CASE REPORT

Severe hypocalcaemia as a cause of seemingly idiopathic bilateral lower limb oedema

Aaron Karnell Dachuan Hung

Independent, Sydney, New South Wales, Australia

Correspondence to
Dr Aaron Karnell Dachuan Hung,
aaron.hung@hotmail.com

SUMMARY

The existing scientific literature has not drawn a link between severe hypocalcaemia and its role in recalcitrant peripheral oedema. This phenomenon is particularly relevant in oncological and geriatric medicine as bone strengthening but serum calcium-lowering agents such as bisphosphonates and denosumab are used for osteoporosis and/or bone metastasis. This case report, through metastatic prostate cancer in a 66-year-old man with bone metastasis being treated with a monoclonal antibody denosumab, proposes the mechanism of hypocalcaemic oedema as being akin to calcium deprivation such as those induced by calcium channel antagonism. It demonstrates the importance of calcium supplementation as a concurrent treatment while patients are on these osteoclast inhibiting agents.

BACKGROUND

Bilateral lower limb oedema is a prominent sign of the congestive heart failure, among other differential diagnoses. In the context of the iatrogenic bilateral lower limb oedema, often clinicians think of common drugs such as calcium channel blockers (CCB), of which oedema is a common side effect¹ and may cause a lack of compliance with the medication. This case report, using the clinical presentation of a 66-year-old man with metastatic prostate cancer on docetaxel and lenalidomide therapy, as well as denosumab for bone metastases, explores hypocalcaemia and calcium channel antagonism as two sides of the coin of calcium ion deprivation causing peripheral oedema. Calcium ion deprivation is a shared theme in these two seemingly different, but in fact similar situations.

CASE PRESENTATION

A patient with advanced prostate cancer presented to the emergency department with bilateral leg swelling of sudden onset that started 1 week ago. There was no history of trauma, congestive heart failure, symptoms consistent with deep vein thrombosis (DVT) or liver disease. At the time he had 19 cycles of 150 mg docetaxol, 25 mg lenalidomide daily as well as a fully human monoclonal antibody for the management of bone metastasis, denosumab. The other medications that the patient took regularly on presentation were OxyContin 10 mg twice daily (slow release oxycodone), enalapril 20 mg mane and Slow K (potassium chloride 600 mg) three times a day. Since the onset of the oedema he was prescribed high-dose furosemide of 250 mg daily by his general practitioner (GP). He had no known allergy.

INVESTIGATIONS

On routine blood tests, it was found that the patient's corrected serum calcium was 1.33 mmol/L, which was critically low. The patient exhibited some of the usual symptoms associated with hypocalcaemia such as paresthesia (pins and needles) in the feet and lower legs, and pain both probably worsened by the excessive swelling. He did not exhibit tingling sensations in the fingers and circumoral regions, or tetany.^{2 3} On ECG he showed long QTc (486 ms) which was also consistent with low serum calcium.^{2 3}

DIFFERENTIAL DIAGNOSIS

A number of differential diagnoses had been considered including bilateral DVT, lymphoedema due to lymphatic infiltration of prostate cancer, or oedema as a side effect of docetaxel and/or lenalidomide.^{4 5}

In the first differential, bilateral venous Dopplers were negative for DVT. In the second, the patient exhibited bilateral pitting oedema which was not typical for lymphatic blockage (non-pitting). Only the third option seemed the most likely so a presumptive diagnosis of peripheral oedema due to the chemotherapy agents used was made.

TREATMENT

Interestingly as aforementioned, prior to the patient's presentation his GP had prescribed high-dose furosemide of 250 mg daily, which not only did not help, but gave the patient acute pre-renal kidney impairment as a result of dehydration. On admission to the medical oncology team the furosemide was promptly ceased.

It has been documented in recent case reports that denosumab produces profound hypocalcaemia in some patients, such as those with renal impairment.^{6 7} However, a 2013 case report suggested that patients with normal renal function are not exempt from denosumab's hypocalcaemic effects.⁸

The 66-year-old man mentioned in this case report was such a patient with a normal baseline renal function. Because he had presented with profound hypocalcaemia, an effect believed to be caused by denosumab^{9 10} the calcium had been replaced intravenously and orally. Ten millimoles of magnesium sulfate was administered on the first day by the emergency department and five bags of 10% calcium gluconate in 100 mL of normal saline had been administered over the second and third days of admission to the ward. Oral calcium carbonate 1500 mg (equivalent to 600 mg elemental calcium) three times a day was started on the

CrossMark

To cite: Hung AKD. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201387

second day of admission which continued until discharge on day 6. On discharge the patient was stepped down to calcium carbonate 1500 mg twice daily as per manufacturer directions.

Prior to admission the patient had been advised to take regular oral calcium supplementation to prevent the known hypocalcaemic side effect of denosumab, an osteoclast inhibitor that acts by binding directly to the RANK ligand, thereby preventing the activation of RANK receptors. The result of this is prevention of preosteoclast precursor maturation and osteoclast mediated bone resorption.⁹ However, the patient had not been compliant as he did not think it was important.

