CASE REPORTS

Acute intermittent porphyria and phaeochromocytoma: shared features

Acute intermittent porphyria (AIP) is rare in Europeans, with an estimated prevalence of 1-2 per 100 000.¹ Acute attacks of porphyria cause severe abdominal pain and a range of neurological and other features, including hypertension, tachycardia and excessive sweating. Some of the clinical features of AIP have been attributed to adrenergic hyperactivity.²

Phaeochromocytoma is a neuroendocrine tumour, with an incidence of approximately 0.15 cases per 100 000 per year in the UK.³ The presenting symptoms are sustained or paroxysmal hypertension, sweating, palpitations and anxiety, secondary to excessive production of catecholamines and their metabolites. Diagnosis is based on raised urinary excretion of catecholamines or their metabolites, followed by localisation using CT and/or MRI and specific radio-localisation, usually with metaiodobenzylguanidine (MIBG).

We present a patient with AIP and fluctuating hypertension in whom the finding of raised catecholamine excretion led to an incorrect diagnosis of co-existent phaeochromocytoma.

Case report

A 34-year-old woman, diagnosed with AIP at age 29, developed intermittent labile hypertension which was difficult to control. Urinary catecholamine excretion was found to be abnormal

(tables 1 and 2). Abdominal CT and MRI scans were normal but MIBG scintiscan was reported as showing increased tracer uptake in an area corresponding to the right adrenal gland, suggesting the possibility of a right-sided phaeochromocytoma. A further CT scan showed no lesion in the right adrenal. Based on the positive MIBG scan, in the presence of raised catecholamines, an exploratory laparotomy was performed and the right adrenal removed. Histology of the adrenal gland was normal, showing no evidence of phaeochromocytoma. This finding was confirmed by an expert endocrine pathologist. Twelve weeks postoperatively, two further 24 h urine collections revealed abnormal norepinephrine and normetadrenaline levels and the question was raised whether she continued to harbour a phaeochromocytoma, not detected at the original operation.

Following referral to our centre, review of her history revealed that a number of the 24 h urine collections had been performed when she was an inpatient and acutely unwell with abdominal pain due to her porphyria. Further, she did not require the prescription of any antihypertensive drugs by her general practitioner while an outpatient.

Two subsequent 24 h catecholamine collections were taken when she was recovering from an acute attack. The first of these (21.05.02) showed only borderline raised norepinephrine levels which had returned to normal the following day (22.05.02). One month later, when she was completely well and normotensive on no antihypertensive medication, free catecholamines and metadrenalines were entirely normal on two consecutive days (25.06.02 and 26.06.02). It was concluded that there was no evidence of

phaeochromocytoma and that the raised urinary catecholamine excretion observed prior to and following the removal of the right adrenal gland was due to sympathetic hyperactivity consequent to pain and AIP. Three years later she remains free of any evidence of phaeochromocytoma.

Discussion

Acute intermittent porphyria and phaeochromocytoma are both rare conditions. Consequently few clinicians gain experience in recognising the spectrum of their clinical presentation. Lack of awareness of the features of an acute porphyria attack led, in this case, to another explanation being sought for a clinical sign (severe, labile hypertension) which was in fact compatible with the original diagnosis of AIP. This was compounded by "false positive" results of biochemical and radiological investigations. In retrospect this patient had an unnecessary major operation removing a normal adrenal gland.

Hypertension and tachycardia occur in approximately two-thirds of patients presenting with acute attacks of porphyria.⁴ This is thought to be secondary to sympathetic hyperactivity, stimulated by extreme pain, leading to increased production and release of catecholamines. However, the evidence base is limited to reports on small numbers of patients, relying on assay methodology which is no longer in clinical use.⁵⁻⁷

More recently, there has been one report of diagnostic confusion between the clinical features of phaeochromocytoma and AIP,⁸ and a further single case report documenting markedly raised urinary free catecholamines, metadrenalines and vanillylmandelic acid during one of two acute attacks of AIP complicated by severe hypertension.⁹

