	63	M	Cerebellar syndrome; pyramidal disturbance	N	Inflammatory myelopathy	No	21
20	59	M	Atypical motor neurone syndrome	N	Motor neurone disease	No	44
21	63	M	Sensory neuropathy	ND	Idiopathic sensory neuropathy	N	30
22	45	F	Sensory neuropathy	N	Idiopathic sensory neuropathy	N	16
23	76	M	Myeloradiculopathy	N	Necrotic myelopathy	No	30
24	86	M	Myelopathy, weight loss, raised ESR	ND	Inflammatory myelopathy	No	14
25	72	M	Necrotic myopathy	ND	Inflammatory myopathy	No	6
26	39	F	Brainstem syndrome, limbic encephalitis	P (Hu)	Unknown	N	6
27	66	M	Sensory neuropathy	ND	Idiopathic sensory neuropathy	N	24

ESR = erythrocyte sedimentation rate; LEMS = Lambert–Eaton myasthenic syndrome; ND = not done; N = negative; P = positive; M = male; F = female.

impractical. In this study, only half of the PET-positive patients had a pathologically confirmed tumour and one case had further imaging that was highly suggestive of a carcinoma; this patient subsequently developed a metastasis, presumably from her primary small-cell lung cancer. The false-positive rate was ~10%, as subsequent investigations in two of the 16 patients were negative for malignancy.

The strength of this study lies in the heterogeneous nature of the patients having PET scans. This reflects the diagnostic uncertainties often associated with patients presenting with

severe and progressive neurological dysfunction, in whom extensive investigations are non-contributory. The final neurological diagnoses and the index of clinical suspicion for a PND were varied. It was known that anti-neuronal antibodies were present in some patients, which increased the likelihood of a positive scan, but in most of the patients either this information was not available at the time of scanning or the test was negative.

The detection rate within the group as a whole was 37%, which, we suggest, is sufficiently cost-effective to justify introducing FDG-PET as a routine clinical technique, particularly as this may obviate the need for other investigations, such as isotope bone scanning, abdominal and pelvic ultrasound, endoscopy, colonoscopy and bronchoscopy. It can also direct high-resolution imaging to the appropriate area of the body, thus minimizing the time needed for further CT scanning and the exposure to ionizing radiation.

As the symptoms and signs of a PND usually precede those of the underlying malignancy, early diagnosis has implications for patient management, particularly when a cancer can be resected before it has metastasized. This occurred in Cases 2 and 5, both patients surviving for $>$18 months after diagnosis of a small-cell lung cancer.

It would have been useful to identify other laboratory markers, which may increase the likelihood of a positive scan. Both serum anti-neuronal antibodies and CSF oligoclonal bands were present more frequently in the PET-positive patients, but the differences in proportions were not statistically significant for either test.

The overall sensitivity of anti-neuronal antibodies as a diagnostic marker of PND varies with the type of PND and the diagnostic criteria applied. For example, the sensitivity and specificity of anti-Hu antibodies in paraneoplastic sensory neuropathy is 82 and 99%, respectively (Molinuevo *et al.*, 1998), whereas a variety of anti-neuronal antibodies are present in 60% of patients with paraneoplastic limbic encephalitis (Gultekin *et al.*, 1999). In our study, only six out of 13 patients (46%) with positive PET scans tested positive for paraneoplastic antibodies, but this was an unselected series and the methods used in our laboratory to identify these antibodies may not have picked up less common antibodies, such as anti-CV2 and anti-amphiphysin.

