Metastatic hepatic carcinoid associated with ectopic ACTH syndrome, resistant to octreotide and ketoconazole therapy

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The syndrome of ectopic ACTH secretion from an occult carcinoid tumor is a well-recognized entity. There are roughly two types of ectopic ACTH syndrome, one associated with overt malignancy like oat cell carcinoma and the other with occult neoplasm. Carcinoid tumors are the most common occult source of ACTH.[1] In a recent review of 68 cases of ectopic ACTH-secreting tumors, 60% were carcinoid followed by small cell carcinoma of the lung (10%), pancreatic neuroendocrine neoplasia, and miscellaneous other tumors.[2]

Typically, ectopic ACTH is suspected when a patient with a known malignancy is found to have refractory hypokalemia and metabolic alkalosis. Less frequently patients may present with typical clinical and/or biochemical features of Cushing syndrome before the oncologic diagnosis. Somatostatin receptor scintigraphy (SRS) allows us to differentiate between patients with somatostatin receptor positive tumors, which are likely to respond favorably to treatment with somatostatin analogue (octreotide) and those who are SRS negative, for whom chemotherapy may be indicated. [3]

A reduction in cortisol excess in response to ketoconazole can be expected in most patients with ectopic Cushing syndrome, and clinical improvement in hypokalemic metabolic alkalosis, diabetes mellitus, and hypertension may occur even in the absence of a complete hormonal response. Ketoconazole is an effective and safe treatment for ectopic Cushing syndrome, but ultimate control of the syndrome is dependent on successful treatment of the underlying malignancy.[4]

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Case

A 54-year-old woman was admitted to King Faisal Specialist Hospital and Research Centre on 16 April 2002 with complaints of abdominal pain, diarrhea, generalized weakness, low back pain and skin rash. She had been well until 7 months previously when she started to have recurrent right upper quadrant pain with loose watery bowel movements without mucus or blood, 3 to 6 times/day. She lost about 10 kg of weight during this period. Her lower backache started 3 months before admission. The pain was not radiating, but worsened on slight movements, which had made her bedridden for the previous 2 months. There was no history of bowel or bladder incontinence. She was seen in a private hospital where a CT scan of the abdomen showed multiple hypo-echoic lesions of varying size scattered over the liver. She was also found to have severe hypokalemic metabolic alkalosis. Her past medical history was significant for prolonged diabetes mellitus complicated by diabetic nephropathy and retinopathy requiring insulin and metformin. She gave a history of hypertension controlled by an ACE inhibitor. She also had undergone laparotomy for complicated appendicitis 15 years previously, but unfortunately, the histopathology report could not be traced.

On admission, physical examination showed an ill looking lady, with cushingoid faces, afebrile, pulse 84/min, BP 140/90, no pallor, edema, icterus or lymphadenopathy. A diffuse palpable purpuric rash was noticed over the upper and lower extremities, suggestive of vasculitis (Figure 1).

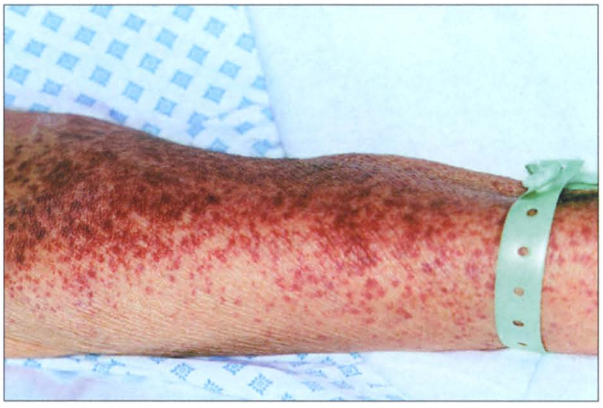

Figure 1. Diffuse palpable purpuric rash over the forearm.

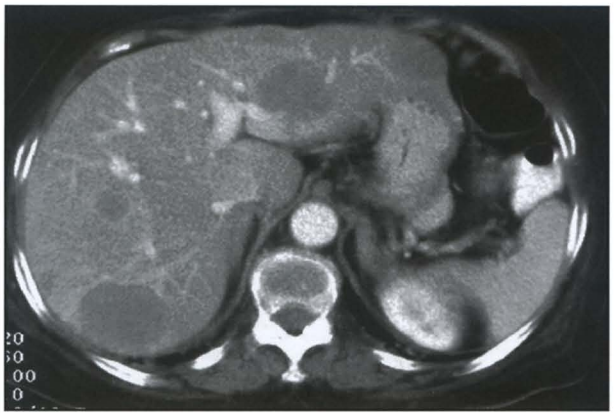

Figure 2. Multiple low attenuated lesions of varying size distributed throughout the liver.

