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Educational Case Report

Skin Staining Following Intravenous Iron Extravasation in a Patient With Chronic Kidney Disease: A Case Report

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Abstract

Rationale: Intravenous iron is commonly use in anemia related to chronic kidney disease. Skin staining due to iron extravasation is a rare adverse reaction that can leave a long-term staining of the skin.
Presenting Concerns of the Patients: During iron derisomaltose infusion, patient reported iron extravasation. Five months after the incident, the skin stain related to the extravasation was still present.
Diagnosis: A case of skin staining due to iron derisomaltose extravasation was diagnosed.
Interventions/Outcomes: She was reviewed by dermatology and laser therapy was offered.
Teaching Points: Patients and clinicians need to be aware of this complication, and protocol needs to be put in place to minimize extravasation and its complication.

Abrégé

Justification: L'administration de fer par voie intraveineuse est une procédure courante pour traiter l'anémie liée à l'IRC. La coloration cutanée due à l'extravasation du fer est un effet indésirable rare qui peut perdurer à long terme.
Présentation du cas: Une patiente ayant signalé une extravasation du fer au cours d'une perfusion de dérisomaltose ferrique. Cinq mois après l'incident, la coloration de la peau liée à l'extravasation était toujours présente.
Diagnostic: Un diagnostic de coloration cutanée due à une extravasation de dérisomaltose ferrique a été posé.
Interventions/Résultats: La patiente a été revue en dermatologie et une thérapie au laser lui a été offerte.
Enseignements tirés: Les patients et les cliniciens doivent être au fait de cette possible complication. Un protocole doit être mis en place pour minimiser l'extravasation et sa complication.

Keywords

iron staining, ferric derisomaltose, extravasation, cutaneous siderosis, laser therapy

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Background

Extravasation is a rare adverse drug reaction in adults, with a reported incidence between 0.1% and 6%.[1] The risks of extravasation identified can be classified under 3 categories: patient-related, procedure-related, and product-related factors (Table 1).[1] Extravasation can be minimized by careful infusion techniques, early recognition of drug leakage, and training in management if extravasation occurs.[1]

Skin staining due to iron, also known as cutaneous siderosis or hemosiderin staining, is an uncommon adverse effect previously well-characterized with intramuscular iron injections.[2] There have been a few reports of skin staining since the use of intravenous (IV) iron, with reported cases being limited to iron sucrose,[3] iron polymaltose,[4-7] and ferric carboxymaltose infusions.[8-10] To our knowledge, there have been no reported cases of iron staining with ferric derisomaltose. We describe the case of a 41-year-old patient with chronic kidney disease (CKD) and iron deficiency anemia who had skin staining following IV ferric derisomaltose extravasation.

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Table 1. Risk Factors for Extravasation.

Patient-related risk factors	Procedure-related risk factors	Product-related risk factors
• Small and fragile veins in children or elderly	• Untrained or inexperienced staff	• Inadequate choice of equipment (eg, peripheral catheter choice, size or steel needle)
• Patient skin color (darker color may delay detection time)	• Multiple attempts at cannulation	• Inadequate dressings
• Patients with cancer with hardened and thickened vessels due to frequent venipuncture	• Need for catheter readjustment	• Poor cannula fixation
• Patients with vessels that move easily during venipuncture attempts	• High flow pressure	• Duration of infusion and infusion rate
• Patients with excised lymph nodes, limb amputation, or closed vena cava		• Catheter location
• Patients with obesity, in whom peripheral venous access is more difficult		
• Excessive movements		
• Hypotension		
• Peripheral vascular disease, Raynaud disease		
• Clot formation at cannulation site		
• Peripheral neuropathy or decreased sensory perception		
• Decreased ability to verbalize pain		
• Variation in venous and arteriolar anatomy		
• Some medications (eg, anticoagulants, antiplatelets, vasodilators, steroid diuretics, antihistamines, analgesics)		

