Intermittent hypercalcaemia and vitamin D sensitivity in Hodgkin's disease

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Summary: A patient with Hodgkin's disease spontaneously developed steroid-responsive hypercalcaemia during two consecutive summers. Administration of 3000 U/day of vitamin D, while he was normocalcaemic, caused a sharp increase in serum $1,25(\text{OH})_2\text{D}_3$ (from 59 pg/ml to 142 pg/ml) and subsequently hypercalcaemia while serum $25(\text{OH})\text{D}_3$ rose moderately within the normal range (from 2.8 ng/ml to 10 ng/ml). During a spontaneous episode of hypercalcaemia which was accompanied by increased circulating $1,25(\text{OH})_2\text{D}_3$ concentrations, administration of hydrocortisone decreased serum $1,25(\text{OH})_2\text{D}_3$ rapidly (from 115 pg/ml to 62 pg/ml) and eventually led to normocalcaemia while serum $25(\text{OH})\text{D}_3$ remained unchanged. Thus the disturbances of mineral metabolism found in this patient with Hodgkin's disease are very similar to those previously described in sarcoidosis.

Introduction

Hypercalcaemia with increased circulating concentrations of $1,25$ dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$) has been well established in sarcoidosis^{1,2} and has been also reported in other situations involving granulomatous processes such as in disseminated candidiasis,³ silicone-induced granulomata,⁴ tuberculosis,⁵ plasma cell granuloma⁶ and leprosy.⁷ Recently it has been suggested that the same biochemical combination of hypercalcaemia, with suppressed parathyroid function and inappropriate circulating concentrations of $1,25(\text{OH})_2\text{D}_3$ can occur in patients with Hodgkin's^{8–12} or non-Hodgkin's lymphoma.^{8,13,14} Here we describe a patient with Hodgkin's disease in whom calcium and vitamin D metabolism behaved in a similar manner to that associated with sarcoidosis¹⁵ with a typical response to steroid therapy and to a vitamin D challenge test.

Methods

Serum calcium, corrected for serum albumin, phosphate, creatinine, urea and alkaline phosphatase were measured by automated methods. Serum parathyroid hormone (iPTH) was measured in an amino-terminal immunoradiometric assay.¹⁶ Vitamin D metabolites were measured as described previously.¹⁷

Case report and results

A 70 year old patient was referred to us following episodes of symptomatic hypercalcaemia (up to 3.9 mmol/l) which occurred during two consecutive summers. The raised calcium was corrected on each occasion by prednisolone which was given only for a few weeks. He came to us shortly after the second hypercalcaemic episode and was still on steroids. His past medical history was unremarkable and he denied ingestion of drugs such as vitamin D, vitamin A or thiazides. Physical examination showed mild anaemia only. Results of blood and urine investigations at admission to this hospital are shown in Table I. In addition he had a low haemoglobin (9.8 g/dl) with normal red cell indices. Chest X-ray skeletal survey and bone scan were both normal. Computed tomographic scan of the abdomen showed only minimal enlargement of the spleen. Prednisolone was stopped and 6 weeks later a Kveim test was performed and was found to be negative. Since there was no obvious explanation for the intermittent character of the hypercalcaemia, he underwent a vitamin D challenge test during which he was given 3000 U of cholecalciferol (vitamin D_3) per day. At the beginning, he was normocalcaemic (2.32 mmol/l) and normocalciuric (4.2 mmol/24 hours) with a creatinine clearance of 54 ml/min. Serum concentrations of $25(\text{OH})\text{D}_3$ and $1,25(\text{OH})_2\text{D}_3$ were normal being 2.8 ng/ml and 59 pg/ml respectively. As shown in Figure 1, serum $25(\text{OH})\text{D}_3$ rose gradually within the normal range up to 10 ng/ml. In contrast, serum $1,25(\text{OH})_2\text{D}_3$ showed a dramatic and sharp increase reaching

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Table 1 Blood and urine measurements at admission

	Patient values	Normal range
Blood		
Calcium	2.31 mmol/l	2.25–2.55
Phosphate	1.01 mmol/l	0.60–1.50
Alkaline phosphatases	242 IU/l	100–280
Urea	6.2 mmol/l	3.0–7.0
Creatinine	101 µmol/l	45–110
iPTH	<40 pg/ml	<120
25(OH)D ₃	11.0 ng/ml (28 nmol/l)	3–40 (8–102)
1,25(OH) ₂ D ₃	65 pg/ml (156 pmol/l)	20–65 (48–156)
Protein electrophoresis	normal	
Angiotensin converting enzyme	30 IU/l	16–50
Urine		
Calcium	3.1 mmol/24 hours	2.5–7.5
Creatinine clearance	55 ml/min

Figure 1 Effect of vitamin D₃ (3000 U/day) on circulating 1,25(OH)₂D₃ (top panel, 25(OH)D₃ (middle panel) and serum calcium (bottom panel). Hatched areas represent the normal range.

