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

E J Lamb, R M Heddle, A Ellis

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 nodule: more than one of every 200 patients with thyroid nodules have MTC.

Early diagnosis of MTC and surgical intervention lowers the significant mortality risk associated with the disease. Increased plasma calcitonin concentration nearly always indicates MTC and is more sensitive for MTC than fine needle aspiration cytology (FNAC).

It has been suggested that plasma calcitonin should be measured in all patients with nodular thyroid disease, and that thyroidectomy should be performed in such patients demonstrating increased plasma calcitonin concentration.

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. Thymic 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. Standard clinical practice in such circumstances is to perform a pentagastrin stimulation test. However, the normal response to pentagastrin stimulation is not well established; sex-related differences in response (peak male response 2.9 times higher...
than female) are not well appreciated; additionally, Marsh et al\(^6\) have shown that, in individuals from informative families who are negative for the familial MTC-causing RET proto-oncogene mutation, pentagastrin stimulation commonly produces false positive results. Often, as seen here, pentagastrin stimulation is not elucidatory in such cases.\(^7\)

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.\(^6\) 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 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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**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

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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 afebrile. 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 and urine culture were sterile. 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.

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 nmol/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 afebrile 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
insulin responses are usually normal in non-diabetic individuals although as many as one-third may show impaired glucose tolerance and inadequate insulin response to a glucose load. In thyrotoxicosis, both glucose absorption and production from glycogen, lactate, glycerol and amino acids are increased. Deterioration of diabetic control with thyrotoxicosis could be due to enhancement of basal hepatic glucose production and its reduced suppressibility by insulin. Other mechanisms include increased peripheral insulin resistance and insulin clearance. The insulin resistance in thyrotoxicosis may be a consequence of increased hepatic glucose output rather than a post-receptor defect because euglycaemic insulin clamp studies suggest insulin responsiveness, clearance and basal insulin delivery rate increase in thyrotoxicosis. Nijs demonstrated increased insulin clearance in patients with insulin-dependent diabetes mellitus and thyrotoxicosis, which becomes normal with amelioration of the thyrotoxic state. Thus, insulin secretion, hepatic glucose output, its suppressibility by insulin, peripheral tissue insulin responsiveness and insulin degradation may all be compromised in thyrotoxicosis, but probably to a different extent in different individuals.

Thyroid hormones appear to stimulate virtually all aspects of lipid metabolism, including synthesis, mobilisation and degradation. Thyroid hormone excess increases lipolysis (thereby increasing circulating free fatty acids) both by a direct effect through the adenylyl cyclase–cyclic AMP system and by sensitising adipose tissue to other lipolytic agents such as catecholamines, growth hormone, glucocorticoids and glucagon. Oxidation of free fatty acids is also increased and may account for some of the calorogenic action of thyroid hormones. Metabolism of ketone bodies, however, appears normal, at least in rats.

We can find no reported case of DKA precipitated by thyrotoxicosis. Rolald et al reported one case of DKA with thyrotoxicosis (with normal serum triiodothyronine) but the precipitating factor of DKA was omission of insulin for two days. Our cases emphasise the importance of a thorough search for precipitating factor(s) in cases of DKA once common causes such as infection and omission of insulin are excluded. Although thyrotoxicosis is apparently a very rare precipitant for DKA, persistent tachycardia in aseptic patients with DKA should raise the possibility of thyrotoxicosis, even when other features are absent.

Learning points
- in every case of DKA, attempts should be made to identify precipitating factor(s)
- persistent tachycardia following correction of dehydration in aseptic patients with DKA should raise the possibility of thyrotoxicosis
- thyrotoxicosis can precipitate DKA

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Lobular carcinoma-in-situ within a fibroadenoma of the breast


Summary
We present a case of an in-situ lobular carcinoma within an otherwise benign fibroadenoma in a 45-year-old woman.

Keywords: fibroadenoma; carcinoma-in-situ

Fibroadenoma are one of the most common benign tumours of the breast. We present a case of an in-situ lobular carcinoma within an otherwise benign fibroadenoma.

Case report
A 45-year-old woman presented with a painless mass in her right breast which she had discovered one week earlier. She was pre-menopausal and had no history or any known risk factors for breast cancer. A firm, well-defined, mobile mass, 1.5 × 1 cm in diameter was found in the upper inner quadrant of the right breast. No enlarged axillary or supraclavicular lymph nodes were palpable. Mammography revealed a well-circumscribed density corresponding to the palpable mass. Fine-needle aspiration yielded benign cells. A diagnosis of fibroadenoma was made. Three months later when the mass had grown to 2.5 × 2 cm, the patient requested surgery. Local excision of the mass was therefore done. Histological examination of the mass revealed a fibroadenoma with a focus of lobular carcinoma-in-situ that was completely confined within the fibroadenoma (figures 1 and 2). After discussing treatment options with the patient, a policy of continued surveillance was decided upon. The patient remains asymptomatic 25 months later.

