North Middlesex University Hospital NHS Trust

Cushing's syndrome is an important constellation of symptoms to recognise due to malignancy being a possible underlying cause

A ALKREKSHI, A PATEL, A GARG
North Middlesex University Hospital, Sterling Way, London N18 1QX

Case history

A 45-year-old female presented with four-month history of worsening blurred vision, dry mouth and lethargy. In the hindsight, for the past three years she had weight gain, easy bruising, oligomenorrhoea, facial flushing and difficulty with activities such as walking upstairs and above head arm activities. She was hypertensive and hypokalaemic in addition to the physical signs of facial plethora, interscapular fat pad, purple striae, central obesity, thin skin, leg bruises and proximal myopathy. Past medical history included Poland's syndrome, PCOS and migraine.

Investigations

Routine blood tests results are shown in (table 1). 48-hour low dose dexamethasone suppression test; 0-hour cortisol of 1034 nmol/L and 48-hour cortisol of 1227 nmol/L. Adrenocorticotrophic hormone 231 ng/L (0-46), chromogranin A 155 pmol/L (0-60), and chromogranin B 89 pmol/L (0-150). Fasting gut hormones were within normal limits, except for gastrin which was raised secondary to PPI use.

CT chest, abdomen, and pelvis showed lobulated pancreatic tail tumour with multiple enhancing liver metastases (figures 1-3). MRI pituitary was normal. Gallium-68 PET-Octreotate scan showed avid uptake.

Ultrasound guided liver biopsy showed metastatic well differentiated neuroendocrine neoplasm of intermediate grade, Ki-67 of 5%, with morphologic features in keeping with the clinical suspicion of pancreatic primary. Immune staining for ACTH was negative.

Results and Treatment

Diagnosis of paraneoplastic Cushing's syndrome was made. Patient was started on metyrapone 500mg tds and spironolactone 50mg od, and that resulted in rapid symptomatic improvement and normalization of potassium levels. Cortisol levels dropped to less than 100 nmol/L and oral replacement doses of hydrocortisone were commenced.

Case was discussed in neuroendocrine multidisciplinary meeting and the plan was to start with chemotherapy to shrink the tumour, and subsequent peptide radio-receptor therapy.

Variable	Result	Reference range
Haemoglobin (g/L)	152	115-155
White cell count ($x10^9$/L)	17	3.0-10.0
Platelets ($x10^9$/L)	322	150-400
Neutrophils ($x10^9$/L)	14.6	2.0-7.5
Sodium (mmol/L)	142	135-145
Potassium (mmol/L)	2.5	3.5-5.1
Urea (mmol/L)	5.5	1.7-8.3
Creatinine (umol/L)	86	49-92
Bilirubin (umol/L)	9	0-20
Alanine transaminase (IU/L)	37	0-31
Alkaline phosphatase (IU/L)	114	34-104
Albumin (g/L)	38	34-50
HBA1c (mmol/mol)	38	20-42
Calcium (mmol/L)	2.31	2.20-2.60
Phosphate (mmol/L)	0.6	0.87-1.45

Table 1

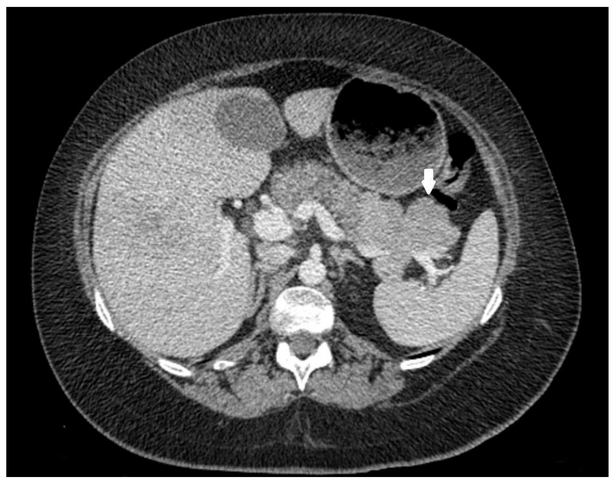

Figure 1. Lobulated pancreatic tail tumour (white arrow).

