Hypercalcemia Induced by Rosai-Dorfman Disease in a Hemodialysis Patient: Histological Evidence of Extrarenal Calcitriol Overproduction

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Abstract

Rosai-Dorfman disease (RDD) is a rare disorder characterized by the proliferation of histiocytes in the sinus of the affected lymph nodes, which leads to massive lymphadenopathy. RDD usually presents as an increased inflammatory response and lymph node swelling. We herein report the case of a hemodialysis patient with a fever, hypercalcemia and increased serum calcitriol level who was histologically diagnosed to have RDD. Immunohistochemistry revealed an increased expression of 1α-hydroxylase by histiocytes in the dilated sinus, indicating the extrarenal overproduction of calcitriol. Treatment with oral prednisolone decreased the serum levels of inflammatory markers and calcitriol, normalized the serum calcium level and mitigated the systemic lymph node enlargement.

Key words: histiocytes, 25-hydroxyvitamin D-1α-hydroxylase, hypercalcemia, lymphadenopathy, Rosai-Dorfman disease

Introduction

Hypercalcemia is a common complication associated with high mortality in dialysis patients (1). In the general population, primary hyperparathyroidism and malignant neoplasms are the leading causes of hypercalcemia (2). In dialysis patients, hypercalcemia is often related to secondary hyperparathyroidism, and the condition is commonly treated with vitamin D derivatives and calcium-based phosphate binders. In relatively rare situations, hypercalcemia accompanies granulomatous disease, including sarcoidosis, tuberculosis and Crohn’s disease (3, 4). In some cases, an elevated serum calcitriol level is noted and the extrarenal overproduction of calcitriol in granulomatous tissue is histologically confirmed (5, 6).

We herein present the case of a hemodialysis patient with calcitriol-mediated hypercalcemia who was histologically diagnosed with Rosai-Dorfman disease (RDD), a rare disorder of histiocytic proliferation in the systemic lymph nodes (7). Interestingly, immunohistochemistry revealed an increased expression of 25-hydroxyvitamin D-1α-hydroxylase by the histiocytes in the affected lymph nodes, indicating the involvement of the extrarenal overproduction of calcitriol in the hypercalcemia observed in the present case.

Case Report

A 64-year-old man with a 33-year history of hemodialysis was admitted to our institution with a low-grade fever, fa-
tigue, elevated serum inflammatory markers and hypercalce-
mia. He had been receiving three four-hour hemodialysis
sessions per week. The cause of end-stage kidney disease
was considered to be chronic glomerulonephritis, although
this was not proven on a kidney biopsy. The concentration
of dialysate calcium was 3.0 mEq/L. The patient’s past
medical history included total parathyroidectomy with fore-
arm auto-transplantation for secondary hyperparathyroidism
at 46 years of age and proctosigmoidectomy for colorectal
cancer at 57 years of age. He had not been treated with a
vitamin D receptor activator after parathyroidectomy. The
low-grade fever and hypercalcemia had begun five months
prior to admission. One month prior to admission, systemic
lymphadenopathy was detected on plain computed tomo-
graphy, and the patient was referred to our hospital for a fur-
ther evaluation.

On admission, the patient was alert, with a blood pressure
of 124/66 mmHg in the supine position. His heart rate was
64 beats/min, his respiratory rate was 15/min and his body
temperature was 36.1°C. His height was 166 cm, his body
weight was 65.0 kg and his body mass index was 23.6 kg/
m². A physical examination showed an extremely decreased
muscle mass and pretibial pitting edema. There were no skin
lesions on any part of the patient’s body. The cervical and
inguinal lymph nodes were palpable, ranging in size from 1
to 2 cm in diameter. Laboratory tests performed immediately
before hemodialysis showed a serum albumin level of 2.0 g/
dl, blood urea nitrogen level of 26 mg/dL, creatinine level
of 4.6 mg/dL, calcium level of 10.6 mg/dL, albumin-
corrected calcium level of 12.6 mg/dL, phosphorus level of
3.2 mg/dL, hemoglobin level of 9.1 g/dL, C-reactive protein
level of 4.0 mg/dL, soluble interleukin-2 receptor (sIL2-R)
level of 4,274 pg/mL, ferritin level of 124.7 ng/mL, adeno-
sine deaminase level of 33.4 U/L (N: 5-20), angiotensin-
converting enzyme level of 20.0 U/L (N: 8.3-21.4), immu-
noglobulin G level of 1,926 mg/dL (N: 872-1,815), immu-
noglobulin A level of 756 mg/dL (N: 95-405) and immuno-
globulin M level of 93 mg/dL (N: 31-190), with polyclonal
hypergammopathy and negative findings for M protein. A
tuberculin test, blood culture and procalcitonin test were
negative.

