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TREATMENT-RESISTANT HYPOPHOSPHATAEMIA AFTER FERRIC CARBOXYMALTOSE: EXPANDING THE SPECTRUM OF 6H SYNDROME (HYPOPHOSPHATAEMIA, HYPERPHOSPHATURIA, HYPOVITAMINOSIS D, HYPOCALCAEMIA, SECONDARY HYPERPARATHYROIDISM, HIGH FIBROBLAST GROWTH FACTOR-23)

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ABSTRACT

Background: Ferric carboxymaltose (FCM) is widely used to treat iron deficiency anaemia (IDA), particularly in patients with gastrointestinal disease who are intolerant of oral iron. While generally well tolerated, FCM is increasingly recognised to cause hypophosphatemia. Most cases are mild and transient, but severe and prolonged episodes remain uncommon.

Case report: A 40-year-old woman with newly diagnosed coeliac disease and severe IDA, received two intravenous FCM infusions (total 1.5 g). Within 1 week she developed profound symptomatic hypophosphatemia (0.34 mmol/l), presenting with escalating fatigue, exertional dyspnoea and arthralgia. Investigations revealed renal phosphate wasting (109.4 mmol/day) and secondary hyperparathyroidism, consistent with FCM-induced fibroblast growth factor-23 phosphaturia; also described as "6H syndrome". Coexistent coeliac-related malabsorption further compounded the condition and rendered oral phosphate supplementation ineffective. The patient required continuous intravenous phosphate infusions via a peripherally inserted central catheter for 5.5 weeks, in addition to dietary optimisation and calcitriol. Gradual recovery was achieved 8.5 weeks after onset, with stabilisation of serum phosphate at 0.9 mmol/l and resolution of symptoms.

Conclusion: This case highlights an uncommon, severe and resource-intensive manifestation of FCM-associated hypophosphatemia. It reinforces the clinical utility of the 6H syndrome framework in recognising the biochemical pattern of FCM-induced phosphate wasting and underlines the importance of considering coexistent malabsorptive disorders, such as coeliac disease, which can magnify severity. Clinicians should remain vigilant, monitor phosphate in at-risk patients, and provide clear safety-netting to enable early detection and intervention.

KEYWORDS

Ferric carboxymaltose, hypophosphatemia, fibroblast growth factor-23, coeliac disease

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LEARNING POINTS

- Ferric carboxymaltose can cause severe, prolonged hypophosphatemia that is treatment-resistant and may necessitate weeks of continuous intravenous phosphate and activated vitamin D therapy.
- The full constellation of 6H syndrome (hypophosphatemia, hypophosphaturia, hypovitaminosis D, hypocalcaemia, secondary hyperparathyroidism, high fibroblast growth factor-23) offers a practical diagnostic framework when evaluating post-iron infusion phosphate disturbances.
- Coexistent malabsorptive disorders can exacerbate renal phosphate wasting and complicate management, therefore at-risk patients need proactive phosphate monitoring and early specialist input, and consideration of fibroblast growth factor-23 directed management.

INTRODUCTION

Iron deficiency anaemia (IDA) is commonly managed with intravenous iron when oral therapy is not tolerated or ineffective. Ferric carboxymaltose (FCM) is widely used because of its efficacy and convenience, but it is increasingly recognised to cause clinically significant hypophosphatemia via fibroblast growth factor-23 (FGF23) mediated renal phosphate wasting. We present an unusually severe, prolonged case in which coexistent coeliac disease amplified the clinical course and complicated management.

CASE DESCRIPTION

A 40-year-old woman presented with a 6-month history of 10 kg unintentional weight loss, severe fatigue, night sweats, diarrhoea and abdominal bloating. Her medical history was significant only for obsessive compulsive disorder and menorrhagia. Initial blood tests revealed severe IDA, along with vitamin D and folate deficiencies. While she had suffered from mild IDA previously due to menorrhagia, she had never found herself struggling to get out of bed due to such profound fatigue. The patient was commenced on oral ferrous sulphate and duodenal biopsies 2 weeks later confirmed coeliac disease as the underlying cause of the anaemia and fatigue. However, the patient was unable to tolerate oral iron due to gastrointestinal upset (a well-recognised side effect), so received parenteral iron. Two infusions of ferric carboxymaltose, (FCM) 1 week apart were given, totalling 1.5 g. Following the infusions, the patient reported no improvement in her symptoms, and conversely, reported escalating fatigue, exertional dyspnoea and new-onset arthralgia.

