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Case report

A rare presentation of multiple endocrine neoplasia (MEN) type 2A syndrome

Elroy Patrick Weledji

Department of Surgery, Faculty of Health Sciences, University of Buea, PO Box 126, Limbe S.W. Region, Buea, Cameroon

HIGHLIGHTS

- Patients presenting with 1^0 HPT represent a population at increased risk for either of the two MEN syndromes (MEN1, MEN2).
- Hypercalcaemia should always be excluded as a cause of recurrent, or complicated peptic ulcer disease.
- The clinical manifestations of hyperparathyroidism may be non-specific and requires a high level of clinical suspicion.

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ABSTRACT

Peptic ulcer disease may be a manifestation of symptomatic primary hyperparathyroidism. A case of an intractable complicated peptic ulcer disease secondary to hypercalcaemia from multiple endocrine neoplasia type 2A is presented. Hypercalcaemia should always be excluded as a cause of recurrent, or complicated peptic ulcer disease.

1. Introduction

Primary hyperparathyroidism (1^0 HPT) is the commonest form of hyperparathyroidism with the over-production of parathyroid hormone (PTH) and hypercalcaemia [1]. The aetiogy of 1^0 HPT are radiation (10%), multiple endocrine neoplasia syndromes (MEN) and sporadic multiple gland hyperplasia. These may manifest as a parathyroid adenoma (80%), hyperplasia (10%), nodular hyperplasia (8%) and carcinoma (1%) [1,2] 80% of patients with persistent hypercalcaemia will have either HPT or malignancy (Table 1) [2]. Because many patients remain asymptomatic (50%), the reported prevalence varies according to the means of diagnosis and the population studied and has increased significantly since the use of multichannel biochemical analysers [3]. In the UK the incidence was estimated to be 25 per 100,000 general population but it may be 1 in 1000 of a blood donor panel [1,3]. Biochemical tests would show increased serum calcium and alkaline phosphatase as a result of calcium and phosphate mobilization from bone and the increased resorption of calcium and decreased resorption of phosphate in the kidney. There is an increased or normal PTH [4]. Since 1° HPT is the commonest component of the MEN syndromes it might be assumed that patients presenting with 1^0 HPT represent a population at increased risk for either of the two syndromes (MEN1 and MEN2) (Table 2). The incidence of peptic ulcer disease and complications is greater in these groups than in the general population [5]. This case demonstrated a rare presentation of a patient with MEN type 2A syndrome with hypercalcaemia and advanced peptic ulcer disease being his main symptoms.

2. Presentation of case

A 56-year-old Caucasian man was admitted as an emergency with a 3-day history of nausea and vomiting, confusion, neck stiffness, dystonia, generalized weakness, sweating and abdominal pain. He had a 6- month history of epigastric pain with associated weight loss of about 3 kg in 2 months. He had undergone a vagotomy and gastroenterostomy for a refractory duodenal ulcer 15 yrs previously, and received triple therapy for *Helicobacter-pylori* eradication in the recent 3 months. He was on symptomatic treatment with antiemetic (domperidone 10 mg tds) and antispasmodic (merbentyl 10 mg tds). He lived alone, smoked 15–20

E-mail address: elroypat@yahoo.co.uk.

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Table 1
Differential diagnosis of hypercalcaemia.

Hyperparathyroidism
Malignancy
Multiple myeloma, lymphoma, leukaemia
Milk Alkali Syndrome
Immobilisation
Paget's disease
Excessive Vitamin D or A
Familial
Thyroid/Adrenal dysfunction
Thiazide diuretics

cigs per day for several years and consumed 5 units of alcohol per week. On physical examination he had a normal body habitus and vital signs were normal. Central and peripheral nervous systems examination were unremarkable. There was no neck stiffness and Kernig's sign was negative. There was no mass or palpable lump in the neck nor cervical lymphadenopathy. The abdomen was soft but tender in the epigastrium at the top of the upper midline scar. Bowel sounds were normal. Rectal examination showed melaena. A full blood count was within the normal limits. Serum biochemistry revealed a mild hypercalcaemia 2.7 mmol/l (N 2.1–2.6 mmol/l), hyponatremia and a raised alkaline phosphatase (ALP) 215U/L (N 30–140 U/l). Blood gases were normal and a coagulation screen – the international normalized ratio (INR) was normal (1.2). A lumbar CSF examination was negative for meningitis A computed tomography (CT) scan of the abdomen showed a duodenal mass only. A laparotomy revealed a dilated oedomatous duodenum that contained blood clot overlying a large inferior ulcer in the first part of the duodenum which was not actively bleeding. The ulcer was over-ran and the gastroenterostomy refashioned after excluding a stomal ulcer. He received the proton pump inhibitor (PPI), omeprazole 20 mg b.d post-operatively for acid suppression. The symptoms recurred 10 days later, and a gastroscopy showed stigmata of a bleeding duodenal ulcer. This was injected with 3% sodium tetradecyl sulphate (STD) in portions of 0.5 ml surrounding the bleeding point. The haemetemesis and melaena recurred once more on day 20 with haemodynamic instability which prompted a second laparotomy. This revealed severe diffuse gastric bleeding and haemostasis was attained by intraoperative packing of the bleeding bed and i/v infusion of the somatostatin analogue (octreotide) for acid suppression. On the 29th day he developed a duodenal fistula which was successfully managed conservatively. At this stage serum calcium and PTH were significantly raised. A corrected calcium showed a high serum calcium 3.20 mmol/l and a fasting serum gastrin of >400 pmol/l (N 40) was suggestive of a gastrinoma or a multiple endocrine neoplasia, syndrome. A further CT scan confirmed a large (R) adrenal mass and a hypertrophied left adrenal gland suggestive of phaeochromocytoma/s but there was no evidence of a pancreatic endocrine tumour (gastrinoma). In retrospect these were not looked for in the previous laparotomies. The clinical diagnosis of hypercalcaemia secondary to 1^0 HPT from MEN type 2A was made. The hypercalcaemic crisis responded to bisphosphonate (pamidronate) infusion and the adrenal mass was being followed-up prior to exploration and excision of the abnormal parathyroid gland/s.