OUTCOME AND FOLLOW-UP

The calcium level never reached the normal range during the patient's 6 days of admission (12–18 July 2012) but it had been

as high as 2.17 mmol/L on the third last day. On the second last day the patient's serum calcium level was 2 mmol/L (likely due to the dilutional effects of hydration). Interestingly as the calcium level recovered, the leg swellings also started to decrease and by the time of discharge the patient was able to walk on his own, all without the use of diuretics (please refer to table 1 for the results of his routine blood tests during admission).

DISCUSSION

A few questions arose: 'What exactly was the cause of the bilateral lower limb oedema? If it was the side effect of docetaxel and/or lenalidomide, why was it that calcium replacement seemed to be correlated with improvement in the oedema? Could it just be a coincidence?' These questions led me to

Table 1 One (summary of blood tests from admission 12/07/12 to discharge 18/07/12)

	12/07/12 (16:47)	13/07/12 (13:00)	13/07/12 (22:05)	14/07/12 (09:05)	15/07/12 (08:25)	16/07/12 (09:05)	17/07/12 (07:47)
<i>Biochemistry</i>							
EUC							
Sodium	140 mmol/L	136 mmol/L					140 mmol/L
Potassium	4.1 mmol/L	4.6 mmol/L					4.7 mmol/L
Chloride	97 mmol/L	97 mmol/L					106 mmol/L
Bicarbonate	28 mmol/L	22 mmol/L					28 mmol/L
Anion gap	19 mmol/L	22 mmol/L					11 mmol/L
Urea	12.9 mmol/L	12.3 mmol/L					6.8 mmol/L
Creatinine	97 µmol	87 µmol/L					76 mmol/L
eGFR	67 mL/min/1.73 m ²	76 mL/min/1.73 m ²					89 mL/min/1.73 m ²
CMP							
Calcium	1.45 mmol/L	1.40 mmol/L	1.74 mmol/L	1.84 mmol/L	2.01 mmol/L	2.09 mmol/L	1.96 mmol/L
Calcium (corrected)	1.33 mmol/L	1.36 mmol/L	1.70 mmol/L	1.82 mmol/L	2.05 mmol/L	2.17 mmol/L	2.00 mmol/L
Magnesium	0.85 mmol/L	1.09 mmol/L	1.08 mmol/L	1.07 mmol/L	0.96 mmol/L	0.88 mmol/L	0.93 mmol/L
Phosphate	2.24 mmol/L	1.98 mmol/L	1.70 mmol/L	1.55 mmol/L	1.32 mmol/L	1.58 mmol/L	1.40 mmol/L
Liver function							
Bilirubin total	9 µmol						
Protein	85 g/L						
Albumin	46 g/L	42 g/L	42 g/L	41 g/L	38 g/L	36 g/L	38 g/L
Total globulin	39 g/L						
ALT	25 U/L						
AST	33 U/L						
GGT	34 U/L						
ALP	147 U/L						
Inflammatory marker							
CRP	27 mg/L	27 mg/L					34 mg/L
Full blood count							
Haemoglobin	115 g/L	110 g/L					104 g/L
WCC	9.4×10 ⁹ /L	7.6×10 ⁹ /L					5.6×10 ⁹ /L
Platelets	302×10 ⁹ /L	301×10 ⁹ /L					313×10 ⁹ /L
RCC	4.1×10 ¹² /L	3.9×10 ¹² /L					3.7×10 ¹² /L
Haematocrit	0.34	0.32					0.30
MCV	83 fL	84 fL					83 fL
MCH	28 pg	28pg					28pg
MCHC	342 g/L	341 g/L					342 g/L
Neutrophils	6.4×10 ⁹ /L	5.4×10 ⁹ /L					3.5×10 ⁹ /L
Lymphocytes	1.9×10 ⁹ /L	1.4×10 ⁹ /L					1.5×10 ⁹ /L
Monocytes	0.9×10 ⁹ /L	0.7×10 ⁹ /L					0.4×10 ⁹ /L
Eosinophils	0.1×10 ⁹ /L	0.1×10 ⁹ /L					0.3×10 ⁹ /L
Basophils	0.1×10 ⁹ /L	0.0×10 ⁹ /L					0.0×10 ⁹ /L

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CMP, Calcium, Magnesium, Phosphate; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; EUC, Electrolytes, Urea, Creatinine; GGT, γ-glutamyl transpeptidase; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RCC, red cell count; WCC, white cell count.

explore another possible explanation for the patient's oedema—a mechanism similar to calcium channel antagonism.

CCBs such as the dihydropyridines (eg, amlodipine) have been associated with peripheral oedema, the likely mechanisms of which were already documented in the scientific literature.^{11 12} We know as a fact that the entry of calcium ions into the smooth muscle cells of the tunica media of the blood vessels will cause their contraction. CCBs block the entry of calcium ions, thereby causing relaxation of the smooth muscles, and hence vessel dilation.

It may be theorised that arterioles dilate to a much larger degree in comparison to the venules. Arterioles have more smooth muscle cells than venules. An arteriole has one or two helically arranged layers of smooth muscle cells in the tunica media, whereas a venule typically only has contractile pericytes in the tunica media, with a few occasional smooth muscle cells.¹³ The basal tonal contraction of an arteriole is therefore greater than that of a venule so that should calcium be deprived, the degree of dilation of an arteriole would be expected to be greater than that of a venule.