A neurological disorder can only be defined as 'paraneoplastic' with certainty if a tumour is identified. In patients with PND associated with anti-Hu and anti-Yo antibodies, a tumour is virtually always found, albeit sometimes only at autopsy (Dalmau *et al.*, 1992; Peterson *et al.*, 1992). Very occasionally, there is either regression of a known or suspected small-cell lung cancer in patients with PND and anti-neuronal antibodies (Darnell and DeAngelis, 1993) or no tumour is found even at autopsy (Lucchinetti *et al*, 1998). This might account for the observation that only six out of nine patients with anti-neuronal antibodies had positive PET scans. In two of the three patients with anti-Hu antibodies but negative PET scans, we still consider the diagnosis to be paraneoplastic sensory neuropathy. The third patient (Patient 26, Table 3) with anti-Hu antibodies has had a non-progressive lower brainstem syndrome for over 6 years, leading to dysphagia and dysarthria, and no malignancy has been detected despite three negative CT scans of thorax and abdomen and, most recently, a negative PET scan. The final diagnosis is unknown and may yet be paraneoplastic, despite the length of the neurological history, as the interval between onset of PND and the discovery of cancer in anti-Hu positive patients has been as long as 8 years (Lucchinetti *et al*., 1998). In the patient with Lambert–Eaton myasthenic syndrome (Patient 16, Table 3), no malignancy has yet emerged despite three PET scans over 18 months. Therefore, a negative PET scan in a patient with a high clinical index of suspicion for a PND should not prevent ongoing follow-up and further investigations for cancer as appropriate. These cases should be regarded as potential false negatives as a tumour may be missed if its size is below the threshold for detection (6–8 mm) by PET or if there has been tumour regression. The importance of not placing undue reliance on a negative test result when the clinical features strongly suggest otherwise has recently been highlighted with reference to the detection of Berry aneurysms by magnetic resonance angiography in patients with a high clinical suspicion of subarachnoid haemorrhage (Johnson *et al*., 2001).

Oligoclonal bands, representing local synthesis of IgG (immunoglobulin G), may be present in paraneoplastic syndromes. As we have shown, all patterns are possible, including matched bands in CSF and serum. Our results are similar to those of an earlier study of IgG in $>$1000 patients from this institution, of whom five out of 10 with PND had local synthesis of IgG and three had serum leakage of bands (McLean *et al*., 1990).

We have also identified the potential for false-negative (as in the patient with breast cancer in whom the increased uptake was only detected retrospectively) and false-positive scans. Improvements in data processing to achieve better spatial and contrast resolution may overcome some of these difficulties. Further assessment of quantitative analysis techniques (standard uptake values) across different instruments is also likely to improve diagnostic accuracy.

The use of PET scanning in the diagnosis of PND has only been reported in four patients, three with anti-Hu antibodies (Antoine *et al*., 2000) and one with anti-Yo-associated cerebellar degeneration and an adenocarcinoma of the omentum (Shinohara *et al.*, 1998). In the latter case report, the patient's ataxia stabilized after removal of the tumour, which emphasizes that the diagnostic benefits of this technique may improve outcome.

We conclude that there is a clear role for FDG-PET scanning in the management of patients with suspected PND. This technique merits further investigation in a prospective study, in particular to define its use in patients who do not have anti-neuronal antibodies or CSF oligoclonal bands.

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References

Akhurst T, Larson SM. Positron emission tomography imaging of colorectal cancer. [Review]. Semin Oncol 1999; 26: 577–83.

Antoine JC, Cinotti L, Tilikete C, Bouhour F, Camdessanche JP, Confavreaux C, et al. [^{18}F]Fluorodeoxyglucose positron emission tomography in the diagnosis of cancer in patients with paraneoplastic neurological syndrome and anti-Hu antibodies. Ann Neurol 2000; 48: 105–8.

Bomanji JB, Costa DC, Ell PJ. Clinical role of positron emission tomography in oncology. Lancet Oncol 2001; 2: 157–64.

Coates G, Skehan SJ. Emerging role of PET in the diagnosis and staging of lung cancer. Can Respir J 1999; 6: 145–52.

Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) 1992; 71: 59–72.

Darnell RB, DeAngelis LM. Regression of small-cell lung carcinoma in patients with paraneoplastic neuronal antibodies. Lancet 1993; 341: 21–2.

Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000; 123: 1481–94.

Johnson MR, Good CG, Penny WD, Barnes PR, Scadding JW. Playing the odds in clinical decision making: lessons from Berry aneurysms undetected by magnetic resonance angiography. BMJ 2001; 322: 1347–9.

Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology 1998; 50: 652–7.

McLean BN, Luxton RW, Thompson EJ. A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectic focusing and the Log IgG-Index. A comparison and diagnostic applications. Brain 1990; 113: 1269–89.

Molinuevo JL, Graus F, Serrano C, Rene R, Guerrero A, Illa I. Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy. Ann Neurol 1998; 44: 976–80.

Moog F, Bamgerter M, Diederichs CG, Guhlmann A, Kotzerke J, Merkle E, et al. Lymphoma: role of whole body 2-deoxy-2-[F-18] fluoro-D-glucose (FDG) PET in nodal staging. Radiology 1997; 203: 795–800.

Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. Neurology 1992; 42: 1931–7.

Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, et al. Preoperative staging of non-small cell lung cancer with positron-emission tomography [letter]. N Engl J Med 2000; 343: 254–61.

Shinohara Y, Ohnuki Y, Yoshii F, Takahashi W, Onoe K, Takagi S. Detection of primary tumour in paraneoplastic cerebellar degeneration by FDG-PET. Ann Neurol 1998; 43: 684.

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Appendix I: illustrative case reports

Cases 1–5 had a positive PET scan and Case 6 had a negative PET scan.

Case 1 (Table 2, Patient 1)

A 66-year-old man woke with dizziness in May 1998 and his gait became gradually more unsteady. Four weeks later he could only walk with support and was admitted to hospital. General examination was normal. Neurological examination revealed downbeat nystagmus and gait ataxia. Over the following weeks there was gradual deterioration, with loss of ankle jerks, hypersomnolence, progressive brainstem signs and deteriorating gait. MRI of the head showed multiple high-signal lesions throughout the basal ganglia, deep white matter and brainstem. CSF examination demonstrated a lymphocyte count of 20/mm^3 and positive oligoclonal bands. CT of the chest and abdomen was normal. He was negative for anti-neuronal antibodies and the peripheral tumour markers CA125 and CEA. FDG-PET demonstrated an area of high metabolic activity within the caecum (Fig. A1). A contrast-enhanced CT pneumocaecogram demonstrated an annular 4-cm caecal mass (Fig. A2). A 5-day course of intravenous immunoglobulin (0.4 g/kg) was administered without benefit. He was deemed too unwell to justify bowel surgery and so no histological diagnosis was made. He died 3 months after presentation. Permission for a post-mortem examination was refused.

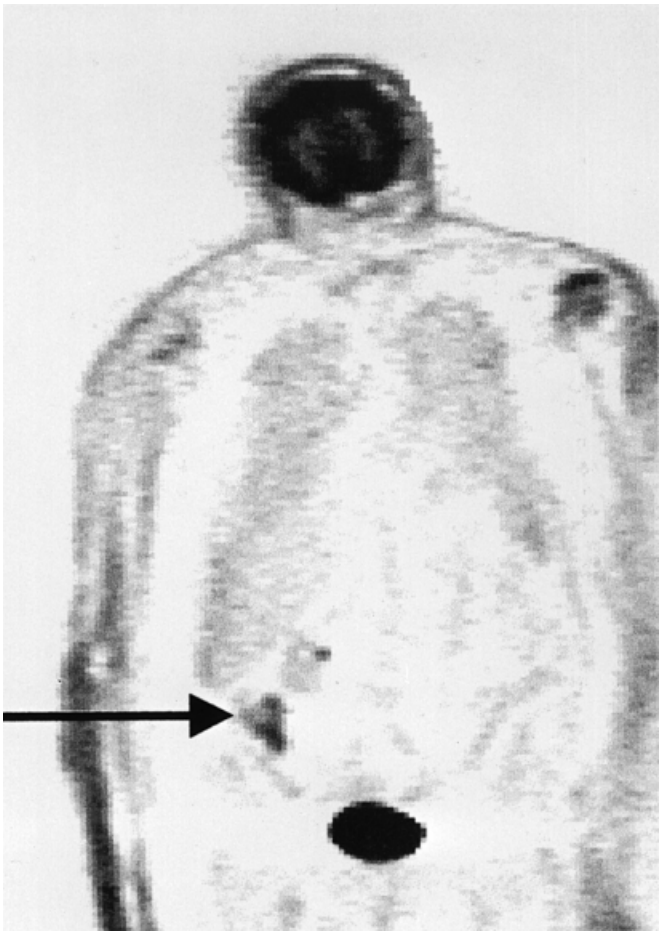

Fig. A1 Case 1. Coronal view of half-body FDG-PET scan showing increased tracer uptake in the right side of the abdomen (arrow).

