Short reports

Spuriously elevated plasma calcitonin in a patient with a thyroid nodule not associated with medullary thyroid carcinoma

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Summary

An increase in plasma calcitonin concentration is widely regarded as a specific and sensitive indication of underlying medullary thyroid carcinoma (MTC). We present a case in which the association of increased plasma calcitonin concentration and a thyroid nodule was not due to MTC. Subsequent measurement of plasma calcitonin by a variety of methods highlighted the variability that exists in calcitonin measurement and the potential for clinically misleading results. The rationale for investigation and treatment of MTC, including a recommendation to screen all patients with thyroid nodules using plasma calcitonin measurement, is based on the use of specific two-site calcitonin assays which are not universally used in the UK or USA.

Keywords: calcitonin; thyroid carcinoma; radioimmunoassay; immunometric assay

Calcitonin is a 32-amino-acid peptide secreted by the 'C-cells' of the thyroid gland. Its measurement is widely used in the diagnosis and management of the calcitonin-secreting tumour, medullary thyroid carcinoma (MTC) which exists in two clinical forms, familial and sporadic. Sporadic MTC usually presents clinically as a thyroid nodule¹; more than one of every 200 patients with thyroid nodules have MTC.²

Early diagnosis of MTC and surgical intervention lowers the significant mortality risk associated with the disease.¹ Increased plasma calcitonin concentration nearly always indicates MTC and is more sensitive for MTC than fine needle aspiration cytology (FNAC).^{3,4} It has been suggested that plasma calcitonin should be measured in all patients with nodular thyroid disease,^{2,4} and that thyroidectomy should be performed in such patients demonstrating increased plasma calcitonin concentration.²

Case report

A small nodule in the lower left thyroid lobe was detected in an otherwise healthy 64-year-old woman at routine medical examination. Her only medical history of note was an episode of hepatitis 30 years previously. Thy-

roid function tests (thyroid-stimulating hormone 0.7 mU/l, free thyroxine 15 pmol/l) and a thyroid radioisotope scan were normal. FNAC showed only benign epithelial thyroid cells and scant giant cells although there was some suspicion that amyloid may be present.

Plasma calcitonin concentration (210 ng/l, normal <80 ng/l), measured by a radioimmunoassay (RIA, polyclonal rabbit anti-human calcitonin antibody with second anti-rabbit IgG antibody precipitation), was lower than generally seen in MTC but over the next 6 months rose progressively. Pentagastrin stimulation produced a peak response (790 ng/l) 76% above the basal value (450 ng/l). The patient underwent a left hemithyroidectomy from which her recovery was uneventful. Histology showed no evidence of MTC: there was microfollicular proliferation but no significant C-cell hyperplasia and staining for chromogranin was negative.

Postoperatively, her plasma calcitonin remained persistently increased (390–750 ng/l) but when measured by a two-site immunoradiometric assay (IRMA, Medgenix, Belgium), was within the reference range for that assay on several occasions (5.3–11.2 ng/l, normal <11.8).

Plasma from this patient was lyophilized and distributed to laboratories participating in the UK National External Quality Assessment Scheme (UKNEQAS) for calcitonin, five of whom were using RIA methods and six immunometric assays (IMA). Although only one laboratory produced a result which exceeded its stated reference range, large differences were seen between the results produced by RIA methods (mean 130, median 64, range 4.1–440 ng/l) and IMA methods (all results <11 ng/l). Overall there was a more than 200-fold difference in the concentrations of calcitonin reported.