3. Discussion

All forms of MEN2 are autosomally inherited as a dominant gene and men and women equally affected [5]. Generalised but asymmetric parathyroid hyperplasia is the most common histological abnormality but the pathogenesis of hyperparathyroidism remains unclear [3]. Hypercalcaemia and an elevated serum PTH level occur in 10–25% of MEN2A patients. It is characterized by mild hypercalcaemia which is usually asymptomatic in 85% of patients with the median age at diagnosis of about 38 years [2,4]. Marked dehydration due to anorexia, nausea and vomiting would lead to more severe hypercalcaemia as in this case. Serum gastrin, prolactin and calcitonin are also useful markers in patients with any clinical indication for MEN syndromes [6]. The rare MEN1 syndrome presents with tumours of the parathyroid glands, pancreatic islets and anterior pituitary and leads to premature death. In MEN2A, there is familial occurrence of phaeochromocytoma (frequently bilateral), medullary carcinoma of the thyroid and 1° HPT, although not all patients will develop all three abnormalities. Excision of the abnormal parathyroid gland is the main option in primary hyperparathyroidism with an excellent prognosis [7]. Parathyroid imaging is not needed before initial surgery because failure to localize will not influence the biochemically confirmed diagnosis and because a unilateral positive image will not obviate the need for bilateral neck exploration. All the imaging techniques available (cervical ultrasonography, subtraction scanning, Sestamibi scans, CT, MRI, PET have insufficient sensitivity and specificity and none is adequate alone [7,8]. With knowledge of normal and anomalous anatomy and with frozen section histological identification of normal and pathological tissue, few develop hypoparathyroidism post excision requiring calcium and vitamin D [8,9]. Bisphosphonates are effective osteoclast inhibitors with 70–100% of patients becoming normocalcaemic but, duration of effect is usually several weeks and varies among patients and with the type of bisphosphonate. Thus, its use in the emergency treatment of hypercalcaemic crisis [10]. In a paracrine manner, somatostatin, produced by antral D-cells potently inhibits both gastrin and pepsin secretion and it has been suggested to be important in the pathophysiology of peptic ulcer bleeding. This is corroborated by the 70% decrease of these cells in duodenal ulcer formation [11,12].

Medullary carcinoma of the thyroid (MCT) and phaechromocytomas are present in both MEN 2A and MEN 2B. The thyroid parafollicular cells and the adrenal medullary cells which give rise to these tumours have a common embryological derivation from the neural crest. In some families only phaechromocytomas occur and in others only MCT. More often MCT precedes phaeochromocytoma. MEN2B is a Scandinavian disease in which hyperparathyroidism is uncommon and in addition to phaeochromocytoma and medullary carcinoma of the thyroid, mucosal neuromas, a marfinoid habitus and sometimes ganglion neuromas in the gastrointestinal tract are added to the phenotype [13]. The patient in this case thus fitted into the MEN2A group with at present an

Table 2
Multiple endocrine neoplasia.

MEN1	MEN2A	MEN2B
Pituitary adenoma	Medullary carcinoma thyroid	Medullary carcinoma thyroid
Parathyroid adenoma	Phaechromocytoma (often bilat)	Phaechromocytoma and/or medullary hyperplasia
Islet cell adenoma pancreas	Parathyroid disease	No obvious parathyroid disease
	Patient has normal appearance	Marfanoid habitus: thick lips, prognathism, ganglioneurmatosis of eyelid

asymptomatic phaechromocytoma. If diagnosed early all MEN2 lesions are treatable and curable. The adrenal disease is invariably bilateral, commencing as hyperplasia as in this case, and progressing to the development of frank phaechromocytoma. Bilateral adrenalectomy is indicated for the management of the adrenal involvement in multiple endocrine neoplasia type 2 on account of the frequent bilaterality of the phaeochromocytomas and the associated adrenal hyperplasia [13,14]. A patient with predominant MCT, may have a past history of adrenalectomy for phaeochromocytoma. Otherwise a phaeochromocytoma needs to be excluded before any operation [14]. A fine-needle cytology of a unilateral or bilateral thyroid nodules or mass and immunocytochemical staining for calcitonin will confirm the diagnosis of MCT. Metastases to cervical lymph nodes are present in half the patients with a palpable nodule, but distant metastases (lung, liver, bone) occur only late in the course of the disease. MCT is best treated surgically (thyroidectomy) if associated with *RET* proto-oncogene [15].

4. Conclusions

Hypercalcaemia should always be excluded as a cause of recurrent, or complicated peptic ulcer disease. The clinical manifestations of hyperparathyroidism may be non-specific and thus requires a high level of clinical suspicion. Patients presenting with 1^0 HPT represent a population at increased risk for either of the two MEN syndromes (MEN1, MEN2).

Ethical approval

Ethical approval was not necessary in this case report.

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Author contribution

Study design: Elroy Patrick Weledji:

Data collections and analysis. Elroy Patrick Weledji, Eleanore Ngounou.

Conflict of interst

The authors have no conflict of interests.

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