Case Presentation

A 41-year-old female presented to our clinic for an outpatient IV infusion of ferric derisomaltose. She has a history of stage 4 CKD secondary to lupus nephritis and has been requiring iron supplementation for treatment of symptomatic CKD-related iron deficiency anemia. The patient's additional comorbidities included hypertension, antiphospholipid syndrome with previous deep vein thrombosis, and several previous complications of systemic lupus erythematosus (cerebellar stroke and seizure secondary to Libman-Sacks endocarditis, inflammatory myopathy, lupus cerebritis, and posterior reversible encephalopathy syndrome). Her medication list at the time of infusion included amlodipine 10 mg orally (PO) daily; azathioprine 50 mg PO daily; calcium carbonate 500 mg PO twice daily; cholecalciferol 1000 IU PO daily; citalopram 20 mg PO daily; darbepoetin 30 µg subcut weekly; labetalol 200 mg PO twice daily; levetiracetam 500 mg PO twice daily; melatonin 1.5 mg PO at bedtime; prednisone 8 mg PO daily; and warfarin alternating 1 and 2 mg PO daily (targeting an international normalized ratio [INR] between 2 and 3). For the iron deficiency anemia, she was initially treated with oral ferrous fumarate; however, she was unable to tolerate the medication due to diarrhea and switched to IV iron therapy. She received her first IV iron infusion with iron sucrose on June 16, 2021, which was well-tolerated. She was then switched to ferric derisomaltose for her second infusion on November 2, 2021, since this option was newly available for CKD patients and a higher dose of elemental iron was indicated.

Most relevant outpatient laboratory values prior to the iron infusion included hemoglobin 92 g/L, reticulocyte count 78×10^9/L, iron 7.3 µmol/L, ferritin 15 µg/L, transferrin saturation 13%, serum creatinine 227 µmol/L, estimated glomerular filtration rate 22 mL/min/1.73 m^2 (using the CKD-EPI equation), and urine albumin-to-creatinine ratio 59.3 mg/mmol. Of note, the patient was anticoagulated with warfarin at the time of infusion and her INR was elevated at 5.5 six days prior to her infusion. Warfarin dosage adjustment was done, and her INR was down to 2.2 two days after the IV iron infusion.

The patient received a single dose of ferric derisomaltose 1000 mg (16.7 mg/kg, weight: 62 kg) IV in clinic, diluted in 100 mL normal saline, infused at a rate 15 mL/h for 20 minutes, with a plan to increase to 120 mL/h if no adverse effects. The infusion was into a vein on the dorsum of her left hand. No cannulation difficulties or trauma was reported or documented, and the patient had not recently received other IV medications. Fifteen minutes into the infusion, the patient started feeling slight pain at the injection site and noticed a significant fluid-filled bump. The nurse was called over to assess and determined that the iron infusion had extravasated into the surrounding tissue. The IV infusion was immediately

Figure 1. Picture of skin staining the day of the extravasation.

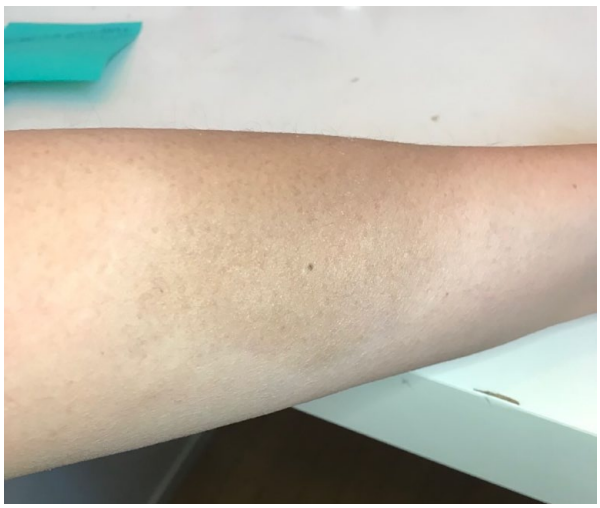

Figure 2. Picture of the skin staining 5 months after the extravasation.

terminated, and the patient was given an ice pack to apply to the area to minimize bruising. The patient reported a large purplish-brown bruise appeared over her forearm following the extravasation incident (Figure 1).

Five months later, the iron staining persists on the patient's left forearm and has increased in size, although faded at the edges, compared to previous (Figure 2). She was referred to dermatology who noted that the skin staining was consistent with IV iron extravasation. Laser therapy was offered to the patient to help reduce the pigmentation, but the patient did not pursue this option yet.