Discussion

The finding of a slightly elevated plasma calcitonin concentration in a patient with a thyroid nodule but negative FNAC and no family history of MTC presents a not uncommon diagnostic conundrum.⁵ Standard clinical practice in such circumstances is to perform a pentagastrin stimulation test. However, the normal response to pentagastrin stimulation is not well established⁶; sex-related differences in response (peak male response 2.9 times higher

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than female) are not well appreciated⁶; additionally, Marsh *et al*⁶ have shown that, in individuals from informative families who are negative for the familial MTC-causative RET proto-oncogene mutation, pentagastrin stimulation commonly produces false positive results. Often, as seen here, pentagastrin stimulation is not elucidatory in such cases.⁵

Elevated serum calcitonin has been reported in renal failure but renal function was normal in the present case (urea 2.7 mmol/l, creatinine 70 µmol/l). Non-thyroidal tumours may secrete calcitonin, particularly tumours of the breast, lung and neuroendocrine system. However, there was no evidence to suggest an ectopic source of calcitonin: bilateral mammography and a computed tomography scan of the chest and abdomen did not reveal any abnormality. Urinary excretion of adrenaline (0.06 µmol/24 h, normal <0.1), noradrenaline (0.41 µmol/24 h, normal <0.57), dopamine (0.92 µmol/24 h, normal <2.5), homovanillic acid (18 µmol/24 h, normal <44), 4-hydroxy-3-methoxy mandelic acid (19 µmol/24 h, normal <35), 5-hydroxyindole acetic acid (16 µmol/24 h, normal <42) and serum chromogranin A (11 U/l, normal <50) were all within laboratory reference ranges.

In the present case, the situation was complicated by the presence of a form of calcitonin which was detected in a standard RIA but not by an assay using antibodies directed against two sites on the molecule (so-called 'sandwich' assays). Immunoreactive calcitonin in the plasma of both normal subjects and patients with MTC has been shown to be heterogeneous, probably reflecting the presence of the prohormone or intermediate forms of the prohormone and fragments of the mature molecule in the circulation.⁷ These peptides may be recognised by the antibodies employed in some assays: interference from calcitonin-like substances in healthy individuals has been documented as a relatively rare occurrence in calcitonin RIAs.⁸ Poor inter-laboratory agreement is a common feature of the UKNEQAS calcitonin scheme,⁹ reflecting calibration differences, non-specific background interference in RIA methods and differing specificities of the antibodies: certainly two-site IRMAs have

Learning points

- elevation of plasma calcitonin concentration normally indicates MTC but can arise due to ectopic calcitonin production or analytical interference from calcitonin-like peptides
- in equivocal cases, the pentagastrin stimulation test will not always enable a diagnosis to be established or refuted
- although there is evidence that screening for MTC in patients with thyroid nodules using plasma calcitonin measurement is warranted, clinicians (and laboratory staff) must be aware of the pitfalls of calcitonin measurement

in some cases been shown to be more selective for calcitonin than RIA,¹⁰ but sandwich assays are used by less than half the laboratories in the UKNEQAS scheme and are not widely available in the USA.⁴

MTC is a relatively uncommon condition which may present to either endocrinologists or surgeons. Although measurement of calcitonin tends to be performed in specialist units in the UK, treatment and management of the disease is often in general hospitals, where clinicians and laboratory scientists may be unaware of the lack of consensus in calcitonin measurement, the problems created by cross-reactivity with calcitonin-like peptides and the difficulties associated with interpretation of the pentagastrin test. In the present case, these analytical problems resulted in a patient being subjected to the inconvenience of a series of diagnostic procedures and unnecessary surgical risk.

The diagnostic problem represented by this case will become more common if recommendations are introduced to screen all patients with a thyroid nodule for MTC using plasma calcitonin measurements, based on the results of studies using two-site assays. Although there now appears to be good evidence that this approach is warranted in patients with thyroid nodules, this recommendation should only be applied when specific calcitonin assays are used.

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Diabetic ketoacidosis precipitated by thyrotoxicosis

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Summary

We report two patients with type 1 diabetes mellitus, previously well controlled with good compliance, presenting with unexplained diabetic ketoacidosis. Following initial correction of the metabolic disorder, persisting tachycardia lead to the diagnosis of thyrotoxicosis. In both cases, treatment with propranolol and carbimazole helped in the stabilization of their metabolic states. Although thyrotoxicosis is known to destabilise diabetes control, we can find no reports of it precipitating diabetic ketoacidosis.