Immunological and endocrinological studies showed a
plasma cortisol level of 7.0 μg/dL (N: 4-18.3), calcitriol
level of 26.0 pg/mL (N: 20-60), free T4 level of 0.84 ng/dL
(N: 2.20-4.40), parathyroid hormone-related peptide level of
<1.0 pmol/L (N: <1.0) and intact parathyroid hormone level
of 13.9 pg/mL (N: 10-65); the patient’s serum calcitriol
level was relatively high for a dialysis patient, with an ex-
tremely decreased kidney function. The serum tartrate-
resistant acid phosphatase 5b (TRACP5b) level was 863
mU/L (N: <590), the interleukin (IL)-6 level was 23.1 pg/
mL (N: <4) and the tumor necrosis factor-alpha (TNF-α)
level was 28.5 pg/mL (N: 0.6-2.8).

Computed tomography of the abdomen revealed mas-
sively swollen cervical, mediastinal, retroperitoneal and in-
guinal lymph nodes. However, no apparent disorders other
than lymph node swelling were detected on computed tomo-
graphy. A positron emission tomography-computed tomo-
graphy examination showed increased glucose uptake in the
para-aortic and bilateral inguinal lymph nodes (Fig. 1A, B). A bone marrow biopsy ruled out the presence
of malignant cells. A percutaneous biopsy of the left ingui-
nal lymph node was performed, and a histological examination revealed the proliferation of histiocytes and lymphocytes in the enlarged sinus. Some histiocytes exhibited emperipolesis, a characteristic of RDD (Fig. 2A, B).

Immunohistochemistry showed that the histiocytes were positive for S-100 protein and CD68 and negative for CD1a. Taken together, the histological results confirmed the diagnosis of RDD, also called sinus histiocytosis with massive lymphadenopathy (6). An additional immunohistochemical analysis identified that the Rosai-Dorfman cells (recruited histiocytes) were positive for 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1, SC-67261, Santa Cruz Biotechnology, Inc., Dallas, USA), a rate-limiting enzyme that catalyzes the conversion of 25-hydroxyvitamin D into calcitriol (Fig. 2C, D).

Although no extranodal lesions were identified, hypercalcemia associated with Rosai-Dorfman disease was prominent; therefore, we administered 20 mg/day of oral prednisolone. The patient subsequently recovered, and the serum level of calcitriol returned to the normal range (6.0 pg/mL), followed by a decrease in the serum corrected calcium level (8.8 mg/dL). One month after starting oral prednisolone treatment, the serum levels of TNF-α, IL-6, sIL-2R and TRACP5b decreased to 8.5 pg/mL, 19.7 pg/mL, 428 mL/U and 2,229 mL/U, respectively, indicating the suppression of bone resorption by inflammatory cytokines. Two months after the initiation of prednisolone treatment, positron emission tomography-computed tomography revealed an attenuated uptake of radioactive glucose and a decrease in the size of the lymph nodes, thus indicating suppression of the disease activity of RDD (Fig. 1C, D). Three months after the initial treatment, the patient was found to be in good health, without relapse, while receiving 15 mg/day of prednisolone.

**Discussion**

Sinus histiocytosis with massive lymphadenopathy (or RDD) is a rare pathological entity of undetermined etiology, first described by Rosai and Dorfman in 1969 (7). RDD is characterized by a fever, lymph node enlargement, neutrophilia, elevated erythrocyte sedimentation rate and polyclonal hypergammaglobulinemia. The lymph nodes show massive sinus infiltration of histiocytes (Rosai-Dorfman cells) often accompanied by emperipolesis, indicating the phago-