145 pg/ml on the 11th day. Hypercalcaemia (2.79 mmol/l) developed on the 17th day and was accompanied by hypercalciuria (11.9 mmol/24 hours) and a fall in creatinine clearance (39 ml/min). Serum iPTH remained undetectable throughout the test. After stopping the vitamin D₃ supplements, serum calcium decreased gradually and the patient became almost normocalcaemic (2.58 mmol/l) 15 days later. During the vitamin D challenge test, there was a strong positive correlation between circulating 25(OH)D₃ and 1,25(OH)₂D₃ ($r = 0.93$; $P < 0.05$).

However, no overt cause could be found for the anaemia and this led to a bone marrow examination which showed that it was infiltrated by lymphoid aggregates with some large eosinophil cells. Typical binucleated Reed-Sternberg cells were present. The histological picture was compatible with that of Hodgkin's disease. He kept well without any treatment until the following summer when he spontaneously developed hypercalcaemia (2.99 mmol/l) and hypercalciuria (16.2 mmol/24 hours) accompanied by a deterioration in creatinine clearance (44 ml/min). Serum concentrations of 25(OH)D₃ and 1,25(OH)₂D₃ were 9.8 ng/ml and 115 pg/ml respectively. He was given hydrocortisone (120 mg/day) and Figure 2 illustrates the evolution of serum calcium and vitamin D₃ metabolites with this treatment. On the 4th day, the 1,25(OH)₂D₃ had fallen within the normal range (62 pg/ml) while the 25(OH)D₃ was unchanged (9.1 ng/ml). On the 10th day, he was normocalcaemic, urinary calcium had decreased to 10.6 mmol/24 hours and creatinine clearance had improved to 65 ml/min. He was then maintained on prednisolone (30 mg/d) and no further episodes of hypercalcaemia occurred. However, 8 months later, an abdominal CT scan showed that the spleen had enlarged markedly and in addition, retroperitoneal lymphadenopathy could be seen. The patient underwent splenectomy and histology was pathognomonic of Hodgkin's disease; no granulomas were present. Lymph nodes showed complete replacement of the normal tissue by a tumour infiltrate resembling that found in the spleen and again no granulomas were seen. Thus these findings confirmed the diagnosis of Hodgkin's disease. Two months later, almost 4 years after the initial presentation, the patient died after a severe respiratory infection. No post-mortem examination was performed.

Discussion

The histological diagnosis in this patient was that of Hodgkin's disease; neither sarcoidosis nor any other granulomatous disease previously associated with hypercalcaemia and increased circulating concentrations of 1,25(OH)₂D₃ could be demonstrated. However, the disturbances of calcium homeostasis reported here are similar to those described in sarcoidosis. There was a seasonal pattern of the spontaneous hypercalcaemic episodes which occurred during the summer months and moreover there was a close association between hypercalcaemia and the abnormally raised circulating concentration of 1,25(OH)₂D₃¹⁵ in the absence of vitamin D intoxication. This relationship was reproduced and documented by vitamin D challenge. When small supplements of cholecalci-

Figure 2 Changes induced by hydrocortisone (120 mg/day) in circulating 1,25(OH)₂D₃ (top panel), 25(OH)D₃ (middle panel) and serum calcium (bottom panel). Normal range is represented by the hatched areas.

ferol were given, in order to mimic the spontaneous situation occurring in summer, serum 25(OH)D₃ increased moderately within the normal range but the 1,25(OH)₂D₃ showed an abrupt rise well over the normal concentrations, preceding by a few days the development of hypercalcaemia. As in sarcoidosis,¹⁵ in this patient, there was also an abnormal positive substrate-product relationship between circulating concentrations of 25(OH)D₃ and 1,25(OH)₂D₃ and in addition the abnormal 1 α -hydroxylase activity was responsive to steroids which corrected not only the abnormal vitamin D meta-

bolism but also disturbances in calcium homeostasis.

The origin of the abnormal 1 α -hydroxylase activity in patients with lymphoma in whom hypercalcaemia is associated with increased serum 1,25(OH)₂D₃ is still not clear but there are arguments suggesting an extra-renal origin to the enzyme. High circulating concentrations of 1,25(OH)₂D₃ have been found in patients with lymphoma and severe renal failure.^{8,13} In addition, normalization of the circulating concentrations of 1,25(OH)₂D₃ and resolution of hypercalcaemia after treatment of the lymphoma have also been reported.^{8,10,12,13} The substrate-product relationship between circulating 25(OH)D₃ and 1,25(OH)₂D₃ and the steroid sensitivity of the 1 α -hydroxylase activity also support the ectopic origin of the enzyme. However, it is not obvious whether this abnormal 1 α -hydroxylase activity is confined to the tumoral tissue or stems from other tissue known to normally possess the enzyme,¹⁸ stimulated by humoral factors secreted by the neoplastic cells. Some observations would favour the location of the abnormal synthesis of 1,25(OH)₂D₃ to the lymphomatous tissue itself, since *in vitro* production of the active metabolite of vitamin D₃ was demonstrated in a lymph node homogenate from a patient with lymphoma¹⁴ and also in T lymphocytes transformed with the HTLV I virus,¹⁹ a virus strongly associated with the adult T-cell lymphoma.

It is, however, not yet clear whether 1,25(OH)₂D₃ is solely responsible for the abnormal mineral metabolism in this condition or acts in concert with other factors known to be associated with hypercalcaemia in malignant disease.²⁰

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