Case report

Hypercalcaemia due to isolated elevation of 1,25-dihydroxyvitamin D in patients with Crohn's disease

Faisal Inayat,¹ Saad Saleem,² Adil Mohyudin,³ Zubair Khan⁴

¹Allama Iqbal Medical College, Lahore, Pakistan

²Mercy Saint Vincent Medical Center, Toledo, Ohio, USA

³Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan

⁴University of Toledo Medical Center, Toledo, Ohio, USA

Correspondence to

Dr Faisal Inayat, faisalinayat@hotmail.com

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SUMMARY

Crohn's disease is frequently associated with hypocalcaemia following poor calcium intake and decreased intestinal calcium absorption due to malabsorption-related vitamin D deficiency. Severe hypercalcaemia found in Crohn's disease is an unusual clinical entity. We chronicle here the case of a patient who developed hypercalcaemia with elevated 1,25-dihydroxyvitamin D during Crohn's disease exacerbation. Furthermore, we conducted a systematic literature search of MEDLINE, Cochrane, Embase, and Scopus databases regarding 1,25-dihydroxyvitamin D-associated hypercalcaemia in Crohn's disease. A comprehensive review of the search results yielded a total of five case reports only. The data on patient demographics, clinical features, serum calcium levels, Crohn's disease activity site, treatment strategy, hypercalcaemia resolution time and outcomes were collected and analysed. This paper illustrates that Crohn's disease should be added to the list of granulomatous disorders responsible for 1,25-dihydroxyvitamin D-mediated hypercalcaemia. Physicians should maintain a high index of clinical suspicion for this potential complication for prompt management.

BACKGROUND

Hypercalcaemia is a commonly encountered metabolic abnormality that is predominantly caused by hyperparathyroidism and cancer.¹ Granulomatous diseases such as sarcoidosis, tuberculosis, Wegener's granulomatosis and eosinophilic granuloma; fungal infections like coccidioidomycosis, paracoccidioidomycosis, candidiasis and histoplasmosis; *Mycobacterium avium*-related infection and *Pneumocystis jirovecii* pneumonia may also cause hypercalcaemia.^{2–4} The pathogenesis of this abnormality in patients with granulomatous and lymphomatous diseases implicates unregulated production of 1,25-dihydroxyvitamin D as a consequence of macrophage activation.^{5,6} Crohn's disease is also a granulomatous disorder that has been found to be associated with several perturbations of body calcium regulation. However, hypocalcaemia due to vitamin D deficiency resulting from ileal resection, malabsorption of fat-soluble vitamins and/or low dietary calcium intake is common in these patients.^{7,8}

We present here a unique case of a patient with Crohn's disease who developed severe

hypercalcaemia following elevated 1,25-dihydroxyvitamin D. Additionally, we undertook a review of the published medical literature for this clinical entity that identified a total of five previously reported cases. This study emphasises that hypercalcaemia should be considered in patients with Crohn's disease in order to avoid inadvertent clinical consequences. Furthermore, this paper highlights that 1,25-dihydroxyvitamin D level parallels the clinical activity of Crohn's disease and rapidly responds to appropriate treatment of this underlying disorder.

CASE PRESENTATION

A 73-year-old woman with a formidable medical history of Crohn's disease for 20 years was brought to our medical centre with abdominal pain, nausea, vomiting and altered state of consciousness. As per collateral information, she was not under therapy with any medications and there was no history of vitamin D supplementation. She was not on any particular diet. The patient was haemodynamically stable. Physical examination was unremarkable for abnormalities. She underwent extensive diagnostic workup. The details of her laboratory evaluation are provided (table 1).

Her CT abdomen showed thickening of the descending colon. Colonoscopy was remarkable for hyperemic and friable mucosa in the left descending colon near the splenic flexure. Histopathological examination of the biopsy specimen showed evidence of transmural chronic inflammation with granulomas.

Differential diagnosis

The differential diagnosis included primary and secondary hyperparathyroidism, cancer, sarcoidosis, milk-alkali syndrome, vitamin D toxicity, thyrotoxicosis, tuberculosis, vitamin A intoxication, immobilisation, familial hypocalciuric hypercalcaemia, untreated Addison's disease and certain drugs (thiazides, poorly administered alfacalcidol and calcitriol, and lithium therapy). Extensive diagnostic workup ruled out the above-mentioned probable aetiologies. Eventually, the patient was diagnosed with hypercalcaemia secondary to isolated elevation of 1,25-dihydroxyvitamin D in the setting of relapsed Crohn's disease.

Treatment

In terms of initial management, she received intravenous fluids mainly 0.9% normal saline solution

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Table 1 Initial laboratory investigations of the patient with respective reference ranges

Laboratory parameter	Patient result	Reference range
Total serum calcium	14.3	8.5–10.2 mg/dL
Ionised calcium	6.9	4.4–5 mg/dL
Serum phosphorous	5.2	1.5–2.4 mg/dL
Serum creatinine	3.06	0.8–1.3 mg/dL
Blood urea nitrogen	69	8–21 mg/dL
Serum albumin	5.2	3.5–5.5 g/dL
Alkaline phosphatase	84	50–100 U/L
Serum 1,25-dihydroxyvitamin D	72	20–60 pg/mL
Serum 25-hydroxyvitamin D	31	20–100 ng/mL
Intact parathyroid hormone	11	10–60 pg/mL
PTH-related peptide	1.2	<1.1 pmol/L
24-hour urine calcium	420	25–300 mg/day

PTH, parathyroid hormone.

and furosemide. Subsequently, she was started on intravenous methylprednisolone.