Discussion

Anemia is a common complication in chronic kidney disease (CKD), affecting approximately 50% of CKD non-dialysis patients. The first-line treatment to correct iron deficiency in CKD anemia is oral iron supplementation. However, for patients with an intolerance or unresponsiveness to oral iron, parenteral iron is a suitable alternative. Available parenteral iron formulations in our practice include iron sucrose, and ferric derisomaltose. Since its recent addition to our formulary in October 2021, ferric derisomaltose has quickly gained favor as the preferred treatment option in CKD non-dialysis related anemia given its shorter infusion time, single-dose administration, and favorable adverse effect profile.

Previous case reports have described iron staining with iron sucrose, iron polymaltose, and ferric carboxymaltose infusions.[3-10] Our case adds to the literature as the first reported case of iron staining with ferric derisomaltose. In initial landmark trials PROPOSE and PROVIDE, no cases of iron staining were reported in patients receiving ferric derisomaltose;[11,12] however, skin discolouration is listed as a post-marketing adverse drug reaction in the Monoferric product monograph.[13] In clinical trials of ferric carboxymaltose, the incidence of skin staining ranged from 0.68% to 1.31%.[14,15] As of December 2022, the US Food and Drug Administration (FDA) pharmacovigilance database reports no case of skin staining or extravasation with ferric derisomaltose, while the EudraVigilance, the European database of suspected adverse drug reaction, reports 4 cases of skin hyperpigmentation. Health Canada reports one case of extravasation and one case of skin discoloration, other than our case.

Iron staining occurs as a result of iron extravasation into surrounding soft tissue. Skin necrosis has not been reported with this drug. This case stresses the importance of taking preventative measures to avoid extravasation. Our patient had some risk factors associated with extravasation including anticoagulation with warfarin and prednisone use. It is important that health care providers who administer IV iron are aware of the risk factors for extravasation and ways to minimize it from occurring.

A maternity hospital in Ireland conducted a quality improvement study using a locally developed IV infusion protocol to mitigate extravasation events.[16] The project included a patient brochure explaining IV iron treatment, mentioning the risk of skin staining, as well as a 10-steps nursing procedure for iron infusion, which included obtaining patient consent, making sure that infusion is provided during the daytime, inserting the cannula and flushing it with normal saline prior to starting infusion,

checking cannula site and integrity prior and during the IV iron infusion, informing the patient to reports any discomfort, pain and discoloration during the infusion, flushing the cannula with normal saline after the infusion and remove the cannula, and finally observing the patient for minimum of 30 minutes for possible adverse reactions. No skin staining was observed in the 8-week study period; however, the study had significant limitations, including its short observation period and low protocol compliance rate (53%).[16] We cannot confirm that all these steps were followed in the case presented. Further investigation and quality improvement initiatives are required to determine optimal preventative strategies.

IV iron extravasation may result in long-term skin staining. This adverse effect may be cosmetically unappealing, and distressing for patients. There are no published trials or guidelines available to direct management of skin staining secondary to iron infusions, which is potentially irreversible.[17] A few cases of spontaneous remission have been reported.[18] Topical therapies, lymphatic drainage, and massage have been tried without success.[19] Some retrospective studies and case-series have shown promising benefits with the use of laser therapy to attenuate the skin staining.[19,20] Current publications show regression of the staining with an average of 5 laser sessions over 1 to 2 years.[20] The patient's individual skin type may influence the success of laser treatment.[17] The type of iron used or the timeline to start laser treatment have not been reported as important determinant of therapy efficacy. Our patient was referred to dermatology and offered laser therapy but decided to not pursue this treatment.

Conclusion

In summary, we report a case of skin staining following ferric derisomaltose extravasation. Intravenous iron therapy is widely used to treat iron deficiency anemia related to CKD. Despite being a rare adverse drug reaction, clinicians and patients should be aware of this complication that can lead to long-term staining of the skin. Infusion clinics that administer IV iron should have protocols in place to minimize extravasation. Patients who develop skin staining following IV iron administration may benefit from referral to dermatology for consideration of laser therapy to reduce skin discoloration.

List of Abbreviations

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IV, intravenous.

Declaration of Conflicting Interests

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Patient Consent

Patient provided consent to present her case.

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