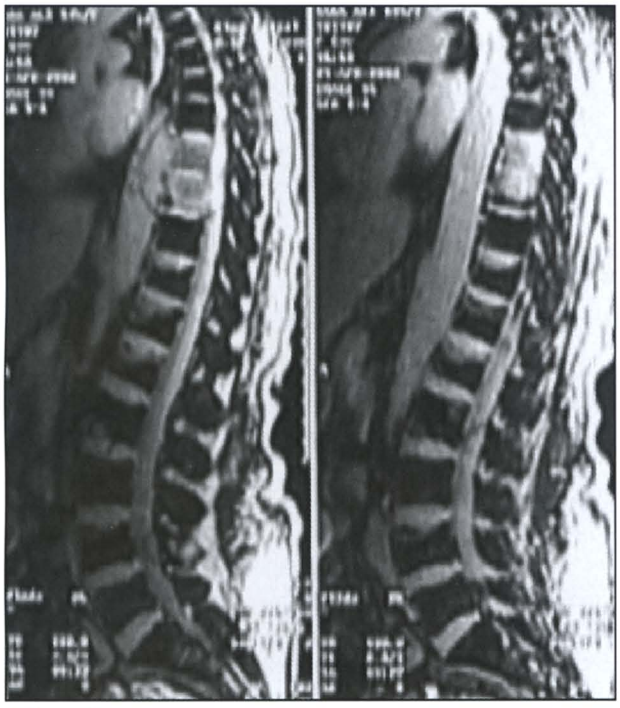

Figure 3. Multiple abnormal signal intensity areas at T8, 9, 11, 12 and L1 consistent with bony metastasis.

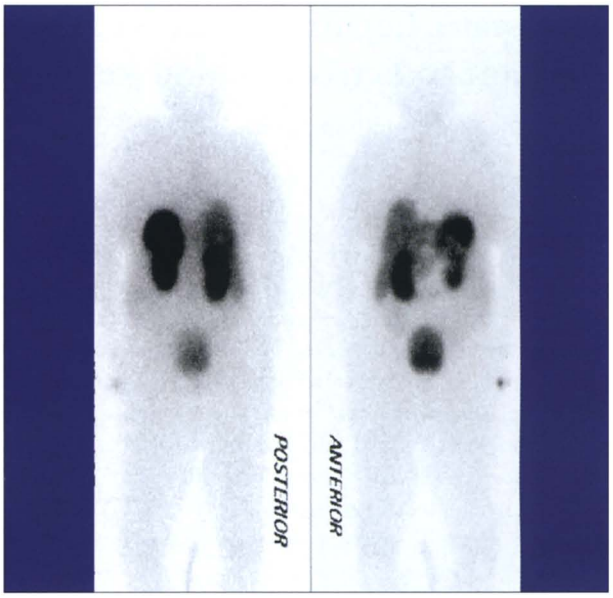

Figure 4. Ocreotide scan of whole body images after injection of 219 MBq of Indium^{111} ocreotide (negative for uptake).

Abdominal examination showed tender hepatomegaly with a liver span of 18 centimeters, with no ascites or splenomegaly. The cardiovascular and chest examination were unremarkable. Neurological examination showed normal higher functions, with intact cranial nerves. She had a power grade 2/5 in both the lower limbs with mild hypotonia and diminished reflexes. The plantars were down-going and sensations were intact. Local tenderness was detected in the lumbo-sacral spine mainly at the level of L1 and L2.

Laboratory test results showed severe refractory hypokalemia and hypercortisolemia (Table 1), with failure of suppression following high-dose dexamethasone suppression, suggesting an ectopic or adrenal source. Screening for hepatitis B and C was negative. Upper GI endoscopy showed mild gastritis with erosive duodenitis. Colonoscopy and bronchoscopy were normal. Echocardiography showed left ventricular hypertrophy, but no right side heart involvement. A chest X-ray showed a few small, rounded opacities in the right lung with very minimal bilateral pleural effusion. CT of the abdomen showed multiple low, attenuated lesions of varying size distributed throughout the liver, the largest 4x5 centimeters, located in segment 7 (Figure 2). Bilateral adrenal hyperplasia was noted, but no isolated adenoma was seen. The pancreas and spleen were normal. CT of the chest showed multiple small, nodular metastatic lesions scattered over the right upper and lower lobe with bilateral small pleural effusions. MRI of the spine showed multiple abnormal signal intensity lesions at T8, T9, T11, T12 and L1, consistent with bony metastasis, but there was no evidence of spinal cord compression (Figure 3).

