Case Report

Insights in Blood Disorders

Osteomalacia As a Rare Complication of Intravenous Iron Supplementation

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ABSTRACT

Iron deficiency (ID) and Iron deficiency anaemia (IDA) are very common among patients with chronic heart failure, chronic kidney disease, inflammatory bowel disease and pre-menopausal and pregnant women. Both ID and IDA can be managed effectively with intravenous Iron supplementation, which has been shown to be superior to oral Iron therapy. We are presenting a patient in her third trimester of pregnancy, who was diagnosed with IDA and treated with intravenous ferric carboxymaltose. This patient developed a rare complication of osteomalacia, which presented as a diagnostic challenged leading to ongoing symptoms until the appropriate diagnosis was made.

Keywords

Iron deficiency, Heart failure, Kidney disease, Inflammatory bowel disease.

Case Presentation

A 39-year-old Sudanese Muslim women, presented to her GP with increasing tiredness, lethargy and hypersomnia. She was in her third trimester of pregnancy and her past medical history was significant for mesial temporal sclerosis (MTS), in the form of by focal epileptic seizures. She was diagnosed with MTS at 20-years-old and is being managed effectively with carbamazepine 100mg BD, with no seizures in the last several years. The patient migrated to Australia at age 19 and works part-time as a cleaner.

Clinical examination was unremarkable apart from mild pallor. There was no postural hypotension and ECG was normal. Routine blood tests showed haemoglobin 110 g/L (normal range 115-165 g/L), serum iron 7 umol/L (7-27 umol/L), serum ferritin 20 ug/L (30-300 ug/L), transferrin saturation 30% (>60%) and red cell width distribution 20 (12.2-16.1). Blood film confirmed hypochromia and pencil cells consistent with a diagnosis of iron deficiency anaemia.

The GP arranged for an iron transfusion of 1000mg Ferric Carboxymaltose (FCM), with no acute complications or concerns. However, the patient re-presented a week later with worsening symptoms and repeat blood tests showed a normal iron study. Physical examination revealed tender muscles, body aches and mild weakness in proximal muscles of the arms and legs. In consultation with a specialist physician, the GP was advised to test for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels and if elevated, treat with Prednisolone for Polymyalgia Rheumatica.

Blood testing revealed elevated inflammatory markers, with CRP 20 mg/L (<10 mg/L) and ESR 30 mm/hr (20 mm/hr). There were no changes in the iron study, with normal alanine aminotransferate, asparate aminotransferase, bilirubin, alkaline phosphatase 130 U/L (30- 110 U/L). In conjunction with the physical symptoms and raised inflammatory markers the patient was treated for

Polymyalgia Rheumatica. After 3 weeks of treatment with oral prednisolone 30mg daily, the patient remained symptomatic with minimal improvement. At this point she underwent a normal vaginal delivery of a healthy baby boy, without complications.

The patient continued to deteriorate, with worsening of proximal muscle weakness. A whole- body bone scan was performed, revealing multiple foci of increased uptake in the rib cage, lumbar spine, bilateral humorous and knees. This was interpreted as osteomalacia. A metabolic screen was performed, showing parathyroid hormone 10.6 pmol/L (2.0-8.5 pmol/L), phosphate 0.32 mmol/L (0.75-1.5 mmol/L), 1,25-dihydroxy vitamin D 24 pmol/L (43-190 pmol/L), 25-hydroxy vitamin D 29.9 nmol/L (>50 nmol/L), alkaline phosphatase 300 U/L (30-110 U/L), urine calcium 30 mg/day (100-300 mg/day), urine phosphate 2 mmol/L (0.74-1.4 mmol/L), corrected serum calcium 1.7 mmol/L (2.15-2.65 mmol/L).

Examination of the urine for proteins, amino acids and uric acid came back normal, excluding Fanconi syndrome. Serum fibroblast growth factor-23 was markedly elevated. Ultrasound and subtraction scan of the neck was negative for any parathyroid hyperplasia and renal ultrasound showed normal sized kidneys and normal corticomedullary differentiation, excluding nephropathology.

Diagnosis was confirmed as Osteomalacia, as a complication of intravenous FCM in combination with the risk factors for vitamin D deficiency. The patients chronic use of the anticonvulsant's carbamazepine and the wearing of a traditional Muslim veil, limiting sun exposure and precipitating vitamin D deficiency.

The patient was treated with a loading dose of vitamin D and calcium phosphate, with ongoing supplementation of vitamin D, phosphate and calcium. The patient started to improve with resolution of all symptoms after 6-weeks of treatment. Repeat metabolic panel including 25-hydroxy vitamin D, 1,25-hydroxy vitamin D, corrected calcium and serum phosphate were within normal limits.

Discussion

Benefits

Iron deficiency (ID) and iron deficiency anaemia (IDA) are very common among patients with chronic heart failure, chronic kidney disease, inflammatory bowel disease and pre- menopausal and pregnant women [1-3].

While symptoms of ID and IDA are non-specific, the condition can be incapacitating, causing significant fatigue and lethargy, body aches, reduced concentration, dizziness and headaches. Less common symptoms include restless leg syndrome, increased tendency to sleep, tinnitus, atrophic glossitis, alopecia, dry skin, koilonychia, and exacerbation of symptoms of systemic diseases, including systolic and diastolic heart failure, ischemic heart disease, inflammatory bowel disease and chronic kidney disease [4].