Estimates of the performance of any diagnostic test are dependent on the patient population to which it is applied and the criteria chosen for positive or negative results. Published studies are therefore difficult to compare. Quantitation by HPLC of 24 h urinary free catecholamines (epinephrine and norepinephrine) was reported to be approximately 86% sensitive and 88% specific for phaeochromocytoma, with similar performance for urinary total metadrenalines.¹⁰ Others have reported considerably higher sensitivity (100%) and specificity (97-98%) for these urinary analytes.¹⁰ Known causes of "false positives" in modern HPLC methods include drugs (e.g. labetalol and linezolid) and unknown co-eluting interferents. In a series of 400 cases, MIBG scanning was 88% sensitive and 99% specific.¹² Causes of false positives include neuroendocrine tumours, adrenocortical carcinoma and adrenal metastases.

Morphological diagnosis of phaeochromocytoma is acknowledged to be difficult. Best

Table 1 Urinary catecholamine excretion: referring hospital analyses

Date	Norepinephrine	Epinephrine
Reference range (µmol/24 h)	0.12-0.59	<0.19
14.04.01	1.29	0.10
23.05.01	3.81	0.73
21.06.01	2.43	0.27
22.06.01	2.25	0.39
23.06.01	1.55	0.10
Post-adrenalectomy		
01.02.02	2.28	0.08
21.05.02*	0.61	0.06
22.05.02*	0.28	0.02

Italicised results indicate specimens collected during a clinical attack of acute intermittent porphyria.

*Specimens collected during recovery following an acute episode of abdominal pain.

All analyses were performed by high performance liquid chromatography. Urine supplemented with 440 µmol/l porphobilinogen and 172 µmol/l amino-laevulinic acid and urine from two other patients with porphyria containing uroporphyrin levels >400 nmol/l and >4000 nmol/l respectively produced no interference in catecholamine or metadrenaline analysis.

Table 2 Urinary catecholamine and metadrenaline excretion: Hope Hospital analyses (all post-adrenalectomy)

Date	Norepinephrine	Epinephrine	Normetadrenaline	Metadrenaline
Reference range (µmol/24 h)	<1.00	<0.20	<4.0	<2.0
05.02.02	1.65	0.10	8.7	1.3
25.06.02†	0.39	0.08	1.7	1.0
26.06.02†	0.45	0.08	1.7	0.5

Italicised results indicate specimens collected during a clinical attack of acute intermittent porphyria.

†Specimens collected when clinically well.

All analyses were performed by high performance liquid chromatography (see table 1).

practice was followed in that histological examination of the resected adrenal gland was confirmed to be normal by two pathologists, one an endocrine specialist. There was no clinical evidence of an extra-adrenal lesion. The normal blood pressure and normal catecholamine excretion observed when the patient was well led us to conclude that her intermittent hypertension and raised catecholamines were a direct consequence of her AIP.

The biochemical investigations gave "false positive" results because of the activity of her underlying disease, i.e. AIP. When performing such tests it is essential to consider coexisting conditions which may produce abnormal results, rendering the investigation at best uninformative, and at worst dangerous. This patient illustrates the need for specialists in inherited metabolic disease who can advise at an early stage on the management of rare conditions such as acute porphyria and prevent inappropriate treatment.

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Leucocyte common antigen (CD45) and CD5 positivity in an "undifferentiated" carcinoma: a potential diagnostic pitfall

CD45 is a transmembrane protein tyrosine phosphatase located on most haematopoietic cells. It has several isoforms, and haematopoietic cells express one or more of the isoforms—CD45RO, CD45RA and CD45RB.^{1,2} CD45 immunoreactivity is recognised to be highly specific for non-Hodgkin's lymphomas.^{3,4} CD45-expressing non-haematopoietic tumours are very rare. This was first noted by McDonnell *et al*⁵ in 1987, who reported a primitive sarcoma expressing CD45. Subsequently, Nandedkar *et al*⁶ reported three cases of undifferentiated large-cell, possibly neuroendocrine, carcinomas expressing CD45. Two of them were lymph node metastasis and one was a pulmonary tumour. All the three cases expressed both CD45 and cytokeratin. Two of the cases behaved in an aggressive manner.⁶

In contrast to CD45, CD5 is expressed in thymic carcinoma and malignant mesothelioma.^{7,8} To the best of our knowledge, this is the first reported case of a carcinoma expressing both CD45 and CD5.