A routine blood test conducted 1 week after the patient's second iron infusion, incidentally, revealed severe hypophosphatemia (0.34 mmol/l), accounting for the persistent symptoms. Notably, the phosphate level had been 1.15 mmol/l 2 days prior to the first iron infusion, suggesting that the hypophosphatemia was induced by the iron therapy. The patient was initiated on intravenous phosphate infusions to replenish their lost phosphate stores. Despite this, the patient suffered from persistent hypophosphatemia. Every attempt to withdraw phosphate supplementation resulted in a rapid decline in phosphate levels *(Fig. 1)*.

A 24-hour urine collection revealed the patient to be excreting up to 109.4 mmol/day of phosphate, indicating renal phosphate wasting. Parenteral phosphate was insufficient in keeping up with the losses, resulting in a net phosphate depletion. This was further complicated by diarrhoea, a consequence of the patient's coeliac disease, which contributed to additional phosphate losses.

Further investigations aimed to identify the cause of the renal phosphate wasting. Urine tests for amino acids and high voltage electrophoresis showed no evidence of proteinuria. Serological testing for autoimmune diseases and urine phosphoethanolamine were all normal. A dual X-ray absorptiometry scan revealed normal bone density, signifying no skeletal complications from the low phosphate and pointing away from metabolic disorders. Overall, the patient was suffering from hypophosphatemia, microcytic anaemia, mild hypocalcaemia (2.1mmol/l) and slightly low vitamin D.

Serial parathyroid hormone (PTH) levels were measured to localise the phosphate loss and assess patient response to vitamin D therapy. A post-replacement serum PTH level of 18.5 pmol/l indicated secondary hyperparathyroidism, supporting a diagnosis of FCM-induced FGF23 phosphaturia, by exclusion. The strong correlation between PTH levels and phosphate levels *(Fig. 2)*, further supported this diagnosis. Collectively, the patient's clinical presentation and laboratory findings were consistent with "6H syndrome": Hyperphosphaturic hypophosphatemia triggered by high FGF23 that causes hypovitaminosis D, hypocalcaemia

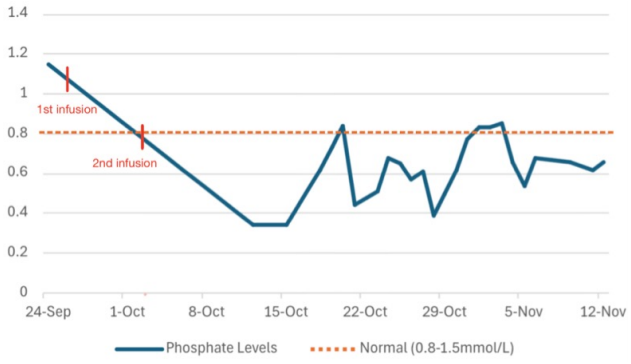


Figure 1. Change in serum phosphate levels over time, following ferric carboxymaltose infusions, showing persistence despite supplementation.

and secondary hyperparathyroidism[1]. This is a proposed constellation of blood results that occur due to iron infusions and FCM in particular.

Given persistent and treatment resistant hypophosphatemia with ongoing urinary losses, the patient was maintained on continuous phosphate infusions. Over the course of 5.5 weeks, the patient received infusions lasting up to 22 hours, through a peripherally inserted central catheter. Following discharge, the patient continued to receive parenteral phosphate for a further 3 weeks, but not on a daily basis. Incorporating symptomatic improvement into clinical decision making, a lower target serum phosphate level of >0.5 mmol/l was established.

Oral phosphate intake was optimised through dietary measures, including the consumption of nuts and phosphate-rich beverages. This was particularly important, as the patient was unable to efficiently absorb sodium acid phosphate tablets due to her coeliac disease.

The patient was also commenced on daily calcitriol supplementation, aimed at suppressing PTH secretion and reducing urinary phosphate loss. The use of an activated vitamin D supplement was essential, as high FGF23 levels inhibit the hydroxylation of 25-hydroxy-vitamin D in the kidneys[2], limiting the efficacy of standard vitamin D preparations.

Over time, the patient's fluctuating phosphate levels began to self-resolve, eventually establishing a new baseline phosphate of 0.9 mmol/l. There was a complete and sustained biochemical resolution 8.5 weeks after the initial low phosphate reading and 11 weeks after the first FCM infusion. The patient has reported significant improvement in their fatigue, weight gain and resolution of their joint pain and diarrhoea. The patient continues to take calciferol supplementation and has adhered to a strict gluten-free diet since their diagnosis of coeliac disease. The patient made a full recovery.