Discussion
Carcinoma within a breast fibroadenoma is very rare, having a reported incidence of 0.1–0.3%.1,2 As in our case, patients with these lesions typically are older than patients with fibroadenoma, having a mean age of 42 years. Although this is similar to the peak age reported for a lobular carcinoma-in-situ, it is considerably older than the 20–25 year average age of patients with fibroadenomas.3

Pre-operative diagnosis of these lesions is difficult because their presenting features are similar to those of benign fibroadenoma. Mammography may reveal an abnormality, but rarely indicates malignancy.3 As in our case, the diagnosis usually is a histological surprise.

Fibroadenomas have been found to contain both in-situ and invasive malignancies.1–4 In 66% of the reported cases of carcinomas occurring in a fibroadenoma, the malignancy has been an in-situ lesion; in 34% of cases, the cancer is invasive.5 In 65% of patients with an in-situ lesion in a fibroadenoma, the lesion is lobular carcinoma-in-situ.1 About two-thirds of the carcinomas arising within a fibroadenoma have lobular morphology; the rest are ductal or mixed ductal and lobular.2,4

The biological behaviour of a carcinoma occurring in a fibroadenoma is no different from that of breast carcinoma unrelated to fibroadenoma.2,5 Although the treatment of invasive cancer within a fibroadenoma is similar to that of carcinoma of the breast, the treatment of in-situ cancer is less well defined. Thirty-three per cent of patients with lobular carcinoma-in-situ in a fibroadenoma develop an invasive carcinoma, intraductal or lobular,
in the same or contralateral breast. This corresponds to the 17–36% incidence of carcinoma developing in patients with lobular carcinoma-in-situ without fibroadenoma. In two large series of patients, the observed and expected ratios of invasive cancer in patients whose lobular carcinomas-in-situ had been treated by excisional biopsy alone were 6.9:1 and 9:1, respectively.

Excision followed by surveillance or mastectomy are the two options that have been used to treat lobular carcinoma-in-situ in a fibroadenoma. Ozzello et al found that of 16 patients treated by local excision, only two developed a recurrence, one after 3 years and the other after 5 years. In another report, one out of five patients with lobular carcinoma-in-situ developed a recurrence after local excision. In a literature review, Pick et al found that of 28 patients with lobular carcinoma-in-situ in a fibroadenoma, 10 had been treated with local excision, two of whom developed recurrences. Eighteen patients had been treated initially with mastectomy (eight simple, seven modified radical, and three radical) with no recurrences. The two patients with recurrences after local excision were then successfully treated by mastectomy. Twenty-seven of the 28 patients were alive, with only one showing evidence of disease. The single death was from an unrelated cause. Follow-up ranged from 0.2 to 26 years.

Forty per cent of patients with lobular carcinoma-in-situ who develop subsequent breast cancer are found to have another lobular carcinoma-in-situ, and 50% of all subsequent cancers, both invasive and in-situ, occur in the contralateral breast. A policy of close observation is advocated for these cases. This policy can also be adopted for lobular carcinoma-in-situ in fibroadenomas. Forty-two to 50% of all cases of carcinoma in a fibroadenoma cancer occur in the adjacent breast tissue.

A wide margin of excision should be obtained in a clinically detected fibroadenoma in middle-aged patients. Lobular carcinoma-in-situ predisposes to subsequent invasive cancer. Moreover, this risk is cumulative, lifelong, and increases with time. In selected patients, especially those with a familial history of breast cancer, bilateral total mastectomy may be the appropriate treatment. The patient’s choice of a particular modality of treatment should ultimately determine management.

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**Lobular carcinoma-in-situ in a fibroadenoma**

- These lesions occur in older patients than do simple fibroadenomas (mean ages 42 years and 25 years, respectively).
- There is a 42–50% incidence of concurrent cancer in surrounding breast tissue.
- Lobular carcinoma-in-situ is the most common noninvasive cancer in fibroadenoma, whereas ductal carcinoma-in-situ is in the most common nonfibroadenomatous breast cancer.
- The biological behaviour of these tumours is similar to that of lobular carcinoma-in-situ in a breast without fibroadenoma.

