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ACTH-secreting 'apudoma' of gallbladder

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SUMMARY The case of a 44-year-old woman is reported. The diagnosis after the appropriate tests and laparotomy was ACTH-secreting 'apudoma' of the gallbladder. This is a rare tumour and this case is believed to be the first reported of an ectopic hormone producing tumour from this site.

In recent years there has been a steadily increasing interest in the APUD (amine precursor uptake and decarboxylation) cell system proposed by Pearse (1966, 1968) and Dawson (1970). These cells occur widely throughout the gut but also in the pituitary, thyroid, bronchus, pancreatic islets, and prostate. Their two distinctive properties are that they take up and decarboxylate the precursors of the arylethylamines 5-hydroxytryptamine, histamine and dopamine, and that they contain short-chain polypeptide hormones which they probably also synthesize. Known hormones considered to be secreted by this type of cell include adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormone (MSH), growth hormone, insulin, glucagon, gastrin, cholecystokinin, caerulin, secretin, gastric inhibitory polypeptide, and vasoactive intestinal polypeptide. It has recently been suggested that tumours producing one or more of these hormones are in fact tumours of APUD cells and should be classified as apudomas (Szijj, Csapó, László, and Kovács, 1969; Pearse and Welbourn, 1973). A case of an ACTH-secreting carcinoma of the gallbladder is reported here and this is believed to be the first reported case of an ectopic hormone-producing tumour from this site.

Case History

A 44-year-old housewife was admitted to a psychiatric hospital with a diagnosis of depression and hysteria. She gave a history of 12 months' gradual increase in weight and one month's increasing weakness, oedema of the legs, and inability to cope with her two teenage children and regular checkout job in a department store. During this time her husband had also noticed an increase in facial hair. Nineteen years previously she had been admitted to hospital with anxiety and depression shortly after her marriage On admission she was found to be obese (73 kg) with a blood pressure of 160/95, and the liver was tender and palpable. Investigations showed: haemoglobin 15·3 g/dl, WBC 11 500 per cmm, alkaline phosphatase 245 iu/l (normal 50-150), and a serum albumin of 3·5 g/100 ml (normal 3·5-5·2).

She remained very depressed and was mute for long periods of time but two weeks after admission she was found to have developed an electrolyte imbalance (Na 141, K 2·5, Cl 85 millimoles/litre) which required intravenous correction. At this time she was also found to have a urinary infection and clinical diabetes mellitus. After two months in hospital she had developed severe generalized weakness and her appearance had become frankly Cushingoid with a 'lemon-on-sticks' appearance, facial plethora and hirsutes (fig 1), an obese abdomen with striae, bruising, and obvious wasting of the quadriceps. Plasma cortisol levels were found to be raised (9.00 am: 38 μg/ml—normal 6-25; midnight: 29 μg/ml—normal 2-6).

She was then transferred to this hospital and by this time was unable to stand unsupported. An enlarged liver was again noted but clinical examination revealed no evidence of tumour elsewhere. Investigations showed: haemoglobin 12·6 g/100 ml, total WBC 10 900, alkaline phosphatase 190 iu/l, albumin 3·1 g/100 ml, normal serum, calcium, prothrombin ratio, and activated partial thromboplastin time. A chest radiograph was normal and radiographs of the skull showed a normal pituitary fossa. Intravenous pyelography and tomography revealed kidneys normal in size and position with no evidence of enlargement of either suprarenal gland. Shortly after her transfer she developed

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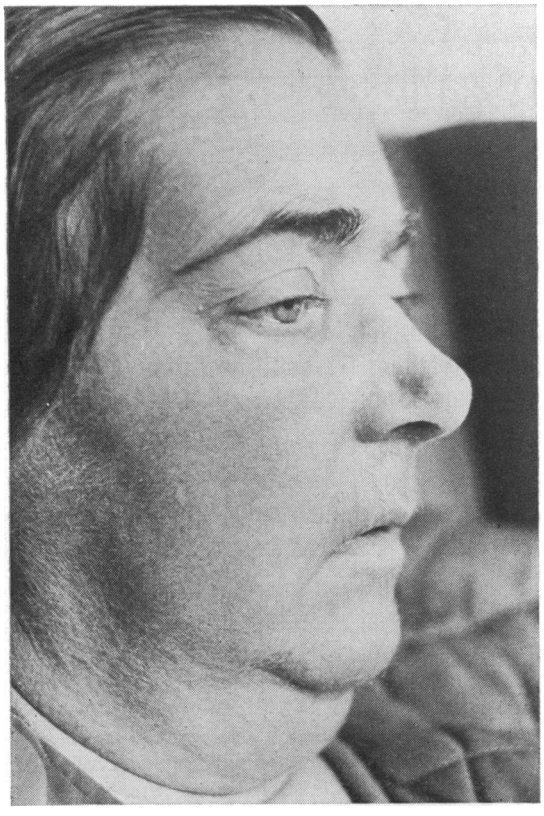