Outcome and follow-up

She responded well to the treatment and her clinical condition rapidly improved. Her calcium level normalised on day 4 of admission. She completed 5 days of intravenous steroids and was then started on mesalamine and budesonide as maintenance therapy for Crohn's disease. With resolution of gastrointestinal complaints, serum calcium and 1,25-dihydroxyvitamin D levels returned to normal. At the subsequent follow-ups, her Crohn's disease remained in remission, with normal biochemical profile.

DISCUSSION

Crohn's disease as a cause of hypercalcaemia is a rare clinical entity. We conducted a systematic literature search in order to access the available studies for hypercalcaemia due to elevated 1,25-dihydroxyvitamin D in the setting of Crohn's disease. Different MeSH terminologies, including 'hypercalcaemia' and '1,25-dihydroxyvitamin D', were combined using the Boolean operators 'AND' and 'OR' with the terms 'Crohn's disease', 'clinical presentation' and 'management'. Although a defined time filter to retrieve related publications was not applied, the data was collected till July 2019. The target medical databases included MEDLINE, Cochrane, Embase, and Scopus. Several articles were obtained through a manual search using the bibliography of the search results. The inclusion criteria for the final comparative analysis consisted of the articles describing the relevant cases in the English language which were accessible in the full-text form, with sufficient data available pertaining to the topic of this study. The results of the above-mentioned search methodology are described in the flow diagram (figure 1). After a comprehensive review of full-text papers, a total of four articles on increased 1,25-dihydroxyvitamin D-associated hypercalcaemia in Crohn's disease were identified.^{9–12} The extracted data, consisting of five case reports only, indicated a slight male predominance (male, $n=3$; female, $n=2$). The mean age of patients was 50 years (range: 27–61 years). The patient data on epidemiology, clinical features, initial calcium levels, time to resolution, management and clinical outcomes are summarised (table 2).

The most frequent presentation of hypercalcaemia is increased serum calcium levels detected on a laboratory evaluation. In symptomatic cases, typical symptoms are 'moans, bones, stones and

Figure 1 Flow diagram representing the search methodology for data synthesis regarding 1,25-dihydroxyvitamin D-mediated hypercalcaemia in patients with Crohn's disease.

groans' indicating depressed mood, musculoskeletal pain, renal colic and abdominal pain.¹³ Neuropsychiatric disturbances such as anxiety and depression as well as cognitive disturbances have also been reported. Renal abnormalities like polyuria, polydipsia and dehydration can also be encountered. These manifestations can be independent or may be a result of associated diabetes insipidus, distal renal tubular acidosis and nephrolithiasis. Musculoskeletal involvement may lead to bone pain, osteopenia, osteoporosis and muscle weakness. Cardiovascular complications include but not limited to hypertension, bradycardia and shortening of the QT interval.¹³ In this comparative review, most patients with hypercalcaemia in setting of Crohn's disease presented with gastrointestinal symptoms such as abdominal pain ($n=3$), diarrhoea ($n=3$), weight loss ($n=2$) and vomiting ($n=2$). Of note, in cases with chronic hypercalcaemia, higher serum calcium levels can be tolerated without any clinical symptomatology.

In terms of pathogenesis, elevated serum 1,25-dihydroxyvitamin D is recognised as the cardinal abnormality. However, 1,25-dihydroxyvitamin D-induced accelerated bone resorption may also have a role.^{14 15} In normal individuals, the changeover of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D occurs in the proximal renal tubular cells, under the action of 1-hydroxylase (CYP27B1) enzyme, which is regulated by parathyroid hormone (PTH), serum phosphate levels and fibroblast growth factor-23. With the rise in serum calcium levels, serum PTH levels are decreased by the feedback loop, which in turn decreases the production of 1,25-dihydroxyvitamin D and normalises serum calcium levels. In granulomatous disorders, activated macrophages produce autonomous 1,25-dihydroxyvitamin D. This PTH-independent mechanism has a pivotal role in the underlying pathology of hypercalcaemia.¹⁵ The synthesis of 1,25-dihydroxyvitamin D increases by 30-fold under the action of THP-1 cells, which are activated by interferon-gamma, released by the activated macrophages. Furthermore, it also minimises the metabolism of 1,25-dihydroxyvitamin D by 42.2%.¹⁶ The aforementioned changes have commonly been implicated in granulomatous diseases and lymphoma. Therefore, similar pathophysiological derangements can also be considered

Table 2 Patient data regarding hypercalcaemia secondary to isolated elevation of 1,25-dihydroxyvitamin D in Crohn's disease