Hypoxaemia – think of the liver! Every internist should be aware of the hepatopulmonary syndrome

Mahesh S Mokhashi

Summary

Hepatopulmonary syndrome is characterised by arterial hypoxaemia, liver disease, and intrapulmonary vascular dilatation. A case is reported in which severe hypoxaemia, detected by chance, led to the diagnosis of liver disease and hepatopulmonary syndrome.

Keywords: hypoxaemia; hepatopulmonary syndrome

When confronted with a severely hypoxic patient, it is unusual for the clinician to make a list of differential diagnoses beyond cardiorespiratory diseases. Hepatopulmonary syndrome (HPS) is characterised by a triad of arterial hypoxaemia, liver disease, and intrapulmonary vascular dilatation. Though the association of chronic liver disease, cyanosis, and digital clubbing was first described over 100 years ago, and the term ‘hepatopulmonary syndrome’ was suggested in 1977, this entity has generated interest only recently. Literature outlining major recent developments in HPS has appeared mainly in specialist journals, whereas it is likely that internists and emergency room physicians (as in this case) would be the first ones facing the diagnostic dilemma of hypoxaemia of obscure aetiology. I report a case in which severe hypoxaemia, detected by chance, led to the diagnosis of liver disease and HPS.

Case report

A 57-year-old man, not known to have liver disease, felt dizzy while waiting for transportation home after a routine orthopaedic clinic visit. In the emergency room, pulse oximetry recording at room air was alarmingly low at 78% and a simultaneous PaO2 of 6.26 kPa (normal 11–13 kPa) confirmed the hypoxaemia. With 100% oxygen delivered by a face mask, his oxygen saturation improved to 88%. On inquiry, he reported mildly progressive exertional dyspnoea for 24 months, dizziness for 18 months, weakness and fatigue for 12 months, and minimal lower extremity swelling for the past 2 weeks. He denied any other cardiovascular symptoms. He reported a 30-year history of alcohol abuse that had ended 18 months earlier. He was an active smoker with a 30-pack-year history. Examination revealed a middle-aged Caucasian male in no apparent distress. His other vital signs were stable. Positive findings were mild jaundice, digital clubbing, numerous spider naevi on the chest, and trace ankle oedema. Pulmonary and cardiac examinations were unremarkable. There was no obvious ascites on abdominal examination and the hepatic span was 8 cm. Spleen was not palpable. Laboratory studies showed a haematocrit of 46% (normal 42–52%), haemoglobin of 161 g/l (140–180 g/l) and a mean corpuscular volume of 107.9 fl (86–98 fl). Whole blood count was 10.9 × 10^11/l (4.3–10.3 × 10^11/l) and the platelet count was 97 × 10^11/l (130–400 × 10^11/l). Total bilirubin was 53.01 µmol/l (5.1–17 µmol/l) with a direct fraction of 20.52 µmol/l (1.7–5.1 µmol/l). Alkaline phosphatase was 148 IU/l (30–120 IU/l), alanine aminotransferase 58 IU/l (0–35 IU/l), and aspartate aminotransferase 135 IU/l (0–35 IU/l). Serum albumin level was 29 g/l (35–55 g/l), total protein 66 g/l (55–80 g/l), and INR was 3.0. Serum glucose, electrolytes, creatinine and blood urea nitrogen levels were normal. Serological testing for viral hepatitis was negative. Antinuclear antibody was not detected. Electrocardiogram and chest radiograph were normal. A technetium-99m labelled macroaggregated albumin (99mTc-MAA) perfusion scan of the lung (figure) showed no perfusion defects suggestive of a pulmonary embolus. However, a significant amount of the radioisotope was taken up by the kidneys and brain indicating an arteriovenous shunt, and the shunt fraction was quantified at 38% (normal < 5%). A contrast echocardiogram using microbubbles generated by agitation of normal saline showed crossover of bubbles from the right ventricle to the left atrium after five ventricular beats, excluding an intracardiac shunt and confirming its intrapulmonary location. Pulmonary function tests showed normal spirometry and lung volumes. The diffusing capacity for carbon monoxide was reduced at 58% of the predicted value. Computed tomography (CT) of the lungs was normal except for minimal pleural thickening at the posterior aspect of the right lung base. A CT scan of the abdomen revealed a small nodular liver, with a preserved caudate lobe. The liver was surrounded by a mild to moderate amount of ascites. Mild enlargement of the spleen with varices in the splenic hilum were noted. These radiological findings were consistent with liver cirrhosis and portal hypertension. Endoscopy showed 2+ oesophageal varices and moderate portal hypertensive gastropathy. A diagnosis of alcohol-related liver disease (probably cirrhosis) and hepatopulmonary syndrome was made.
Discussion