Fig 1 *The patient after admission to Frenchay Hospital. Note facial plethora and hirsutes.*

	Mean of Three Daily Basal Levels	Dexamethasone 2 mg/24 Hours		Dexamethasone 8 mg/24 Hours	
	Day 1-3	Day 4	Day 5	Day 6	Day 7
Adrenal androgens (mg/g creatinine) Normal 2·5, 2SD 1	1·7	2·6	3·0	4·8	5·6
Cortisol derivatives (mg/g creatinine) Normal 6·0, 2SD 3	59·5	79·8	91·7	106·0	176·0
Cortisol precursors (mg/g creatinine) Normal 1·0, 2SD 0·5	2·0	2·6	2·6	3·2	3·8
Plasma cortisol 9 am (μg/100 ml)	100·0	115·0	95·0	85·0	—

Table I *Results of dexamethasone suppression test and 24-hour urinary steroid analysis*

	Basal Level	Metyrapone (six doses 750/mg/4 hrly)	After Metyrapone
	Day 1	Day 2	Day 3
Adrenal androgens (mg/g creatinine) Normal 2·5, 2SD 1	8·8	5·7	16·6
Cortisol derivatives (mg/g creatinine) Normal 6·0, 2SD 3	189·0	137·6	50·1
Cortisol precursors (mg/g creatinine) Normal 1·0, 2SD 0·5	7·2	26·5	120·2
Sum of precursors and derivatives	196·2	164·1	170·3

Table II *Results of metyrapone test and 24-hour urinary steroid analysis*

further electrolyte imbalance (Na 136, K 2·3, Cl 77 millimoles/litre) which again necessitated correction by intravenous infusion.

SPECIAL INVESTIGATIONS

The results of investigation of the pituitary-adrenal axis are shown in tables I and II. A dexamethasone suppression test was carried out followed by a metyrapone test and in both were estimated the levels of adrenal androgens (11 deoxy-17 oxosteroids), cortisol derivatives (11 hydroxy-17 hydroxycorticosteroids), and cortisol precursors (11 deoxy-17 hydroxycorticosteroids) from 24-hour urine specimens. In the dexamethasone suppression test (table I), high basal levels of cortisol precursors and derivatives were demonstrated and two days of dexamethasone administration at 2 mg/24 hours followed by two days at 8 mg/24 hours showed no suppression, but rather a marked increase in all three fractions. High levels of plasma cortisol were found at this time and a raised level of plasma ACTH of 161 μg/ml (normal 10-80). A metyrapone test (table II) two weeks later showed even higher basal steroid levels, and the administration of six 750 mg doses of metyrapone over 24 hours did not show any significant alteration in the sum of precursors and derivatives.

A laparotomy was then carried out in the hope of removing a primary tumour but a large secondary tumour deposit was found in the liver and tumour was present in the wall of the gallbladder where it occluded Hartmann's pouch. In view of the disseminated malignancy, adrenalectomy was not performed. Histology of a biopsy of the hepatic tumour revealed a fibrous, poorly differentiated anaplastic adenocarcinoma. Also first noted at the time of operation was a scattered brown pigmentation of the anterior abdominal wall. Postoperatively, the patient made a good initial recovery, and was able to make weekend visits home. However, although she was greatly improved psychologically after operation, her general condition gradually

worsened. She became progressively more oedematous, the diabetes became more difficult to control, and she eventually died three months after surgery.

By prior agreement with the patient's husband, an immediate postmortem liver biopsy was obtained, portions of which were fixed in glutaraldehyde, buffered formol saline, and small blocks were rapidly deep-frozen in Arcton at its melting point. The tissue was studied by the Department of Histochemistry at the Hammersmith Hospital. Histology of the tumour showed it to be composed of masses of round and polygonal cells separated by delicate strands of connective tissue. Lead haematoxylin stains indicated the presence of 'endocrine' granules, but electron microscopic examination revealed relatively few granules in most of the cells, probably due to poor preservation of the tissue. Silver impregnation showed that the tumour cells were argyrophil (fig 2). Cytochemistry revealed strongly positive enzyme reactions characteristic of APUD cells (non-specific esterase, alpha glycerophosphate dehydrogenase). An immunofluorescent study applying an indirect (sandwich) technique using antisera to gastrin, pentagastrin, caerulein, insulin, glucagon, secretin, calcitonin, VIP, GIP, growth hormone, and ACTH gave a positive reaction with ACTH antiserum only.