Authors	Publication year	Age/gender/country	Clinical presentation	Initial serum calcium (mg/dL)	Disease activity site	Treatment	Time to resolution (days)	Clinical outcome
Bosch ⁹	1998	53/F/Spain	Abdominal pain, bloody diarrhoea	14.6	Terminal ileum	Intravenous hydration, prednisone	7	Recovered
Bosch ⁹	1998	27/M/Spain	Abdominal pain, diarrhoea, weight loss	13.5	Terminal ileum, caecum, left colon	Intravenous hydration, prednisone	10	Recovered
Tuohy and Steinman ¹⁰	2005	61/M/USA	Intermittent abdominal pain, cramping, weight loss	13.6	No endoscopy	Intravenous hydration, furosemide, pamidronate	3	Recovered
Ioachimescu <i>et al</i> ¹¹	2008	50/M/USA	Elective surgery for take-down ileostomy	11.5	Ileum	Intravenous hydration, hydrocortisone, infliximab	14	Recovered
Zemrak <i>et al</i> ¹²	2010	59/F/UK	Diarrhoea, vomiting, dysarthria	20.8	Rectosigmoid	Intravenous hydration	5	Recovered
The present report	2018	73/F/USA	Abdominal pain, nausea, vomiting, altered level of consciousness	14.3	Descending colon	Intravenous hydration, methylprednisolone	4	Recovered

F, female; M, male.

as possible mechanisms causing hypercalcaemia in patients with Crohn's disease.

The patient involved in the present study developed severe hypercalcaemia secondary to elevated 1,25-dihydroxyvitamin D during Crohn's disease exacerbation. The workup data supporting this included the inappropriate 1,25-dihydroxyvitamin D levels with the concurrent presence of hypercalcaemia and hypercalciuria, PTH in the lower normal range, normal PTH-related peptide levels, the histopathological evidence of the left descending colon showing active Crohn's disease, and the resolution of hypercalcaemia with treatment of Crohn's disease using corticosteroid therapy. Additionally, an increased ACE inhibitor level is a common feature and a useful therapeutic marker in patients with sarcoidosis and hypercalcaemia.¹⁷ However, the significance of elevated ACE levels in patients with Crohn's disease remains to be determined.^{18,19} This patient responded adequately to the prednisone treatment; therefore, we did not measure the serum ACE levels.

The appropriate treatment of hypercalcaemia depends on the underlying aetiology and the severity of the imbalance. In patients with severe hypercalcaemia, intravenous hydration with normal saline remains essentially important, regardless of the underlying pathology.²⁰ In difficult-to-treat cases, calcitonin, mithramycin, denosumab and/or dialysis are recognised as useful adjuncts in the emergency management.²⁰ Long-term treatment in granulomatous disorders mainly depends on managing the underlying disorder. The calcium levels return to normal when the disease process goes into remission. Decreasing the calcium intake to <400 mg and reducing the oxalate intake to decrease the risk of oxalate stone formation in kidneys are also important.²¹ Glucocorticoid therapy (10–30 mg/day of prednisone) is commonly used to treat sarcoidosis.²² Calcium levels begin to fall in 2 days of initiation but an optimal response has

usually been achieved in 7–10 days of treatment. Ketoconazole can be used as the second-line therapy in steroid non-responders and/or in order to decrease or avoid corticosteroid exposure.²³ Doty *et al* described a number of patients with refractory hypercalcaemia who eventually responded to anti-tumour necrosis factor monoclonal antibody, infliximab.²⁴

Tuohy and Steinman described significant improvement in their patient's clinical and biochemical profiles after only 1 week of budesonide therapy. They attributed it to rapid response of macrophage 1-hydroxylase enzyme activity to this oral gastrointestinal-selective corticosteroid.¹⁰ Therefore, budesonide may serve as a better choice than prednisone for 1,25-dihydroxyvitamin D-related hypercalcaemia in active Crohn's disease because this agent minimises the systemic side effects of corticosteroids. In patients with sarcoidosis, the medications like chloroquine and hydroxychloroquine have also been used to decrease calcium and 1,25-dihydroxyvitamin D levels.^{25,26} These agents may also be safe options in hypercalcaemia due to elevated calcitriol in active Crohn's disease, but they have not been previously tested. In this review regarding Crohn's disease, intravenous hydration ($n=5$), prednisone ($n=2$), hydrocortisone ($n=1$), ethylprednisolone ($n=1$), infliximab ($n=1$) and bisphosphonate such as pamidronate with furosemide ($n=1$) were administered. These agents resulted in promising responses. Future research should investigate steroid-sparing agents for their potential therapeutic role in complications like hypercalcaemia in patients with Crohn's disease.

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Learning points

- The present report represents the sixth reported case of hypercalcaemia secondary to elevated 1,25-dihydroxyvitamin D in a patient with active Crohn's disease.
- While evaluating a patient with hypercalcaemia, unregulated 1,25-dihydroxyvitamin D production by macrophages in the setting of active Crohn's disease should be considered among aetiologies.
- Population-based studies should be conducted to delineate the magnitude of this association and related clinical implications.

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