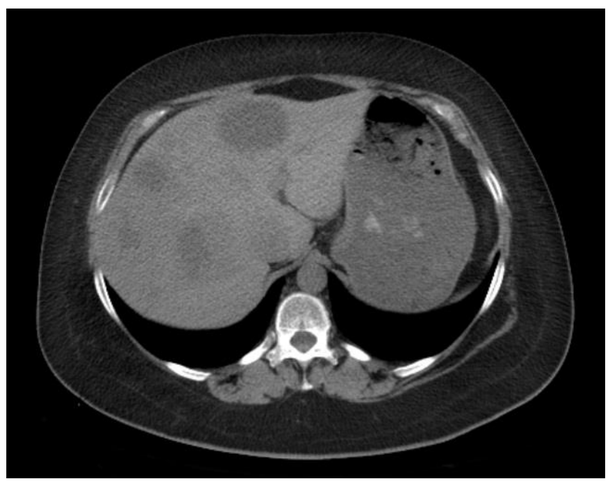

Figure 2

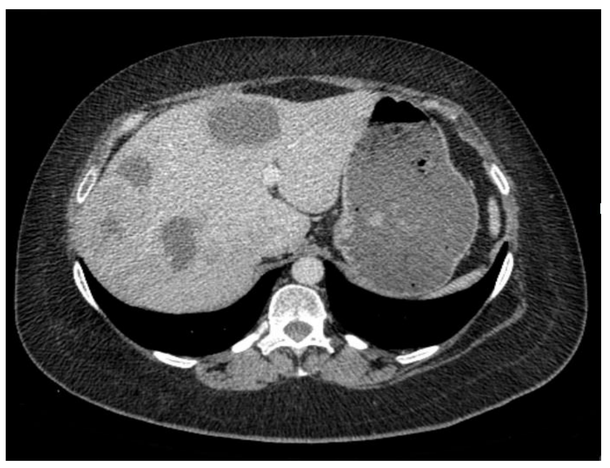

Figure 3

Conclusions and points for discussion

Pancreatic neuroendocrine tumours (NETs) are rare with incidence of ~ 2 in a million [1]. In large single centre study with 86 patients with pancreatic NETs, 86% were non-functional, and of the functioning NETs, insulinoma and gastrinoma were the most common [2]. Paraneoplastic Cushing's syndrome in it self is a rare disease and is usually associated with small lung cancer or bronchial carcinoid tumour. Pancreatic NETs that are responsible for 4-16% of cases [3]. All patients reported presented with features of Cushing's syndrome, and almost all had metastatic liver disease at presentation [4].

Up to 80% of cases the tumour stains positive for ACTH immune staining [4]. In our case it was negative, however, only limited tissue from liver biopsy was examined. There are no recent data on mortality, and historically; 5-years survival was only 16% [4]. Patients with poorly differentiated tumour, and having a clinically functional carcinoma carries a much worse prognosis[5]. Given the rarity of such disease, we believe that such patients are best managed in a tertiary neuroendocrine referral center.

1. Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AK, Modlin IM. Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer. 2008 Nov 15;113(10):2655-64. doi: 10.1002/cncr.23883.
2. Figueiredo FA, Giovannini M, Monges G, Charfi S, Bories E, Pesenti C, Caillol F, Delpero JR. Pancreatic endocrine tumors: a large single-center experience. Pancreas. 2009 Nov;38(8):936-40. doi: 10.1097/MPA.0b013e3181b365db.
3. Wajchenberg BL, Mendonca BB, Liberman B, Pereira MA, Carneiro PC, Wakamatsu A, Kirschner MA. Ectopic adrenocorticotropic hormone syndrome. Endocr Rev. 1994 Dec;15(6):752-87.
4. Clark ES, Carney JA. Pancreatic islet cell tumor associated with Cushing's syndrome. Am J Surg Pathol. 1984 Dec;8(12):917-24.
5. Fischer L, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, Büchler MW. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. Br J Surg. 2008 May;95(5):627-35. doi: 10.1002/bjs.6051.