An octreotide scan of whole body images following injection of 219 MBq of indium111 octreotide, by FDP-PET (fluorodopa-positron emission tomography), showed no uptake, and was therefore negative (Figure 4). A fine-needle aspiration from the liver mass was consistent with a neuroendocrine tumor; the cell stain was positive for synaptophysin and chromogranin, which are neuroendocrine tumor markers (Figure 5).

On the basis of our clinical, biochemical, pathological and radiological investigations, we made the diagnosis of carcinoid tumor of occult primary with ectopic ACTH syndrome. The patient was started on subcutaneous

Table 1. Laboratory test results.

White blood cell count ($X10^6$)	11.8
Hemoglobin (g/L)	154
Platelets	219 000
INR	0.8
Bleeding time (s)	300 (170-600, normal)
Bilirubin (µmol//L)	12
Alanine aminotransferase (ALT) (U/L)	268
Alkaline phosphatase (U/L)	571
g-Glutamyltransferase (GGT) (IU/L)	1755
a-fetoprotein (µg/L)	11
Calcium (mmol/L)	1.98
Carcinogenic embryonic antigen (CEA) (µg/L)	0.9
Cancer antigen (CA) 19-9 (U/mL)	4.8
pH	7.51
HCO_3 (mmol/L)	38.8
Potassium (mmol/L)	1.4
Sodium (mmol/L)	147
Creatinine (µmol/L)	57
Serum cortisol (AM) (nmoL/L)	7184 (normal, 120-160)
ACTH (ng/L)	362 (normal, up to 46)
Renin (µg/L/h)	0.37
Gastrin (pg/mL)	89
Vasoactive intestinal peptide (pg/mL)	85 (normal, 0-75)
Glucagon (pg/mL)	87 (normal, 50-200)
Urinary 5-HIAA (mg/24h)	75 (normal, 0-6)
Urinary aldosterone (nmoL/d)	30.4 (normal, 8-83)
24-h urinary potassium (nmoL/d)	203
24-h urinary cortisol (mg/L/24h)	8872 (normal, 5-55)
Stool chloride (mmol/L)	18
Stool potassium (mmol/L)	100
Stool sodium (mmol/L)	<25

octreotide 300 µg daily in three divided doses and ketoconazole 800 mg daily in divided doses, with supportive treatment in the form of calcitonin, potassium, calcium, vitamin D and antihypertensive medications. In the early days of admission the patient showed some symptomatic improvement with potassium replacement, but there was no response to the hypercortisolemia and she had recurrent episodes of severe hypokalemic metabolic alkalosis. Unfortunately, after 6 weeks of intensive conventional therapy the patient died of complicated urosepsis.

Discussion

Carcinoids are small, slowly growing tumors that comprise the most common type of neuroendocrine neoplasm.