Keywords: diabetic ketoacidosis; thyrotoxicosis

Diabetic ketoacidosis (DKA) is a major acute complication of type 1 diabetes mellitus and may have devastating consequences if not managed promptly and effectively. Effective management includes identifying and managing any precipitating factor. We report two cases of DKA precipitated by thyrotoxicosis.

Case reports

Case 1

A 30-year-old man with well-controlled type 1 diabetes mellitus for 20 years (HbA1c <8%, normal range 5.5–7.7%), and no episodes of DKA, became generally unwell for one month with worsening glycaemic control. He had no tissue complications of diabetes, smoked 25 cigarettes daily but consumed no alcohol. He denied urinary symptoms, flu, chest infection or diarrhoea. He was dehydrated and shocked with blood pressure 100/70 mmHg and heart rate 130 beats/min, but apyrexial. He had heavy glycosuria and ketonuria, capillary blood glucose 28 mmol/l, HbA1c 11.8%, arterial blood pH 7.17, bicarbonate 8 mmol/l (24–26 mmol/l). Full blood count, liver and renal function, serum electrolytes (potassium 5.1 mmol/l), chest X-ray, and electrocardiogram were all normal. Blood cultures and urine culture were sterile. DKA was diagnosed and treated conventionally with intravenous fluids and insulin, and antibiotics empirically. Improvement was slow, requiring 180 units insulin in the first 24 hours (usually 56 units/day). Tachycardia (120–130 beats/min) remained; fine tremor and grade 2/4 goitre were noted. The suspicion of thyrotoxicosis was confirmed biochemically, thyroid-stimulating hormone (TSH) was <0.06 mU/l, total thyroxine 252

nmol/l (60–156 nmol/l). Thyroid microsomal antibody was positive. Carbimazole 40 mg orally with 80 mg propranolol daily was started on the third day. He improved quickly and went home after 10 days.

Case 2

A 23-year-old woman had had well-controlled type 1 diabetes mellitus for 8 years (HbA1c <7.5% throughout and no episodes of DKA). She smoked 20 cigarettes daily but rarely consumed alcohol. Twelve months previously she presented with typical symptoms of thyrotoxicosis and worsening glycaemic control for 2 months, TSH was <0.06 mU/l, total thyroxine 196 mmol/l and thyroid microsomal antibody positive. Following carbimazole treatment, she regained glycaemic control and continued euthyroid on 10 mg daily.

She was admitted after one week of fatigue, palpitation and worsening glycaemic control despite compliance with insulin and diet. She was dehydrated, hypotensive (90/70 mmHg), tachycardic (120 beats/min), but apyrexial and denied symptoms of respiratory or urinary tract infection. She had heavy glycosuria, ketonuria, capillary blood glucose 24 mmol/l, arterial pH 7.26, bicarbonate 12 mmol/l. Full blood count, liver enzymes, renal function, serum electrolytes (potassium 4.8 mmol/l), chest X-ray and electrocardiogram were all normal. Blood and urine culture were sterile. However, TSH was suppressed with raised plasma thyroxine (192 nmol/l). She then confessed to stopping carbimazole 10 weeks previously, whilst on holiday. She was treated with intravenous fluids, insulin and oral propranolol and carbimazole (30 mg daily). She improved remarkably and went home after 5 days.

Discussion

Diabetic ketoacidosis is characterised by severe alteration in the metabolism of carbohydrate, protein and lipid, mainly as a result of lack or ineffectiveness of insulin with concomitant elevation of counter-regulatory hormones (glucagon, catecholamines and cortisol). A precipitating factor is not always found. In the absence of any other factors appearing after thorough investigation, we believe thyrotoxicosis was responsible for worsening glycaemic status and development of ketoacidosis in both our patients.

Changes in intermediary metabolism are well known in thyrotoxicosis. Plasma glucose and

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