Case report

We report a patient in their 60s who presented initially with weight loss over 1 month and bilateral leg weakness with deterioration in mobility of 2 weeks' duration. On examination, the patient was found to have bilateral cervical lymphadenopathy. Furthermore, the patient was an ex-smoker, and had been treated for chest

infection 1 month earlier, but was otherwise not taking any regular medication.

On admission, an epigastric mass, ascites and jaundice were noted. Blood tests showed low albumin, abnormal liver function tests, and normal blood counts, serum calcium, total cholesterol and thyroid-stimulating hormone.

Upper gastrointestinal endoscopy showed a normal oesophagus and stomach. However, there was a polypoidal lesion in the pharynx, just above the epiglottis, which was biopsied. Furthermore, radiological findings suggested that there was a liver lesion with the appearance of metastasis.

The patient died within a few weeks of diagnosis before any treatment could be instituted. Autopsy was not performed.

Materials and methods

The biopsy specimen was processed for routine paraffin embedding, and 4 µm paraffin sections were stained with H&E stain and used for immunohistochemical analysis with appropriate retrieval techniques, antibody dilutions and controls (table 1).

Pathological findings

Biopsy showed squamous mucosa with a poorly differentiated malignant tumour. The cells were large, with vesicular nuclei, prominent nucleoli and moderate amounts of eosinophilic cytoplasm, which in some cells was more opaque and fibrillar. Cellular cohesion and pleomorphism were observed. However, there was no discernible pattern. The overlying epithelium did not show dysplasia. Small

Table 1 Details of the antibodies used

Antibody	Dilution	Company
MNF-116	1:150	Dako, Cambridgeshire, UK
TTF-1	1:50	Novocastra (Vision Biosystems), Newcastle, UK
CD45	1:10	Dako
CD5 (Leu-1)	1:50	Novocastra (Vision Biosystems)
CAM5.2	1:10	ICRF(CRUK), UK
CD15	1:10	Dako
Synaptophysin	1:40	Dako
EMA	1:100	Dako
Ki-67	1:50	Novocastra (Vision Biosystems)
CD20	1:250	Dako
CD79a	1:10	Dako
Pax-5	1:50	Santa Cruz, Heidelberg, Germany
CD10	1:20	Novocastra (Vision Biosystems)
CD2	1:50	Novocastra (Vision Biosystems)
CD3	1:50	Novocastra (Vision Biosystems)
CD4	1:400	Novocastra (Vision Biosystems)
CD7	1:50	Novocastra (Vision Biosystems)
CD8	1:50	Novocastra (Vision Biosystems)
CD30	1:50	Novocastra (Vision Biosystems)
CD56	1:100	Novocastra (Vision Biosystems)
Alk	1:10	Dako
CD138	1:100	Serotec, Oxford, UK
CD38	1:50	Novocastra (Vision Biosystems)
Myeloperoxidase	1:2000	Dako
CD34	1:200	Dako
CK5/6	1:300	Dako
CK20	1:100	Dako
CK14	1:100	Dako
CK19	1:200	Dako
CK10	1:100	Novocastra (Vision Biosystems)
CA19.9	1:300	Novocastra (Vision Biosystems)
CEA polyclonal	1:1000	Dako
CA125	1:200	Dako
Chromogranin	1:200	Biogenex (Via Launch), Kent, UK
Calretinin	1:100	Zymed (Invitrogen), Paisley, UK
Melan-A	1:50	Novocastra (Vision Biosystems)

EMA, epithelial membrane antigen; TTF-1, thyroid transcription factor 1.