technique with smooth non-pulsatile blood aspirated from both lumens. CXR post-insertion however showed the catheter tip in the right subclavian vein (Figure 1B). Contrast CT thorax confirmed this location with no evidence of vascular injury but there was a filling defect in the superior vena cava (SVC) suggestive of a thrombus (Figure 1C), suggesting that the misdirection of the new catheter into the right subclavian vein could be the result of SVC thrombosis arising from the previous catheter. The catheter was subsequently removed and peritoneal dialysis was planned. Unfortunately, the patient developed ACS and succumbed.

The incidence of catheter malpositioning was reported to be higher for left IJV catheter insertion at 30%[1] compared to right IJV due to the acute anatomic angulation leading to a comparatively more tortuous vascular anatomy. Various causes of catheter malpositioning were reported including stenosed brachiocephalic vein stent,[2] and the presence of an existing catheter blocking the path of a new catheter.[3] The occurrence of SVC thrombosis causing catheter diversion is rare, not to mention the fact that our patient was already on aspirin, clopidogrel and enoxaparin due to her ACS. As real-time fluoroscopic guidance is not always possible in the setting of inserting a temporary catheter, it is prudent to always review the location of the catheter tip by plain X-ray after insertion before proceeding to haemodialysis. Other potentially serious complications of SVC thrombosis include upper airway obstruction from laryngeal and tracheal oedema, and visual disturbances, impaired consciousness and other neurological abnormalities due to increased cerebral pressure.[4]

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Severe hypocalcaemia following denosumab and iron infusion

Hypocalcaemia is a known complication of denosumab and advanced CKD is a risk factor. We describe two cases of severe hypocalcaemia following denosumab occurring in patients with CKD who also received iron infusion.

An 83-year-old male with stable stage 4 CKD presented with symptomatic severe hypocalcaemia (corrected calcium 1.66 mmol/L [N: 2.10–2.60 mmoL/L]; ionized calcium 0.89 mmol/L). Serum chemistries demonstrated low phosphate 0.57 mmol/L (N:0.75–1.50 mmol/L), elevated parathyroid hormone (PTH) 94.6 pmol/L (N: 1.6–7.2 pmol/L), 25(OH)-vitamin D and magnesium were normal. Renal function was at baseline with eGFR 19 ml/min. Blood tests 12 months prior showed corrected calcium 2.39 mmol/L, phosphate 1.41 mmol/L, and PTH 28 pmol/L. The patient had received an infusion of ferric carboxymaltose 1 g 1 month and denosumab 60 mg 3 weeks prior to admission.

A 76-year-old male with stage 4 CKD with history of osteoporosis presented with hypocalcaemia following Denosumab infusion. He received Ferric carboxymaltose within 1 month of presentation. Laboratory tests revealed hypocalcaemia (corrected calcium of 1.77 mmol/L; ionized calcium 1.00 mmol/L). Phosphate 0.8 mmol/L, PTH was elevated at 100 pmol/L, whilst 25(OH)-vitamin D level and magnesium were normal. Renal function was at baseline, with serum creatinine 286micromol/L and eGFR 17 ml/min. Baseline bloods from 4 months prior showed corrected calcium 2.41 mmol/L, phosphate 1.85 mmol/L, and PTH 8.0 pmol/L.

In chronic kidney disease patients, CKD-MBD and iron deficiency often co-exist. Denosumab is the only antiresorptive therapy available to patients with advanced CKD. Furthermore, the use of ferric carboxymaltose for iron deficiency has been increasing.

Hypocalcaemia is a recognized complication of denosumab, with an incidence of up to 14%.[1,2] Whilst advanced CKD is a recognized risk factor[2] evidence supporting baseline serum calcium, 25-hydroxyvitamin D concentration, and the use of calcium and vitamin D supplementation as risk factors have been conflicting.[1,2]

Hypophosphataemia is well-known sequelae of intravenous iron infusion. It is postulated that the carbohydrate moiety of certain iron preparations interferes with degradation of FGF-23, leading to an elevation in serum FGF-23.[3] FGF-23 increases phosphaturia, reduces PTH expression, and decreases 1,25-dihydroxyvitamin D, resulting in hypocalcaemia with an impaired PTH response. Risk factors include ferric

carboxymaltose, disorders of phosphate homeostasis (hyperparathyroidism, vitamin D deficiency, and malnutrition), and comorbid states that predispose to hypocalcaemia, including use of antiresorptives.[4]

The interaction of denosumab and intravenous iron causing severe hypocalcaemia has been reported.[5] The mechanism is proposed to be an elevation in FGF-23 from the intravenous iron, which leads to hypophosphataemia and a diminished PTH response to the hypocalcaemia which ensues after denosumab administration.

Hypophosphataemia occurs 1 and 2 weeks after intravenous iron and can persist for to 6–12 weeks. Reductions in serum calcium occur up to 6 months after denosumab. We suggest that the highest risk for co-administration of these drugs is within 2 weeks, but this risk may persist for up to 3 months.

In our cohort of chronic kidney disease patients, CKD-MBD and iron deficiency often co-exist. We recommend an interval of at least 3 months between denosumab and intravenous iron infusion and a reminder to monitor serum calcium and phosphate levels in these patients to avoid potentially life-threatening electrolyte disturbances.

AUTHOR CONTRIBUTIONS

Adrienne Cohen wrote the manuscript. Bobby Chacko edited and revised the manuscript.

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CONFLICT OF INTEREST

All authors report no competing interest to disclose.

ETHICS STATEMENT

Case report has been completely de-identified and is exempt from approval by an ethics review board.

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