DISCUSSION

FCM has been proven to be a well-tolerated and convenient form of iron replacement in patients with IDA, offering quicker restoration of iron levels compared to oral alternatives. Side effects from oral iron can lead to poor adherence, making intravenous iron particularly useful in patients with gastrointestinal co-morbidities.

Hypophosphatemia is a recognised complication of some intravenous iron formulations. Early identification is essential to prevent complications such as osteomalacia, muscle weakness and neurological damage[3]. A systematic review comparing FCM to other iron formulations, showed that FCM was associated with more frequent and a substantially greater mean decline in phosphate levels[4]. Other contributing factors included preserved renal function (high glomerular filtration rate) and high FGF23 levels. A sub-group analysis showed that patients with chronic kidney disease taking FCM were less likely to suffer from hypophosphatemia and experienced less pronounced

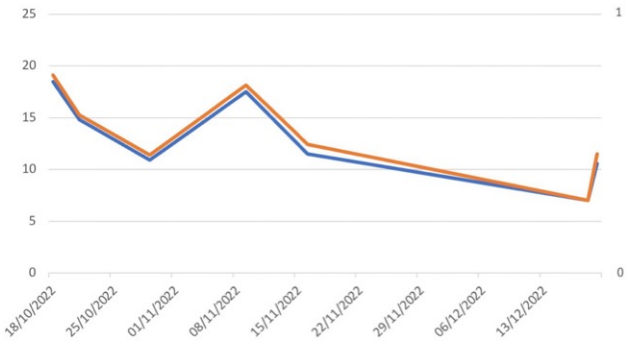


Figure 2. Correlation between parathyroid hormone levels (blue) and phosphate levels (orange) during treatment course.

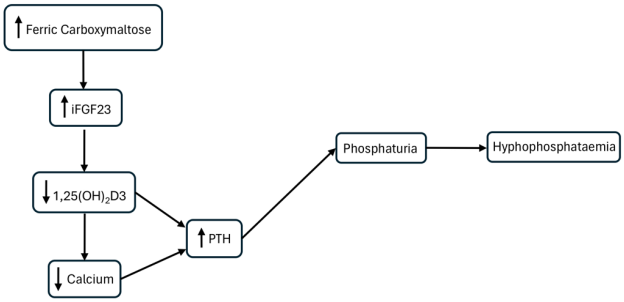


Figure 3. Proposed pathophysiology of FCM induced hypophosphataemia mediated by FGF23. Abbreviations: FCM, ferric carboxymaltose; FGF23, fibroblast growth factor 23; IFG23, intact FGF23; PTH, parathyroid hormone.

phosphate depletion (mean nadir of 1.11 mmol/l compared to 0.69 mmol/l). Impaired kidney function protects against low phosphate, likely due to the reduced capacity for renal phosphate wasting.

The precise mechanism by which FCM causes hypophosphatemia is not fully understood, but is widely believed to be mediated by an increase in the biologically active intact fibroblast growth factor 23(iFGF23)[5]. Synthesised by osteocytes, iFGF23 directly inhibits phosphate re-absorption in the renal tubules. iFGF23 also downregulates renal 1α-hydroxylase activity, leading to a subsequent reduction in 1,25-D3 production[6]. Both the hypovitaminosis D and subsequent hypocalcaemia, stimulate PTH secretion (secondary hyperparathyroidism) and further phosphate wasting[7] *(Fig. 3)*. This PTH-mediated phosphaturia can persist even after FGF23 levels normalise, potentially explaining the protracted duration of hypophosphatemia seen in some patients.

Management of FCM-associated hypophosphatemia is typically supportive and focuses on repletion of phosphate and other nutrient stores. Although monoclonal antibodies such as burosumab have been used with success in both children with X-linked hypophosphatemia and some adults with secondary hypophosphatemia[8], they are seldom required due to the self-limiting nature of the condition. A recovery is usually made within a few months, which is consistent with our patient.

While similar cases of FCM-induced hypophosphatemia

have been reported, prolonged and treatment-resistant hypophosphatemia necessitating 5.5 weeks of continuous phosphate infusions remains exceptionally rare. This case adds to the limited literature, by highlighting the diagnostic value of the 6H framework and the management challenges posed by co-existent malabsorption.

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