Resistant iron-induced hypophosphatemia following colorectal surgery

Yu-Jen Chen, Christopher Lim, Jacob McCormick

ABSTRACT

Iron-induced hypophosphatemia represents an increasingly recognised complication of iron infusion. A 34-year-old woman presented for surgical management of her colorectal cancer. Post-operative blood tests revealed severe hypophosphatemia, resistant to oral phosphate supplementation and large volumes of intravenous phosphate replacement. Further questioning and biochemical investigation led to the recognition of iron-induced hypophosphatemia as a contributory cause, secondary to iron infusion administered as part of pre-operative optimisation. Early consideration, diagnosis and management of this complication has the potential to reduce fluid burden associated with intravenous phosphate supplementation and optimise post-operative care.

Iron-deficiency anaemia is the most common form of anaemia worldwide. The incidence is particularly high in patients with colorectal cancer, as unexplained iron deficiency anaemia often prompts further investigation for malignancy. Intravenous iron supplementation is frequently used for pre-operative optimisation, as it offers superior bioavailability and convenience compared to oral supplementation.[1] Among available preparations, ferric carboxymaltose (FCM) is a common choice due to accessibility, a low incidence of allergic reaction, and fast infusion time. Hypophosphatemia is an increasingly recognised adverse effect of FCM infusion, and delays in recognition, diagnosis and management may lead to suboptimal clinical outcomes. Consequently, clinicians must consider the adverse effects of FCM infusion when caring for patients undergoing colorectal surgery.

Clinical record

A 34-year-old woman with a new diagnosis of transverse colon adenocarcinoma presented for elective laparoscopic subtotal colectomy. Although the procedure was performed without intra-operative complication, post-operative investigations revealed significant hypophosphataemia of 0.31mmol/L, decreased from a pre-operative level of 0.60mmol/L (Table 1). Despite aggressive oral and intravenous replacement of phosphate over the following 72 hours, serum phosphate levels remained low between 0.37–0.58mmol/L (Table 2). Throughout this time, the patient was asymptomatic of hypophosphataemia. The patient's renal function and other electrolyte levels remained within normal limits.

On further questioning, the patient reported recent ferric carboxymaltose (FCM) infusion for iron-deficiency anaemia. Two infusions of FCM were administered one week apart, with the second infusion administered six days prior to her operation. Subsequent biochemical investigations demonstrated low levels of 25-hydroxyvitamin D, calcitriol and a significantly raised urinary fractional excretion of phosphate of 29.8%, suggestive of renal phosphate wasting secondary to fibroblast growth factor 23 (FGF-23) excess. Differential diagnoses included prolonged poor phosphate intake, post-operative ileus, refeeding syndrome and Fanconi syndrome.

The patient was commenced on additional oral 25-hydroxyvitamin D and calcitriol replacement, with gradual

Table 1: Blood test results with reference ranges. The pre-operative blood tests were taken six days before the day of operation.

Blood test result (ref. range)	**Pre-operative**	**Day 1 post-op**	**Day 6 post-op**
Haemoglobin (115–155g/L)	96	98	109
WCC (4.0–12.0x10^9/L)	5.5	10.9	5
Platelet (150–400x10^9/L)	357	243	321
Sodium (135–145mmol/L)	142	139	138
Potassium (3.5–5.2mmol/L)	4.8	3.8	3.9
Chloride (95–110mmol/L)	108	108	112
Bicarbonate (22–32mmol/L)	26	23	20
Urea (3.0–8.0mmol/L)	2.6	2.3	0.6
Creatinine (45–90umol/L)	56	53	41
eGFR (>90)	>90	>90	>90
Calcium (2.10–2.60mmol/L)	2.3	2.06	1.98
Magnesium (0.70–1.10mmol/L)	0.86	0.72	0.8
Phosphate (0.75–1.50mmol/L)	0.6	0.31	0.43
Albumin (35–50g/L)	36	31	30
CRP (<5.0mg/L)	1	72	3
25-hydroxyvitamin D (>50nmol/L)			19
1,25-dihydroxyvitamin D (1.7–10.0 pmol/L)			8.9
PTH			36
Iron studies			
Ferritin (20–204ug/L)	591		633
Iron (9–30umol/L)	185		10
Transferrin (2.0–3.6g/L)	2.4		1.6
Transferrin saturation (15–45%)	>100		25
Random urinary sample			
Creatinine (3.0–24.0mmol/L)			1.6
Albumin (<3.5mg/L)			<5.0
Glucose (mmol/L)			11.3
Phosphate (mmol/L)			5
Fractional excretion of phosphate (15–20%)			29.8

Table 2: Trend of the patient's phosphate level along with the total amount, in mmol, of supplemental phosphate given to the patient.