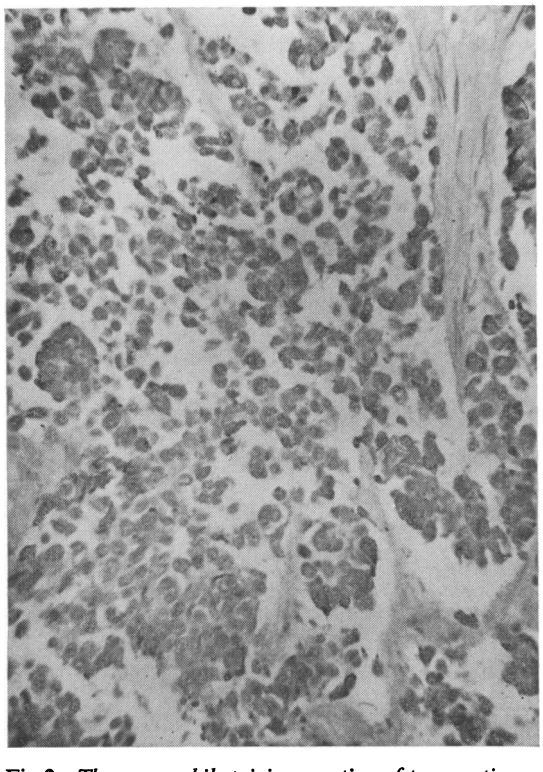

Fig 2 *The argyrophil staining reaction of tumour tissue obtained from the liver at necropsy.*

Formal postmortem examination revealed numerous deposits of secondary tumour in the liver with almost complete replacement of liver tissue in the region of the gallbladder. The latter contained a mucocoele and much of the neck around the cystic duct was widely infiltrated by tumour. Situated in the beginning of the cystic duct was a papillary ingrowth of tumour. Some of the lymph nodes along the pancreatic margin were replaced by secondary carcinoma, but the pancreas itself was free of tumour (confirmed histologically). No other organ contained tumour. The adrenal glands weighed 25 g each and showed marked hyperplasia of the zona reticularis with gross diminution of the two outer cortical layers. The pituitary gland was macroscopically normal but Crooke's cells were present on histological examination.

Discussion

The patient described here presented with the features of Cushing's syndrome. In addition she developed a severe hypokalaemic alkalosis (low plasma potassium and chloride, normal sodium), and this electrolyte imbalance occurring in a case of Cushing's syndrome is strongly suggestive, indeed is the biochemical hallmark, of the ectopic ACTH syndrome (Ratcliffe and Rees, 1974). The excessive urinary potassium loss has been shown to be due to overproduction of deoxycorticosterone and corticosterone (Schambelan, Slaton, and Biglieri, 1971).

A dexamethasone suppression test in this case showed a paradoxical rise in the three urinary steroid fractions estimated. This has been described elsewhere in association with ectopic ACTH production (Bailey, 1971), and in one case of Cushing's disease was shown conclusively by Liddle (1972) and Brown, Van Loon, Orth, and Liddle (1973) to be due to a regular periodic cycle of hormone secretion. In the latter instance the observed rises in hormone levels during dexamethasone administration were entirely fortuitous. However, in our case, a metyrapone test a fortnight later demonstrated a further gross increase in urinary steroid levels suggesting an actively increasing hormone-producing cell mass. The metyrapone test also failed to reveal any pituitary dependance of adrenal function in our patient. A careful clinical and radiological search did not reveal a primary tumour in the suprarenal glands or elsewhere and the only preoperative evidence of possible disseminated malignancy was the finding of hepatomegaly, a raised level of serum alkaline phosphatase,

low serum albumin, and a falling haemoglobin. The discovery of a carcinoma at laparotomy and the observation at that time of a newly developed extensive brown pigmentation of the anterior abdominal wall were both strongly suggestive of a parallel production of ACTH and MSH by this tumour.

Histochemical studies performed on tumour tissue obtained from the liver immediately after death demonstrated properties characteristic of APUD cells, and specific positive immunofluorescence was obtained with ACTH antiserum. This was perhaps the more remarkable in view of the metastatic situation and histologically anaplastic nature of the tumour biopsied. Laparotomy and postmortem examination both yielded clear evidence that this tumour had arisen from the wall of the gallbladder or cystic duct.

We conclude that this was a case of ectopic ACTH syndrome resulting from an apudoma arising in the gallbladder or cystic duct.

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