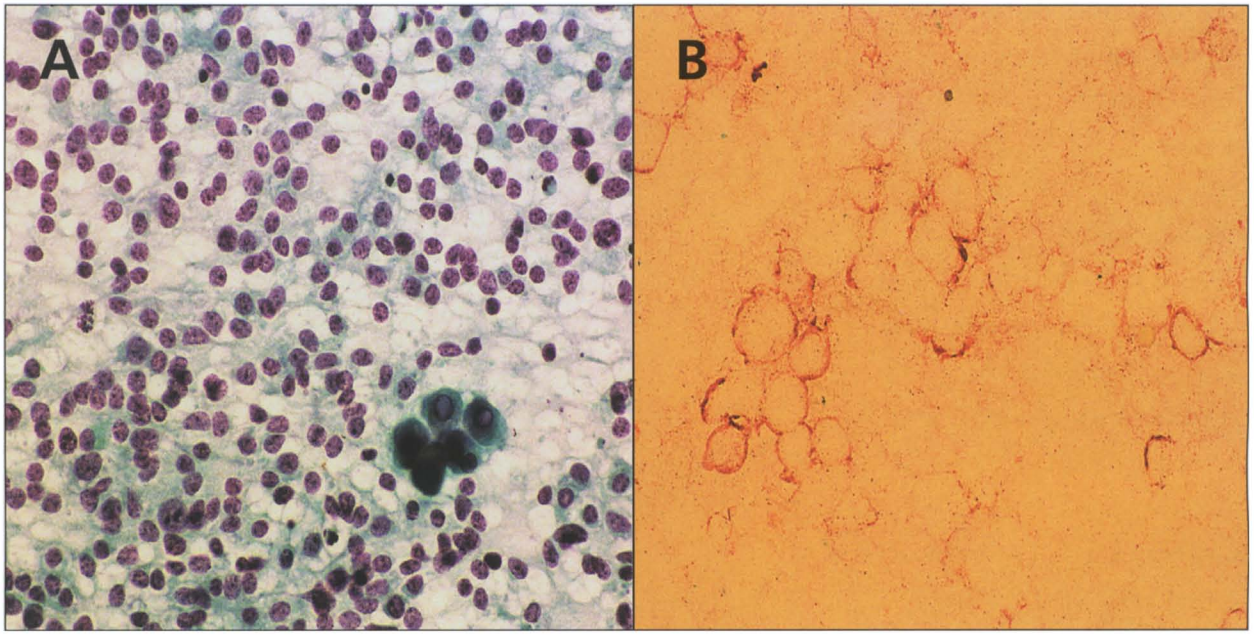

Figure 5. (A) Fine needle aspiration of the liver showing a highly cellular smear and clusters of individual cells with eccentric nuclei and abundant cytoplasm. (B) Cell stain positive for synaptophysin and chromogranin.

They are found mainly in the gastrointestinal tract. The occurrence of metastasis relates to the site and size of the primary lesion. Because of the small size of most carcinoids, primary lesions are difficult to localize using conventional techniques such as CT and ultrasonography in 10% to 40% of cases,[5] by MRI in 20%,[6] and by barium meal in 30%.[7] Scintigraphy with octreotide detects more metastatic lesions than ^{123}I-MIBG (meta-iodobenzylguanidine) in patients with carcinoid and pancreatic islet cell tumors.[8] Somatostatin receptor scintigraphy (SRS) showed that carcinoid tumors (primary lesions or metastasis) were visualized in 80% to 95% of cases and therefore SRS might be superior to conventional imaging techniques,[9] but the disadvantage of SRS is that it is usually unable to detect tumors of <1 centimeter in diameter or those that are somatostatin receptor-negative outside the liver.[10] In addition, liver spleen and renal excretion cause a high background activity during scintigraphy and may therefore mask small receptor positive spots. In our case the octreotide scan was negative, suggesting the absence of somatostatin receptors. However, there are five subtypes of somatostatin receptor on carcinoid tumor cells and not all bind to octeriotide.[11] It may be possible that somatostatin receptor status changes as the tumor spreads and becomes more dysplastic, not favoring octreotide binding with a sparing effect, which highlighted the poor response to octreotide. Somatostatin analogue (octreotide) was first shown directly to reduce ACTH production from a bronchial carcinoid tumor in 1988.[12] The effect has been confirmed elsewhere,[13] but later various other reports showed a failure of somatostatin analogue to control Cushing syndrome,[14] while others showed a variable response.[15]

We treated our patient with ectopic ACTH-producing tumor by octreotide for more than 6 weeks but there was no significant fall in the serum cortisol, ACTH or urinary-5-HIAA level. In addition, hypokalemic metabolic alkalosis also did not improve with octreotide therapy. In the cases previously reported by Cheung et al[14] octreotide failed to control the biochemical and clinical features of hypercorticosolemia in two patients with ectopic ACTH carcinoid tumor responding to octreotide therapy. Chemotherapy was considered, but in the presence of widespread metastasis and a deteriorating general condition, the plan to initiate the chemotherapy was withheld.

The usefulness of ketoconazole in the management of Cushing syndrome secondary to primary adrenal and pituitary causes is well recognised.[16] Its use in Cushing syndrome secondary to ectopic ACTH production by the tumor has been reported less frequently. Through our literature review, we could identify only 27 other patients who were treated with ketoconazole for presumed ectopic Cushing syndrome. The primary tumors in 7 patients were carcinoid, 2 patients showed complete response, 2 a partial response and 3 no response. Therapeutic escape has been described in patients with nonmalignant causes of Cushing syndrome treated for long periods.[17] This effect is more difficult to assess and probably less relevant to patients with malignant disease, since therapeutic escape inevitably occurs due to tumor progression unless the cancer can be cured. This was certainly true in our patient because she

showed no clinical or biochemical response to ketoconazole, possibly because of the metastasizing tumor, other co-morbid conditions and poor response to somatostatin. In the literature, most patients died of progressive disease and worsened manifestations of hypercortisolemia, and by overwhelming infection, despite ketoconazole therapy.

In conclusion, we found that octreotide failed to control the biochemical and clinical features of hyper cortisolemia in carcinoid tumor with ectopic ACTH due to the absence of somatostatin receptors. By identifying somatostatin-receptor positive tumors, SRS is useful for selecting patients who might benefit from octreotide therapy. We suggest that SRS be performed in all cases of suspected carcinoid tumor before deciding to start octreotide therapy. Ketoconazole therapy is an effective and safe treatment for ectopic Cushing syndrome, but the ultimate control of the syndrome is dependent on successful treatment of the underlying malignancy.

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