Case 2 (Table 2, Patient 2)

A 62-year-old lifelong smoker presented with a 2-month history of deteriorating balance and slurred speech. On examination he had severe gait ataxia and required assistance from two people to walk. His speech was dysarthric with a scanning robotic quality and he had a coarse rest and postural tremor. There was diplopia on right lateral gaze and bilateral gaze evoked downbeat nystagmus. His limbs were grossly ataxic with normal power and coordination. All blood and imaging investigations were normal, including tumour markers, anti-neuronal antibodies, MRI of the brain and CT of the thorax. The CSF contained oligoclonal bands. FDG-PET scanning revealed an area of high metabolic activity within the right hilum. Repeat fine-cut CT scanning showed a possible area of abnormality in the right upper lobe that could not be confirmed at bronchoscopy. On the basis of the PET scan and the high clinical index of suspicion, he underwent right upper lobectomy which revealed a small-cell lung carcinoma. He received chemotherapy after surgery with some benefit to the cerebellar syndrome but developed metastatic disease and died 2 years later.

Case 3 (Table 2, Patient 3)

A 70-year-old man who had had intermittent episodes of diplopia, vertigo and vomiting in April 1999 presented with a 6-month history of worsening balance, hearing loss, diplopia and sensory disturbance down the left side. He had lost >20 kg in weight but had no other systemic symptoms. General examination revealed a cachectic man but was otherwise unremarkable. He had normal cognition and cranial nerve testing revealed complete ophthalmoplegia, convergence spasm and bilateral sensorineural deafness. His limbs were weak proximally and he was unable to walk as a result of a combination of gait ataxia and muscle weakness. During the course of his admission he developed complete dysphagia requiring nasogastric feeding. All investigations, including MRI of the brain, EMG, anti-neuronal antibodies and CT of the thorax and abdomen at the referring hospital, were negative. There were oligoclonal bands in the CSF and he was positive for protein 14-3-3. A brain biopsy looking for evidence of spongiform encephalopathy was negative, as was Western blotting for prion protein. FDG-PET scanning revealed two areas of increased glucose uptake in the retrocardiac region (Fig. A3). Repeat fine-cut CT scans of the appropriate area now revealed masses at the right heart border, in the aortopulmonary window and in the posterior mediastinum. The patient was referred for bronchoscopy but died within 24 h of transfer. A coroner's post-mortem confirmed carcinoma of the lung.

Case 4 (Table 2, Patient 4)

A 76-year-old man was admitted for further investigation of leg pain, weakness and numbness which had been present for 5 months. There was relentless progression initially, with weakness of the left leg then the right leg, associated with double incontinence and patchy asymmetrical sensory loss. His appetite was poor and he had lost 2 stones (12.7 kg) in weight over 5 months. On examination he looked unwell. Movements of the leg were very painful. He had asymmetrical flaccid paraparesis, with marked weakness proximally in the left leg and distally in the right leg. Sensation was reduced in a patchy distribution up to the level of T4 on the left and T11 on the right; this was more for pinprick than for joint position sense. Lower abdominal and lower limb deep tendon reflexes were absent and plantar responses were flexor. There were no abnormalities of the cranial nerves or upper limbs. General examination was negative. Routine blood tests were normal, apart from an