Day	Serum PO4 (mmol/L)	Total IV replacement (mmol)	Total PO replacement (mmol)
1	0.31	40	-
2	-	-	-
3	0.28	70	64
4	0.54	50	64
5	0.37	60	64
6*	0.43	60	144
7	0.57	-	144
8	0.66	-	144

*25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (calcitriol) supplements were started.

improvement of serum phosphate levels. Management of hypophosphataemia prolonged her hospital stay to eight days. The patient's phosphate levels normalised within one week of discharge.

Discussion

Hypophosphatemia is an increasingly recognised adverse effect of FCM infusion. A recent randomised trial by Wolf et al reported an incidence of 50% in patients receiving FCM.[2] This is likely mediated by an increase in FGF-23 concentration following FCM infusion.[3] As one of the main regulators of plasma phosphate concentration, FGF-23 suppresses renal tubular phosphate reabsorption, increasing urinary excretion of phosphate. FGF-23 also suppresses renal production of 1,25-dihydroxyvitamin D (calcitriol), which further acts to reduce intestinal uptake of dietary phosphate.[4] While FCM-induced hypophosphatemia is usually asymptomatic, cases with classical symptoms of tiredness, diffuse muscle pain and weakness have been described in the literature.[5]

Appropriate fluid balance is a vital component of post-operative management. 'Enhanced Recovery After Surgery' (ERAS) protocols recommend discontinuing or restricting intravenous fluids following colorectal surgery.[6] In such patients, excess intravenous fluid administration is associated with a higher incidence of complications, including anastomotic leakage and wound dehiscence.[7] Fortunately, our patient's post-operative course remained uncomplicated due to her age and otherwise good health. The risk of complications from excessive intravenous fluid administration may be higher in an elderly population, or in those with significant comorbidity.

Patients undergoing colorectal surgery may develop hypophosphatemia through other mechanisms affecting phosphate uptake and regulation. These commonly include poor oral intake, post-operative ileus and refeeding syndrome. Delays in recognising the contribution of FCM infusion to hypophosphatemia in this patient were likely precipitated by its multifactorial nature, in addition to a lack of awareness surrounding FCM-induced hypophosphatemia.

This case highlights the potential impact of delayed recognition of FCM-induced hypophosphatemia in the post-operative period. These delays led to a deviation from standard ERAS protocol, resulting in suboptimal fluid management and increased length of hospital stay. Early consideration, diagnosis and management of iron-induced hypophosphatemia may act to optimise patient recovery and reduce the risk of post-operative complication.

Competing interests:
Nil.

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URL:
http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2019/vol-132-no-1499-26-july-2019/7948

REFERENCES:

1. Munoz M, Gomez-Ramirez S, Bhandari S. The safety of available treatment options for iron-deficiency anemia. Expert opinion on drug safety. 2018; 17(2):149–59.
2. Wolf M, Chertow GM, Macdougall IC, Kaper R, Krop J, Strauss W. Randomized trial of intravenous iron-induced hypophosphatemia. JCI insight. 2018; 3(23).
3. Farrow EG, Yu X, Summers LJ, Davis SI, Fleet JC, Allen MR, et al. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108(46):E1146–55.
4. Schouten BJ, Hunt PJ, Livesey JH, Frampton CM, Soule SG. FGF23 elevation and hypophosphatemia after intravenous iron polymaltose: a prospective study. The Journal of clinical endocrinology and metabolism. 2009; 94(7):2332–7.
5. Anand G, Schmid C. Severe hypophosphataemia after intravenous iron administration. BMJ case reports. 2017; 2017.
6. Carmichael JC, Keller DS, Baldini G, Bordeianou L, Weiss E, Lee L, et al. Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery From the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Diseases of the colon and rectum. 2017; 60(8):761–84.
7. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Annals of surgery. 2003; 238(5):641–8.