Due to the high prevalence of ID and IDA, investigations to exclude ID and IDA should be standard clinical practice in GP clinics. While the gold standard investigation is a bone marrow biopsy, this test is invasive and carries risks of infection and bleeding at the site of biopsy, hence is only used in rare and complex clinical scenarios [4]. Blood testing is a more accepted investigation and can confirm the diagnosis whilst indicating the severity of the iron deficiency and level of stored iron.

Iron deficiency is characterized by reduced mean corpuscular volume (MCV), increased red cell width distribution (RCWD), low ferritin, low transferrin saturation, reduced number of reticulocytes, increased soluble transferrin receptors, absent bone marrow stainable iron and reduced hepcidin.

Hepcidin is the liver peptide responsible for Iron homeostasis. In response to low levels of circulating Iron, hepcidin is reduced allowing for increasing levels of ferroportin, a transmembrane protein involved in Iron transport across cells [5]. This in turn increases Iron absorption in the duodenum and allows release of Iron from stores in the liver and spleen [5]. In addition, conditions that result in chronic inflammation cause elevated levels of hepcidin, leading to a reduction in ferroprotin and consequently reduced absorption of Iron [5].

Iron deficiency without anaemia is characterized by the same symptoms of anaemia, especially in pregnant women, that being normal haemoglobin, reduced ferritin, reduced transferrin saturation and elevated soluble transferrin receptors [6]. Bone marrow stainable Iron is low to absent, MCV is usually normal, RCWD is normal to high and hepcidin is again reduced [6].

ID and IDA are easily treated through Iron replacement, leading to improved symptoms and reduced burden of disease. Historically oral Iron was used in the treatment of ID and IDA, however many patients complained of side effects including gastritis and constipation, making non-compliance a concern. The modern use of Iron transfusions has transformed the course of disease, leading to improved symptoms and faster recovery. In Australia, FCM is the most commonly used compound and is indicated in patients with ID, where oral Iron has been ineffective or poorly tolerated, this was used for our patient. Other less common products include Iron Polymaltose and Iron Surcose.

The benefits of intravenous Iron can be seen in a range of diseases and in pregnant women. A meta-analysis of 15,637 studies and 20 randomised control trials looked at the difference between the use of Iron transfusions compared with oral Iron, in the treatment of ID and IDA in pregnant women [3]. They found that Iron transfusions were associated with higher birth weights, higher maternal haemoglobin and reduce side effects [3]. Similar data demonstrating the effectiveness of Iron transfusions has been shown in patients with heart failure, inflammatory bowel disease and chronic kidney disease [1,7].

A systemic review looking at patients with heart failure and

preserved ejection fraction, found 59% of these patients had ID without anaemia and Iron restricted anaemia [1]. The release of IL-6 in heart failure leads to increased levels of hepcidin, resulting in reduced Iron absorption [5]. The treatment of these patients with intravenous Iron improved Oxygen consumption, VO2 max, increased 6-minute walk times, improved exercise tolerance and improved quality of life [1]. However, there was no significant improvement on the mortality rate [1].

Another study looking at the quality of life of patients with inflammatory bowel disease found that the treatment of Iron deficiency had a marked improvement in the patient's quality of life [7]. The study found that although oral Iron was well tolerated in most patients, the use of Iron transfusions was associated with improved tolerance and was more effective in patients with severe anaemia [7].

In addition to this, further studies have shown that the treatment of ID without anaemia resulted in a marked and dramatic improvement in quality of life in pregnant women and their new born babies. It has been shown to reduce the risk of sepsis, improve maternal and perinatal mortality, as well as increase birth weight [8]. The treatment of ID is also associated with improved quality of life in patients with chronic heart failure, inflammatory bowel disease, multiple sclerosis, chronic kidney disease and patients with malignancy. Together these studies emphasize the effectiveness of Iron transfusions and its superiority to oral Iron therapy.

Potential complications

While it has been demonstrated that Iron transfusions are effective at treating ID and IDA with reduced adverse effects when compared to oral Iron therapy, there are still complications that need to be considered. Although rare, acute anaphylaxis should always be recognized as a potential complication.

Osteomalacia is another uncommon complication following the treatment with IV Iron therapy, particularly with FCM. While the exact mechanism is unclear, it may involve increasing levels of fibroblast growth factor-23, which through lowering of 1,25- dihydroxy vitamin D, reduces phosphate reabsorption in the proximal tubules and the intestine. The subsequent hypophosphatemia leads to reduced mineralization of newly formed osteoid, resulting in osteomalacia (REFERENCE).

The presentation is often non-specific, making diagnosis difficult. It can include diffuse body aches, proximal muscle weakness, gait instability, falls and fragility fractures (REFERENCE). Due to the non-specific presentation, osteomalacia is often misdiagnosed. This was the case with our patient who presented with generalised body aches and mild proximal muscle weakness of the arms and legs. The unspecific presentation led to an incorrect diagnosis and treatment of Polymyalgia Rhematica.

In patients with risk factors for Vitamin D deficiency, osteomalcia should be suspected. In the case presented, our patient had several risk factors for Vitamin D deficiency, including the chronic use of Carbamazepine and limited sun exposure due to her religious veiling. These patients are at high risk of developing osteomalcia following the treatment with Iron transfusions, particularly with FCM.

As stated above we suggest that investigations to exclude ID and IDA should be standard clinical practice in GP clinics. In addition to this, patients who are at high risk of developing Vitamin D deficiency should be screened, including testing 25-hydroxyvitamin D levels, and treated appropriately before commencing iron supplementation therapy.

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