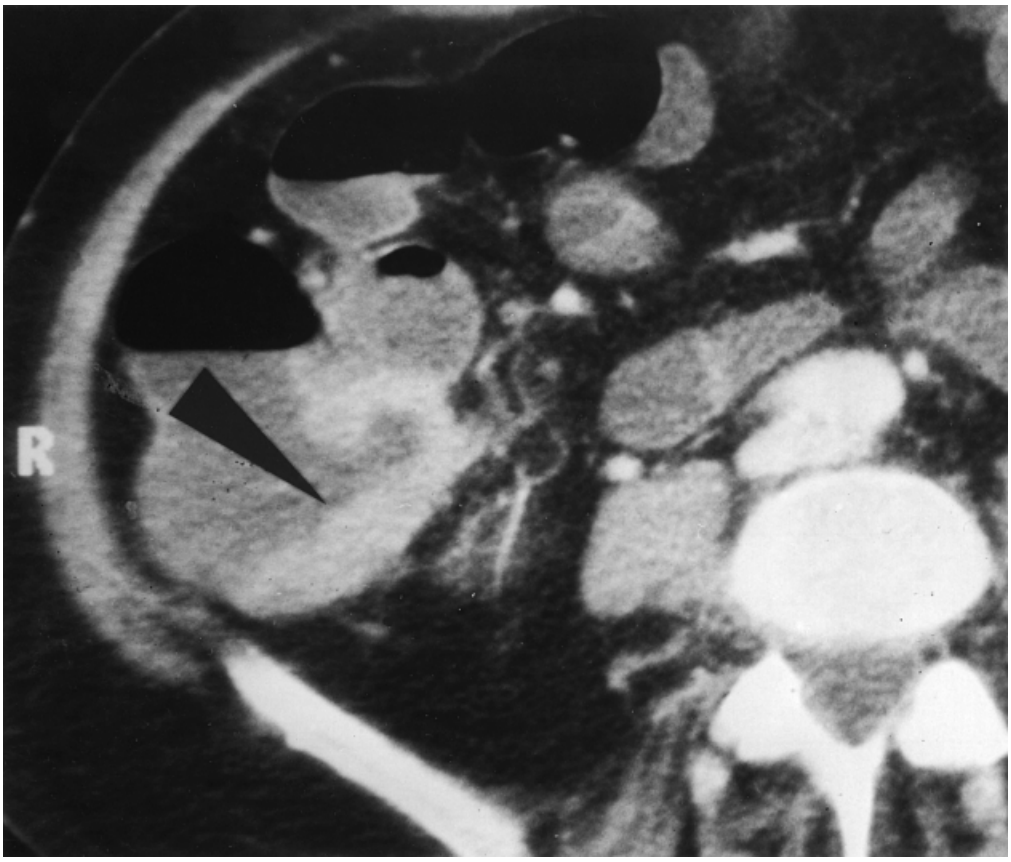

Fig. A2 Case 1. CT pneumocaecogram showing annular lesion in the caecum (arrowhead), which was thought to be a carcinoma on radiological evidence.

elevated CRP (C-reactive protein; 26 mg/l); the ESR (erythrocyte sedimentation rate) was normal. He was negative for rheumatoid factor, anti-nuclear antibody, antineutrophil cytoplasmic antibody and anti-neuronal antibodies. Chest X-ray and abdominal ultrasound tests were negative. Nerve conduction studies showed severe and slightly patchy motor sensory neuropathy affecting the lower limbs, with extensive denervation in all limb muscles studied, including the iliopsoas and paraspinals up to the mid-thoracic region, although the extent was variable. It was felt that neoplastic spinal canal infiltration was the most likely cause, but gadolinium-enhanced MRI scanning of the brain and spine and CSF examination, including cytology and oligoclonal bands, were entirely normal. FDG-PET scanning revealed two foci of abnormal hypermetabolism in the pelvis, one in the base of the bladder and one to the right of the midline. The PSA (prostate-specific antigen) concentration was elevated at 25.8 IU/l. These appearances raised the suspicion of prostate cancer but trans-rectal prostatic biopsies were negative for malignancy. A bone marrow aspirate was done and was normal. A sural nerve biopsy was taken and revealed a severe axonal neuropathy with evidence of vasculitis. The patient was treated with intravenous cyclophosphamide and methylprednisolone and made a remarkable recovery to the point that he was able to walk unaided on discharge 3 months later.

Case 5 (Table 2, Patient 5)

A 58-year-old woman presented in November 1998 with small bowel obstruction which settled on conservative treatment. A subsequent barium enema was normal. In March 1999 she developed mood change, nausea, weight loss and mild unsteadiness. This was initially ascribed to a psychiatric illness in view of the negative investigations, including gastroscopy, two MRI brain scans and a lumbar puncture. Over the next few months she developed gross leg, arm and truncal ataxia and became unable to walk or stand unaided. She also had oscillopsia and dysarthria. On general examination, there was evidence of weight loss but no other abnormalities. She had coarse titubation and tremor of the upper body on standing. Initially, her eye movement abnormalities were limited to nystagmus on right and left lateral gaze but within a few months she had developed chaotic eye movements with square-wave jerks, ocular flutter and possible opsoclonus. There was gross cerebellar ataxia in all four limbs and her speech was virtually incomprehensible because of severe dysarthria. Sensory testing revealed reduced pinprick and temperature sensation distally with loss of deep tendon reflexes in her lower limbs. She had anti-Hu antibodies in her serum but all imaging investigations, including chest X-ray, abdominal ultrasound and CT of the thorax, abdomen and pelvis, were normal. FDG-PET scan revealed an area of increased uptake next to the apical segment of the left lower lobe. Further fine-cut CT imaging of the thorax confirmed the presence of enlarged nodes in the aortopulmonary window. It was felt too dangerous to biopsy them, and bronchoscopy was negative. She was treated with mediastinal radiotherapy to a total dose of 45 Gy, with benefit in terms of general well-being and weight gain and a mild but definite improvement in her cerebellar syndrome. She received a course of intravenous immunoglobulin both before and

