Nephrology
dialysis
transplantation

Nephroquiz for the Beginner
(Section Editor: M. G. Zeier)

Supported by an educational grant from

Nasty shock after an anti-emetic

Case

A 66-year-old previously healthy woman had been vomiting for 7 h and contacted her family physician, who gave her an intramuscular injection of metoclopramide. Forty-five minutes later she felt cold, short of breath, anxious and wheezy with blue lips and heavy legs. She was admitted to hospital as an emergency. In the admission room she was breathless at rest, the blood pressure was 175/120 mmHg, and the pulse was 100 bpm (sinus rhythm). There were crackles throughout both lung fields. She was treated with frusemide, diamorphine, metoclopramide and oxygen but deteriorated over the following hour with increased respiratory rate and falling blood pressure. She was transferred to the intensive care unit, and when she was intubated froth was aspirated from the endotracheal tube. She was mechanically ventilated and treated with dopamine, dobutamine, nitrates and broad spectrum antibiotics. Her blood pressure fell to 60/40 mmHg and an adrenaline infusion was commenced.

The initial abnormal investigations included creatinine 216 μmol/l, white cell count 20.8 × 10⁹/l (74% neutrophils), and C-reactive protein of 124 mg/l (normal range 0-8). Arterial blood gave a pH 6.9, P⁰₂ 7.4 kPa, P⁰₂ 8.8 kPa and [HCO₃⁻] 17.6 mmol/l. A chest radiograph showed widespread airspace filling (Figure 1). There was no evidence of myocardial infarction on the electrocardiogram.

The presumptive diagnosis was septicemia. For the subsequent 48 h blood pressure remained labile and there was persistent metabolic acidosis. No cause or site of sepsis was identified and all cultures were negative.

Renal size was normal. Renal replacement therapy was required and there was intermittent hypertension over the following days on the intensive care unit. On day 12 a diagnosis was made.

Question

What unusual diagnosis would you have considered and how would you have confirmed it?
Answer to quiz on preceding page

Diagnosis

The initial presentation was with acute respiratory distress, which would most commonly be due to pneumonia, left ventricular failure, or severe sepsis. However, in this case the actual diagnosis was of a phaeochromocytoma. Every aspect of this patient’s presentation, including precipitation by the anti-emetic, are recognized features.

Diagnostic work-up

The clinicians involved had more information. An abdominal CT scan performed to identify any source of sepsis showed a 4.5 × 3.5 cm adrenal mass (Figure 2) but this was initially disregarded. Without clinical pointers to a functional adenoma this would be reasonable, since the majority are non-functional. The tests finally used to establish the diagnosis in this case were measurements of circulating catecholamines (Table 1) an MRI scan and a metaiodobenzylguanidine (MIBG) uptake scan.

Table 1. Measurements of circulating catecholamines

<table>
<thead>
<tr>
<th></th>
<th>Day 14</th>
<th>Day 19</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline (nmol/l)</td>
<td>3.28</td>
<td>6.4</td>
<td>&lt; 5.6</td>
</tr>
<tr>
<td>Adrenaline (nmol/l)</td>
<td>5.06</td>
<td>4.2</td>
<td>&lt; 2.11</td>
</tr>
</tbody>
</table>

Selection of patients for investigation to confirm or exclude the presence of phaeochromocytoma is discussed elsewhere [1,2]. Urinary metanephrine excretion is often measured initially (not possible here), followed by plasma catecholamines. Plasma normetanephrine and metanephrine are not in routine use, but may offer higher sensitivity and specificity [3]. Important points are that tumour catecholamine release is often erratic and that the ratio of catecholamines to their metabolites varies. Since non-functional adrenal tumours are more common than phaeochromocytomas, imaging studies are not generally performed unless there is a biochemical abnormality.

Prevalence of adrenal adenoma

Incidental, non-functional, adrenal cortical masses are found in 1–9% of patients at autopsy and are typically less than 6 cm in diameter, as in this patient [4,5]. Phaeochromocytoma is relatively rare, with prevalence estimated at 0.13% [6], so about one in 13 patients with an adrenal mass will have a phaeochromocytoma [1]. However, in this case disregarding the adrenal tumour turned out to be a mistake! At the time, the clinical features appeared typical of septicaemia, and those involved did not consider other, rarer, possibilities.

Clinical symptoms

The most common symptom at presentation is headache (80%), followed by perspiration and palpitations [7]. Hypertension is usually sustained rather than paroxysmal. Importantly, chest pain and myocardial
Unusual features of this case

Recognized, but unusual, presentations of phaeochromocytoma include hypertension and respiratory distress, hypotension and cardiovascular collapse, and acute renal failure. Leucocytosis and fever are well described. This patient was given metoclopramide shortly before she became severely unwell. In 1976, Plouin et al. described a patient with phaeochromocytoma with an immediate rise in systolic blood pressure from 200 to 340 mmHg following intravenous metoclopramide [11]. Another group showed a sharp rise in noradrenaline within 3 min of intravenous metoclopramide [12]. This is mediated by the dopamine D2 receptor, and is sufficiently reliable for some authors to have suggested it as a diagnostic test. D2 receptors are found in the adrenal medulla, isolated chromaffin cells and phaeochromocytomas [13,14] and other antagonists, including sulpiride and phenothiazines show the same effect.

Outcome

Renal failure was presumably due to acute tubular necrosis, and recovered with supportive treatment. Blood pressure was controlled with phenoxybenzamine. Four months after initial presentation a 4 cm phaeochromocytoma was removed (Figure 3). Two years later creatinine is stable at 150 μmol/l and blood pressure is 140/80 mmHg.

References


Infarction can occur in the absence of coronary artery disease. Of course headaches, perspiration, palpitations, hypertension, and chest pain are all much more commonly due to other factors than an underlying phaeochromocytoma.

Genetic predisposition

In a proportion of cases phaeochromocytoma is due to von Hippel Lindau (VHL) disease or multiple endocrine neoplasia type 2 (MEN2). In one series 23% of patients with phaeochromocytoma were found to have a familial syndrome [8], so it is important to take a family history. This also gives clues to the molecular pathogenesis by implicating the underlying tumour suppressor genes. The MEN2 syndromes are caused by gain of function mutations in the RET proto-oncogene, which is a receptor tyrosine kinase [9], and the VHL syndrome is due to germline mutations in the VHL gene whose functions include regulated destruction of oxygen responsive transcription factors [10].

Fig. 3. Surgical specimen showing the circumscribed adrenal tumour. Microscopic examination confirmed this was a phaeochromocytoma.


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