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**Figure 2.** Histological and immunohistochemical analysis of the excised inguinal lymph node. Hematoxylin and Eosin staining of the section showed the recruitment of histiocytes (yellow arrows) and numerous lymphocytes in the dilated sinus (original magnification, ×50) (A). Some Rosai-Dorfman cells (histiocytes) exhibited emperipolesis (yellow arrow) (B) (original magnification, ×200). Note that some histiocytes were multinucleated. The low magnification (original magnification, ×50) (C) and high magnification (original magnification, ×200) (D) results of the immunohistochemical staining for 25-hydroxyvitamin D-1α-hydroxylase are shown. The Rosai-Dorfman cells were positively stained for 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1, SC-67261, Santa Cruz Biotechnology, Inc., Dallas, USA) (yellow arrows).
cytosis of intact erythrocytes and leukocytes by Rosai-Dorfman cells. Immunohistochemistry shows such cells to be positive for S-100 and negative for CD1a (8). The histiocytes in RDD are now considered to be reactive macrophages. While the pathogenesis of RDD remains unknown, the disease is usually self-limited and the prognosis is favorable, if the condition is not accompanied by extranodal lesions (e.g. oral cavity, orbital cavity, skin, soft tissue, central nervous system, salivary glands, respiratory tract or gastrointestinal tract) (9). RDD associated with extranodal lesions is treated with surgery, radiotherapy and immunosuppression (9, 10). Although hypercalcemia related to abnormal histiocyte proliferation is occasionally seen in cases of Langerhans cell histiocytosis (11), hypercalcemia related to RDD has rarely been reported. In this regard, the present case is the first to demonstrate an increased expression of 25-hydroxyvitamin D-1α-hydroxylase by histiocytes, suggesting a potential cause of hypercalcemia in patients with RDD.

The extrarenal overproduction of calcitriol may cause hypercalcemia (4-6, 11). Sarcoïdosis, tuberculosis, leprosy, berylliosis and Crohn’s disease are well-known granulomatous disorders associated with hypercalcemia (4, 5). In these disorders, macrophage-lineage cells express 25-hydroxyvitamin D-1α-hydroxylase, leading to the overproduction of calcitriol in the extrarenal lesions; the negative feedback of calcitriol is disrupted in these cases (6, 12, 13). Glucocorticoid treatment is effective because it suppresses the 25-hydroxyvitamin D-1α-hydroxylase expression in macrophage-lineage cells by inhibiting interferon-gamma production, leading to the amelioration of hypercalcemia via a reduction in the level of serum calcitriol (12-15) In the present case, the serum calcitriol level was relatively high compared to that observed in chronic dialysis patients; the mean serum calcitriol level in anuric hemodialysis patients has been shown to be 5.5±2.4 pg/mL (16). In addition, Rosai-Dorfman cells in the affected lymph nodes exhibited an increased expression of 25-hydroxyvitamin D-1α-hydroxylase, and low-dose prednisolone treatment rapidly improved the patient’s hypercalcemia. Because an increased serum level of calcitriol enhances calcium absorption from the gastrointestinal tract, positioning glucocorticoid treatment usually controls the serum calcitriol level within days to weeks (19, 20). Glucocorticoid therapy also helps to decrease the serum calcium level by inhibiting calcium absorption from the gastrointestinal tract, positioning the administration of glucocorticoids as the most appropriate and effective treatment for calcitriol-induced hypercalcemia.

Recent clinical studies have partly unveiled the pathogenesis of RDD. For example, Kuo et al. reported that IgG4-positive plasma cells were recruited to a skin lesion in a patient with cutaneous RDD, indicating the potential role of IgG4 in the development of RDD and an association with IgG4-related disorders (21). Furthermore, viral infections, including that involving the Epstein-Bar virus, human herpes virus-6, parvovirus B19 or human-immunodeficiency virus, have been reported to be associated with the development of RDD (22). These previous reports suggest that immunological disorders may be involved in the pathogenesis of RDD. In the present case, the serum IgG4 level was not measured and immunohistochemistry for IgG4 of the lymph node specimen was not performed, although the serum total IgG level was found to be slightly elevated and no organ dysfunction associated with IgG4-related disorder was detected on a systemic review. In addition, no antecedent infections were observed, and the titers of IgG for these viruses were not determined. Therefore, it remains unknown whether the above viruses are involved in the development of RDD or if IgG4-related diseases were present in the current case.

In summary, we herein described the case of a hemodialysis patient with RDD complicated by hypercalcemia, which was possibly mediated via extrarenal calcitriol overproduction by abnormal histiocytes. The present case highlights the importance of determining the serum calcitriol level when making the differential diagnosis of hypercalcemia and considering the possibility of granulomatous disease as the pathogenesis of an increased serum calcitriol level in dialysis patients.


References