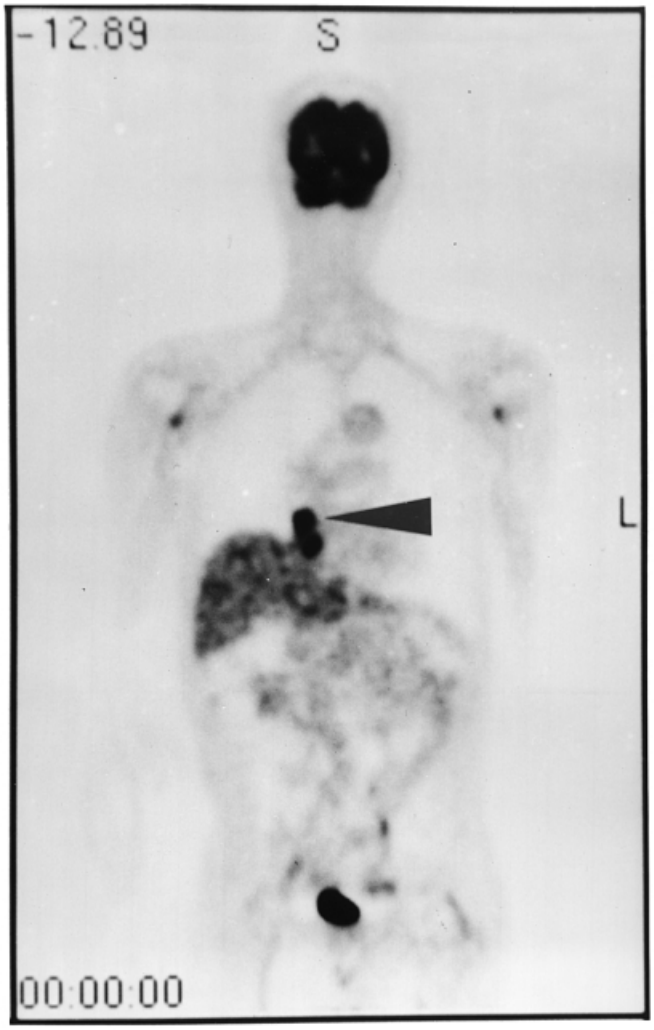

Fig. A3 Case 4. Coronal view of half-body FDG-PET scan showing two confluent areas of increased tracer uptake in the retrocardiac region adjacent to the right heart border (arrowhead). Post-mortem examination confirmed that these were due to a carcinoma of the bronchus.

after treatment of the presumed carcinoma, with no clear benefit. Sixteen months later she presented again with a subcutaneous nodule in her thigh, which was excised and shown to be a metastatis from a small-cell lung cancer.

Case 6 (Table 3, Patient 2)

A 66-year-old woman with a history of irritable bowel syndrome, polymyalgia rheumatica and sclerosing cholangitis presented in 1998 with diarrhoea, vomiting and weight loss, which lasted a few days. Six months later, the diarrhoea and vomiting recurred and this was followed shortly afterwards by numbness, pain and ataxia in the left leg and right arm. There was marked postural hypotension. Neurological examination revealed loss of tendon reflexes and severe sensory ataxia. The pupils were not affected. Nerve conduction studies showed a severe patchy sensorimotor axonal neuropathy. A sural nerve biopsy confirmed a severe and acute axonal neuropathy associated with scattered mononuclear cells in the epineurium. She was positive for anti-Hu antibodies on two occasions but chest X-ray and CT of the thorax and abdomen were negative for malignancy. She did not respond to intravenous methylprednisolone but after 5 days of intravenous immunoglobulin treatment there was a definite reduction in her ataxia and neuropathic pain and she could mobilize with the help of a frame, when she had been previously been bed-bound. Six months later she developed episodes of altered consciousness, which resolved after carbamazepine was prescribed by her general practitioner. An MRI scan of the brain showed extensive signal change in the left hippocampus and amygdala consistent with limbic encephalitis. She was referred to this institution for further investigations. FDG-PET scanning revealed two areas of slightly increased uptake in therecto-sigmoid junction. Flexible sigmoidoscopy and rectosigmoid biopsies were all normal. At review 18 months later, the neurologist recorded some return of sensation in her feet.