



EXCEPTIONAL CASE

Type B lactic acidosis from fluorouracil in fluorouracil, oxaliplatin and leucovorin treatment for carcinoma of the colon in a hemodialysis patient

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ABSTRACT

Type B lactic acidosis complicating malignancies is rare. Increased lactate production from abnormal metabolism of tumor tissue and extensive liver metastases impairing clearance are usual causes. Fluorouracil, commonly used as adjuvant cancer chemotherapy, is not well recognized among drugs that can lead to lactic acidosis. We report a hemodialysis patient, tumor free after surgery for colon carcinoma, developing acute severe lactic acidosis and encephalopathy. Pharmacogenetic studies failed to show common variants predisposing to the more typical patterns of fluorouracil toxicity. Routine monitoring of hemodialysis patients after fluorouracil is the only practical way to detect this potentially lethal complication.

Keywords: carcinoma, fluorouracil, FOLFOX, hemodialysis, lactic acidosis

BACKGROUND

Lactic acidosis, defined as pH < 7.35 and serum lactate > 5 mmol/L, may complicate malignancy if complications lead to tissue hypoxia (Type A). Type B lactic acidosis in malignancy is uncommon and results from abnormal tumor metabolism when tumor burden is high or from severe liver involvement from metastases leading to impaired clearance. Renal clearance plays only a minor role. Fluorouracil is commonly used in adjuvant chemotherapy for cancers. Lactic acidosis complicating its use is little recognized.

CASE REPORT

A 59-year-old Asian male on chronic hemodialysis had successful resection of a sigmoid adenocarcinoma, stage pT3 N1c Mx.

Adjuvant chemotherapy with modified fluorouracil, oxaliplatin and leucovorin (mFOLFOX) was started at a 20% reduced dose. After dialysis he received an intravenous (IV) fluorouracil bolus of 320 mg/m², along with oxaliplatin and leucovorin, followed by continuous IV infusion of 2000 mg/m² over the next 46 h. Fatigue, anorexia and headache developed within 4 h and he slept through the day. He was confused and drowsy when taken to the hospital 32 h after starting chemotherapy. On admission he was encephalopathic, with a Glasgow Coma Scale of 12. His neck was supple with no lateralizing neurological signs. His blood pressure was 120/60 mmHg (usual 140/90 mmHg on dialysis), heart rate 150 bpm, respiratory rate 38/min. He was afebrile with a flat jugular venous pressure and dry mucous membranes. Investigations showed a hemoglobin of 144 g/L, white blood cell count of 20.7 × 10⁹/L, platelets 286 × 10⁹/L, urea

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36.5 mmol/L, creatinine 1112 μ mol/L, sodium 144 mmol/L, potassium 4.6 mmol/L, chlorine 89 mmol/L and total carbon dioxide 11 mmol/L. Extended electrolytes were unremarkable. L-lactate was markedly elevated at 28 mmol/L with an osmolar gap of 15.6. Blood gas showed a pH of 7.17, partial pressure of carbon dioxide 29 mmHg, partial pressure of oxygen 252 on 50% oxygen and bicarbonate 10 mmol/L. Liver enzymes were unremarkable and drug screens for salicylate, acetaminophen and alcohol were negative. Triglyceride was 3.22 mmol/L. His ammonia level was not available.

Chest X-ray, computed tomography scans of the head and abdomen and a lumbar puncture were all normal. Fluorouracil was discontinued 33 h after the infusion was started. Fluids and empiric antibiotics were given, though all cultures later returned negative. Seven hours after stopping fluorouracil, lactate was 21.6 mmol/L despite being normotensive with a stabilized heart rate. Encephalopathy worsened and intubation was required. Continuous renal replacement therapy (CRRT) was started 12 h after admission. Lactate fell rapidly to 12.5, 6.4, 3.6 mmol/L at 35 min, 6.4 h and 7 h after initiation, respectively. Acidosis and encephalopathy corrected in parallel and he was extubated after 24 h. He was discharged 4 days after admission. No mucositis, neutropenia, diarrhea, dermatopathy or neuropathy was ever noted.

Fluorouracil sensitivity genotyping showed a dihydropyrimidine dehydrogenase (DPYD) gene (NM_000110.3) cDNA change: [c.1627A>G (heterozygous)] and a thymidylate synthetase (TYMS) gene (NM_001071.2) cDNA change [c.-58_-31del (heterozygous)].

DISCUSSION

Lactic acidosis can occur by various mechanisms [1]. While lactic acidosis may occur with malignancies, the acute development in this patient cannot be explained by complications leading to tissue hypoxia (Type A) or by the malignancy itself (Type B), as there was no tumour burden or liver disease. The close relation to the start of adjuvant chemotherapy with fluorouracil as part of the mFOLFOX regimen indicates a drug-related Type B lactic acidosis. Fluorouracil is the most likely offending agent and is rarely recognized [2].

Lactic acidosis has not been reported with oxaloplatin and is also not typical of fluorouracil toxicity, which are commonly hematologic, gastrointestinal or dermatologic. As fluorouracil is an effective chemotherapeutic agent in cancer chemotherapy with potentially lethal toxicity, pharmacogenetic sequence and

allelic variants of key genes in fluorouracil metabolism and action have been studied to predict susceptibility. However, commonly reported variants [3] cannot comprehensively predict less typical patterns, as evidenced by the genotype of this patient, who might have otherwise developed typical toxic manifestations were they not preempted by CRRT intervention.

The mechanism of fluorouracil associated Type B lactic acidosis is unclear. Inhibition of the Krebs' cycle by fluoroacetate, a metabolite, has been proposed, with low triglyceride as a potential risk factor [2]. This patient developed acidosis despite a precautionary but unnecessary reduced dose [4] and had a normal triglyceride level. The role of his hemodialysis status is uncertain, as the kidneys only play a minor role in lactate clearance, as previously similarly reported [5]. An associated hyperammonemia could underlie his encephalopathy [2] but was not measured because of his unremarkable liver enzymes.

Pending better pharmacogenetic predictors and understanding of pathogenesis, routine clinical monitoring and measurements of electrolytes, acid base, lactate and ammonia in hemodialysis patients after fluorouracil should be implemented within 24 h of administration to detect this potentially lethal but treatable complication.

CONFLICT OF INTEREST STATEMENT

None declared.

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