HPS is characterised by the triad of arterial hypoxaemia, liver disease, and intrapulmonary vascular dilatation. The presence of other comitant pulmonary disorders such as obstructive airway disease does not exclude the diagnosis of HPS.1

There are several compelling reasons why internists need to be aware of the HPS:

- the relatively high prevalence of the syndrome: 47% of patients investigated with endstage liver disease,4 and 38% with less severe liver disease, were shown to have intrapulmonary shunting5
- as in this case, commonly encountered liver diseases can present with HPS. In a review of the aetiologies in 57 patients with HPS, 12 were due to alcoholic cirrhosis and 10 due to chronic active hepatitis6
- clinical features of HPS (dyspnoea and clubbing) are non-specific. Although the majority present with hepatic manifestations, up to 18% of patients with HPS have presented with predominantly pulmonary symptoms,7 as did this patient
- failure to recognise HPS can be serious. Progressive decline in oxygenation can occur despite stable hepatic function5; 41% mortality a mean of 2.5 years after the onset of dyspnoea has been reported8
- another reason to recognise HPS early, is that treatment with selective embolization of the dilated pulmonary vasculature9 or liver transplantation,10 offers hope for a cure.

Learning points

- hepatopulmonary syndrome is not rare
- up to 18% of patients present with predominantly pulmonary symptoms
- patients may present in general practice or in an emergency room setting
- failure to recognise the syndrome can be serious
- diagnosis can be made easily
- treatment for this syndrome exists

- diagnosis of HPS is easy and requires no fancy equipment.


tc-MAA perfusion scanning is one of the modalities used to demonstrate intrapulmonary vascular dilatation. Injected peripherally, the majority of the labelled albumin (20–60 µm in diameter) is normally trapped in the pulmonary capillary bed and the lungs take up most of the radioisotope. In the presence of intrapulmonary or intracardiac shunting, the albumin is not trapped totally in the pulmonary capillary bed and is taken up in the brain, kidneys, liver and spleen.11 The amount of shunted radioisotope can be quantified. To demonstrate the presence of intrapulmonary vascular dilatation causing an arteriovenous shunt and to localise it anatomically to the lungs, the current gold standard is contrast-enhanced echocardiography.9 Agitated saline-generated microbubbles injected intravenously are normally trapped by the pulmonary capillary bed. Should the bubbles appear in the left side of the heart a shunt is implied. Timing of the arrival of the microbubbles in the left atrium helps distinguish intracardiac from intrapulmonary shunting. A 4–6 beat delay after opacification of the right ventricle indicates intrapulmonary shunting.12 Apart from a reduced diffusing capacity for carbon monoxide, pulmonary function tests are normal, but chest radiographs often show bibasilar nodular or reticulonodular opacities.13 Laboratory investigations show evidence of hepatic dysfunction, but there is no correlation between the degree of biochemical abnormalities and the development of HPS.5

The dilated pulmonary capillary has an expanded diameter, oxygen molecules from the adjacent alveoli cannot diffuse to the centre of the dilated vessel to oxygenate haemoglobin in erythrocytes at the centre of the venous stream, thus resulting in hypoxaemia.13 The factors causing the dilatation itself have not been established.
Massive pleural effusions in cryptococcal meningitis

C M M Wong, K H Lim, C K Liam

Summary
Cryptococcal infection uncommonly presents with pulmonary manifestations and even more rarely so as massive bilateral effusions. Pleural involvement is usually associated with underlying pulmonary parenchymal lesions and is unusual while on antifungal therapy. We report a patient with cryptococcal meningitis who, while on intravenous 5-flucytosine and amphotericin B, developed life-threatening bilateral massive pleural effusions with evidence of spontaneous resolution, consistent with prior hypothesis of antigenic stimulation as the cause of pleural involvement.

Keywords: cryptococcosis; pleural effusions

Cryptococcus neoformans infection usually presents as chronic meningitis and is increasingly recognised in immunocompromised patients. Serious underlying illnesses or treatment with corticosteroids and/or immunosuppressants predispose to disseminated cryptococcosis. Pleural effusions are unusual and may be diagnosed with a positive cryptococcal antigen test. We report a case of massive bilateral pleural effusions occurring in an apparently immune-competent woman with cryptococcal meningitis.