This difference in dilation creates a greater differential in the hydrostatic pressure between the arteriolar and the venular ends of the capillaries. The result is greater extravasation of intravascular fluid into the interstitial compartment, a phenomenon clinicians observe as 'oedema'. Obviously the more dependent the body structure, such as the legs, the more marked the oedema will be due to the effect of gravity. Diuretics are usually not effective for such kind of oedema, as it is not due to sodium or fluid overload.¹²

It seemed logical to observe that blocking the calcium channels so that less calcium ions could enter is similar to decreasing the availability of calcium ions in the serum so that less ions are available to the channels. Both represent calcium ion deprivation, so expectedly would also cause similar clinical manifestations.

This hypothesis was supported by the fact that using high-dose loop diuretic did not help the patient even after causing dehydration (note frusemide actually worsens hypocalcaemia as a known pharmacodynamic effect⁴). Moreover, as the serum calcium level rose, the bilateral leg oedema also improved, suggesting that calcium deprivation might have been the mechanism responsible for the patient's condition much like the aforementioned oedema side effect of CCBs.

The correlation between hypocalcaemia and peripheral lower limb oedema was not well documented. After searching in MEDLINE, PubMed and EMBASE with keywords such as hypocalcaemia, oedema, denosumab and bisphosphonate no articles were found which mentioned the probable link between hypocalcaemia and peripheral oedema.

It had been noted in papers that discuss denosumab's adverse effects that oedema and hypocalcaemia were side effects of the monoclonal antibody.^{10 14} However, it appeared none had actually connected the possible relationship between the two.

This case report is pointing a direction to the future research to investigate the significance of hypocalcaemia in patients experiencing peripheral oedema while on serum calcium-lowering agents such as bisphosphonates and denosumab. It

would be interesting to see whether randomised trials involving regular calcium supplementation might demonstrate a statistically significant reduction in the rates of peripheral oedema as a side effect of these bone-strengthening but calcium-lowering agents.

Learning points

- ▶ Hypocalcaemia can cause peripheral oedema similar to calcium channel blockers.
- ▶ When using osteoclast-inhibiting agents such as bisphosphonates and denosumab, it is clinically advisable to start the patient on concurrent calcium supplementation. Vitamin D may be supplemented if the level is found to be deficient on blood test.
- ▶ Diuretics will not work for oedema induced by hypocalcaemia.

Acknowledgements The author would like to thank the patient and his wife for their gracious consent to the publication of the medical condition.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Epstein BJ, Roberts ME. Managing peripheral edema in patients with arterial hypertension. *Am J Ther* 2009;16:543–53.
- 2 Shoback D, Sellmeyer D, Bikle DD. *Metabolic bone disease*. In: Gardner DG, Shoback D, eds. *Greenspan's basic & clinical endocrinology*. 8th edn. McGraw-Hill Companies, 2007.
- 3 Longo DL, Fauci AS, Kasper DL, et al. *Harrison's principles of internal medicine*. 18th edn. McGraw-Hill companies, Inc, 2012.
- 4 MIMS Australia. MIMS Sydney; August 2013.
- 5 Behar A, Pujade-Lauraine E, Maurel A, et al. The pathophysiological mechanism of fluid retention in advanced cancer patients treated with docetaxel, but not receiving corticosteroid comedication. *Br J Clin Pharmacol* 1997;43:653–8.
- 6 McCormick BB, Davis J, Burns K. Severe hypocalcemia following denosumab injection in a hemodialysis patient. *Am J Kidney Dis* 2012;60:626–8.
- 7 Block GA, Bone HG, Fang L, et al. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone and Miner Res* 2012;27:1471–9.
- 8 Milat F, Goh S, Gani LU, et al. Prolonged hypocalcemia following denosumab therapy in metastatic hormone refractory prostate cancer. *Bone* 2013;55:305–8.
- 9 Brown-Glaberman U, Stopeck AT. Role of denosumab in the management of skeletal complications in patients with bone metastases from solid tumours. *Biologics* 2012;6:89–99.
- 10 Fizazi K, Bosserman L, Gao G, et al. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. *J Urol* 2009;182:509–16.
- 11 Pedrinelli R, Dell'Omo G, Nuti M, et al. Heterogeneous effect of calcium antagonists on leg oedema: a comparison of amlodipine versus lercanidipine in hypertensive patients. *J Hypertens* 2003;21:1969–73.
- 12 Makani H, Bangalore S, Romero J, et al. Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate—a meta-analysis of randomized trials. *J Hypertens* 2011;0:1270–80.
- 13 Junqueira LC, Carneiro J, Kelley RO. *Basic histology*. 9th edn. Stamford: Appleton & Lange, 1998.
- 14 Castellano D, Sepulveda JM, Garcia-Escobar I, et al. The role of rank-ligand inhibition in cancer: the story of denosumab. *Oncologist* 2011;0:136–45.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow