Renal tubular acidosis due to oxaliplatin

Oxaliplatin is a third-generation platinum derivative which in combination with a fluoropyrimidine has demonstrated improved overall survival in metastatic colon cancer [1], prolonged progression free survival in an adjuvant setting [2] and prompted recommendations for its use by the National Institute for Clinical Excellence [3]. Initial studies with oxaliplatin did not identify significant renal toxicity but acute tubular necrosis (without dehydration) has been reported [4].

This is a case of a 53-year-old gentleman who developed severe renal tubular acidosis, probably secondary to oxaliplatin. Duke’s B adenocarcinoma of the transverse colon (pT4N0, stage II) was diagnosed following hemicolectomy for perforated bowel in 2002. After 6 months of adjuvant therapy with 5-flourouracil (425 mg/m² on days 1–5, repeated every 28 days for 6 cycles), he re-presented in 2005 with weight loss and a solitary liver metastasis was identified by TELSA MRI and FDG PET-CT. He was commenced on neo-adjuvant oxaliplatin (130 mg/m² on day 1 q21d) and capecitabine (1000 mg/m² BD on days 1–14, q21d) before hepatic resection. On day 14 of the second cycle of oxaliplatin and capecitabine, he was admitted with a 7-day history of lethargy, anorexia, nausea, polyuria and increasing breathlessness. His oral intake had been 2–3 litres of salt lassi (pH 4) and three or four limes a day. He had a past
medical history of type 2 diabetes treated with metformin and hypercholesterolaemia treated with simvastatin.

On examination, he was dehydrated, flushed, and tachypnoeic although the chest was clear. An arterial blood gas revealed a severe metabolic acidosis with partial respiratory compensation (Table 1, day 1). Serum $K^+$ and $Cl^-$ were 3.3 mmol/l and 113 mmol/l, respectively.

Moderate ketones were present in his urine (1.6 g/l) and his blood glucose was 17.8 mmol/l. Blood lactate was 0.8 mmol/l (excludes metformin-induced lactic acidosis). The initial anion gap was 19.2 mEq/l (normal 16–18 mEq/l). Urinary $Na^+$ was 113 mmol/l, urinary $K^+$ was 58.9 mmol/l and urinary pH was 5.0.

Proximal renal tubular acidosis (type 2, pRTA) is characterised by bicarbonate wasting (due to failure of reabsorption) and low serum bicarbonate. Proximal tubular dysfunction leads to impaired reabsorption of other substances (Fanconi’s syndrome) including glucose and phosphate [5]. Here, the urine was markedly glycosuric (even after correction of hyperglycaemia to <6 mmol/l) and serum phosphate was reduced (0.54 mmol/l). In contrast to distal renal tubular acidosis (dRTA), in pRTA distal urinary acidification methods (e.g. $NH_4^+$ production) are still intact so the urinary pH can fall <5.5. Therefore, the findings of a hypokalaemic, hyperchloraemic metabolic acidosis with normal anion gap, urinary pH of 5.0, and indicators of Fanconi’s syndrome were consistent with a diagnosis of proximal/type 2 renal tubular acidosis. The acidosis and hypokalaemia were exacerbated by the high oral acid load (from lassi and limes) leading to increased reabsorption of chloride and urinary loss of potassium.

Potassium requirements remained high over the next 4 days (15–30 mmol/h) during which the acidosis improved (Table 1) without requiring sodium bicarbonate. The patient was transferred from intensive care to the ward on day 5 with oral potassium and phosphate supplements and discharged home 10 days after admission.

We believe that this is the first report of type 2 renal tubular acidosis due to oxaliplatin. With the increasing use of oxaliplatin, extra vigilance with regard to unexpected renal toxicity is warranted.

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Table 1. Arterial blood gas results by day

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
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<tbody>
<tr>
<td>pH</td>
<td>7.15</td>
<td>7.35</td>
<td>7.38</td>
<td>7.46</td>
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<tr>
<td>$pCO_2$</td>
<td>1.05</td>
<td>3.07</td>
<td>3.99</td>
<td>4.36</td>
</tr>
<tr>
<td>$pO_2$</td>
<td>24.7 (FiO2 0.3)</td>
<td>14.7 (air)</td>
<td>12.1 (air)</td>
<td>12.3 (air)</td>
</tr>
<tr>
<td>$HCO_3^-$</td>
<td>7.1</td>
<td>15.4</td>
<td>19.3</td>
<td>24.7</td>
</tr>
<tr>
<td>SBE</td>
<td>−25.6</td>
<td>−12.3</td>
<td>−6.8</td>
<td>−0.1</td>
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