Case report
A 30-year-old previously well woman presented with severe persistent bitemporal and occipital headaches of six weeks duration. There were associated symptoms of night sweats and vomiting but no other constitutional symptoms. She was a non-smoker and had had no prior illness. Medical examination and magnetic resonance imaging of the brain performed at the beginning of the illness at another hospital were unremarkable. On the day of admission to our hospital, she developed diplopia and had a generalised tonic-clonic seizure. She was drowsy but afebrile and had bilateral papilloedema and lateral rectus palsies. Computed tomography (CT) of her brain was normal. Her cerebrospinal fluid (CSF) showed lymphocytosis (240 cells/dl), high protein level (59 mg/dl), normal glucose and chloride levels, elevated pressure of 37.8 cmH₂O and was positive for cryptococcal antigen (titre 1:256) and culture-positive for Cryptococcus neoformans. Her chest X-ray was normal. She tested negative for HIV I and HIV II antibodies.

She was commenced on intravenous amphotericin B (0.5 mg/kg/day) and 5-flucytosine (180 mg/kg/day) for cryptococcal meningitis. On day 8 of therapy, a ventriculoperitoneal shunt was inserted to relieve the increasing CSF pressure (>60 cmH₂O) which was associated with worsening papilloedema and visual loss. On day 10, she was still febrile and had become extremely dyspnoeic overnight; unable to recline from a sitting position. The chest radiograph at this stage revealed bilateral massive pleural effusions, greater on the right side. Thoracocentesis was performed and an intercostal chest tube was left in-situ on the right. Clear pleural fluid amounting to over 3.5 litres was drained over the next three days. Pleural fluid analysis revealed a protein concentration of 2.5 g/dl, lactate dehydrogenase (LDH) 23 IU/l (serum LDH was 218 IU/l), white cell count 230 cells/dl with 91% polymorphs. The pleural fluid was culture and smear negative for pyogenic micro-organisms, mycobacterium and fungus but was positive for cryptococcal antigen. Blood cultures were also negative.

The massive left effusion resolved spontaneously and the right chest drain was removed after 8 days with no further recurrence of the effusion. A repeat chest radiograph while on antifungal therapy was clear but the CT scan of the thorax showed a cavitating infiltrate in the left lower lobe.

The patient made an uneventful recovery after 11 weeks of amphotericin and 5-flucytosine therapy and was functionally normal when last seen. Further questioning revealed she had been living two doors away from a pigeon breeder for the last 3 years. She was discharged on oral fluconazole 400 mg daily but was lost to follow-up.
Discussion

Cryptococcus neoformans infection is now more commonly recognised in immunocompromised hosts especially in those with the acquired immunodeficiency syndrome but may occur even in healthy individuals. Despite the respiratory tract being the major port of entry, pulmonary manifestations are infrequent or mild and chronic meningitis is the commonest mode of manifestation. Pleural cryptococcosis is seldom reported and was thought to connote dissemination in the immunocompromised hosts but later evidence appears to dispute this. It has been postulated that the release of antigen rather than organism growth is responsible for pleural manifestations. Pleural effusions, if present, are almost always associated with underlying lung parenchymal lesions which may manifest as subpleural nodules, interstitial infiltrates, pulmonary masses, miliary nodules, focal or widespread alveolar consolidation and lymphadenopathy. Pleural effusions occurring after commencement of treatment has been reported but are exceptionally rare.

There have been very few documented cases of massive pleural effusions. Our case is of interest as she developed massive bilateral effusions whilst on antifungal chemotherapy. The release of cryptococcal antigens as the stimulus for the pleural effusions appear to be an attractive explanation for the sudden massive accumulation of fluid in this case. The spontaneous resolution of the massive left pleural effusion without additional therapy concurs with previously reported observations.

Normally, diagnosis may be achieved by pleural biopsy, culture and/or detection of cryptococcal antigen in the pleural fluid. The fluid itself may be haemorrhagic or serosanguinous in nature and tends to be lymphocytic in cellular response. Our case is unusual as her pleural fluid demonstrated neutrophilic pleocytosis. Protein levels range from 2.5 to 5.7 g/dl. Treatment is with amphotericin, frequently administered with 5-flucytosine for synergistic effect, especially in the severely immunodeficient patients. Fluconazole alone has received widespread acceptance for less severe infections. Some isolated bronchopulmonary infections have done well without treatment. Likewise, isolated pleural disease may also resolve spontaneously in immunocompetent individuals with localised thoracic disease.

Learning points

- Pleural involvement is unusual in cryptococcosis but may manifest as massive bilateral effusions while on antifungal therapy.
- Pleural cryptococcosis may be reliably diagnosed by cryptococcal antigen test on the pleural fluid.
- Clinical and radiological involvement of the lung and pleura should be sought in cases of cryptococcal meningitis.

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