A case of fatal osteolytic hypercalcemia complicated with IgG4-related ophthalmic disease leading to renal failure

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Abstract

A 40-year-old male was hospitalized with renal impairment and severe hypercalcemia. His concentration of serum IgG4 was high, but serum whole PTH, 1–25(OH)₂ vitamin D3 and PTHrP were not elevated. Computed tomography showed swelling of the bilateral lacrimal glands and systemic lymphadenopathy. The histological findings of lacrimal gland biopsy fulfilled the diagnostic criteria of IgG4-related ophthalmic disease (IgG4ROD). Bone scintigraphy showed increased ectopic uptake in the stomach, heart, lungs, and kidneys. He died on day 16 of admission, although the therapies for hypercalcemia were continued. Autopsy results showed an increase of osteoclasts in the bone marrow and metastatic calcification in multiple organs, and excluded from the differential diagnosis other disorders which present lymph-node swelling and hypercalcemia such as cancer, lymphoma, Castleman's disease, and sarcoidosis. He was given a diagnosis of IgG4ROD with osteolytic hypercalcemia.

Keyword IgG4-related disease · Hypercalcemia · Metastatic calcification

Introduction

IgG4-related disease (IgG4RD) is an immunological disorder which is characterized by the swelling of specific organs such as the pancreas, lacrimal glands, and salivary glands. In most cases, the concentration of serum IgG4, which is one of four subclasses of immunoglobulin G, is higher than 135 mg/dL. In IgG4RD patients, infiltration of lymphocytes and plasma cells is observed in the affected organs and the

ratio of IgG4-positive plasma cells to IgG-positive plasma cells is high [1]. IgG4-related ophthalmic disease (IgG4-ROD) is defined when IgG4-RD is involved in the lacrimal gland, trigeminal nerve, extraocular muscle, and various ophthalmic tissues [2]. Despite IgG4RD causing various symptoms depending on the affected organs, it generally develops subacutely without a conspicuous manifestation of symptoms.

IgG4RD is generally not included in the differential diagnosis of hypercalcemia. However, it has been previously suggested that the autoantibodies which inactivate the calcium-sensing receptor (CaSR) induce hypercalcemia in certain cases of IgG4RD. In those cases, a high concentration of parathyroid hormone (PTH) caused acquired hypocalciuric hypercalcemia as a result of the understimulation of CaSR eliciting the hypersecretion of PTH [3, 4]. On the other hand, hematologic malignancies such as multiple myeloma (MM) are frequently associated with hypercalcemia caused by local humoral factors which mediate excessive resorption and formation of the bone [5]. In this report, we describe the autopsy findings leading to a diagnosis of IgG4ROD in a patient who presented with severe persistent hypercalcemia.

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Case report

A 40-year-old male who had been suffering from swelling of bilateral periocular regions for a year presented to our hospital complaining of a 2-week history of persistent left knee pain following a fall, and a 3-day history of left facial paralysis. He was admitted urgently because of severe hypercalcemia and renal insufficiency. He had no family history of hypercalcemia and had not taken medicine or supplements which could have elevated his serum calcium concentration. He had no history of a medical check-up except for chest radiography.

On admission, his body temperature was 36.9 °C, pulse rate 104 beats per minute, and blood pressure 171/97 mmHg. Physical examination showed swelling of bilateral periocular and parotid regions, and hyperemia of bilateral conjunctivae, but examination of the abdomen was unremarkable. No lung rale or heart murmurs were detected on chest auscultation. Although the urine volume

during the first 24 h after admission was 2460 mL, there were no apparent signs of dehydration.

Urinalysis revealed a moderate degree of proteinuria (0.92 g/gCr), and peripheral blood analysis showed a white blood cell count of 14,800/ μ L with 8% eosinophils and no atypical lymphocytes or blast cells. Laboratory findings (Table 1) showed renal dysfunction and severe hypercalcemia (blood urea nitrogen; 51 mg/dL, serum creatinine; 4.76 mg/dL, serum Ca; 19.2 mg/dL, serum phosphate; 4.6 mg/dL). Excreted Ca in the urine was 0.27 g/gCr, fractional excretion of Ca (FECa) was 6.6%, and the percentage of renal tubular reabsorption of phosphate (%TRP) was 63.6%. Serum alkaline phosphatase was extremely elevated and elevated bone-specific alkaline phosphatase was shown to be the cause. The serum markers which are specifically related to bone formation and bone resorption were markedly elevated and indicated hyperactive turnover of the bone. Contrary to our prediction, serum whole PTH, serum 1–25(OH)₂ vitamin D3 and plasma PTH-related peptide (PTHrP) decreased to 4.1 pg/mL, 5.6 pg/mL, and < 1.0 pmol/L, respectively. The serum levels of interleukin-6

Table 1 Laboratory findings on admission

Urine test		Chemistry			
Protein	2+	TP	6.9 g/dL	IgG	1775 (870–1700) mg/dL
Occult blood	2+	Alb	3.3 g/dL	IgG4	396.0 (4.8–105.0) mg/dL
TP	0.92 g/gCr	AST	30 IU/L	IgA	221.6 (110.0–410.0) mg/dL
NAG	42.9 IU/gCr	ALT	25 IU/L	IgM	91.4 (35.0–220.0) mg/dL
β 2MG	1525 μ g/gCr	LDH	198 IU/L	C3	83.7 (63.0–155.0) mg/dL
Ca	0.27 g/gCr	ALP	6699 IU/L	C4	6.2 (10.0–40.0) mg/dL
		BUN	51 mg/dL	ACE	7.4 (8.3–21.4) U/mL
FECa	6.6%	Cr	4.76 mg/dL	Lysozyme	16.1 (5.0–10.2) μ g/mL
%TRP	63.6%	Na	132 mEq/L	sIL-2R	1641 (135–500) U/mL
FENa	0.55%	K	3.3 mEq/L	IL-6	4.5 (< 4.0) pg/mL
		Cl	88 mEq/L	VEGF	157 (< 38.3) pg/mL
		Ca	19.2 mg/dL		
CBC		iP	4.6 mg/dL	Venous blood gas	
WBC	14,800/ μ L	Mg	2.0 mg/dL	pH	7.439
Nt	73.0%	CRP	3.76 mg/dL	HCO ₃ [–]	32.6 mmol/L
Ly	11.0%	Whole PTH	4.1 (10–65) pg/mL	Ca ²⁺	2.24 mmol/L
Eo	8.0%	1–25(OH) ₂ D	5.6 (20.0–60.0) pg/mL		
RBC	455 $\times$ 10 ⁴ / μ L	PTHrP	< 1.0 (0.0–1.1) Pmol/L		
Hb	13.9 g/dL	Calcitonin	32 (< 9.52) pg/mL		
Plt	22.6 $\times$ 10 ⁴ / μ L				
		Bone formation marker			
		BAP	777.0 (3.7–20.9) μ g/L		
		Osteocalcin	210.0 (2.5–13.0) ng/mL		
		Bone resorption marker			
		ICTP	274.0 (< 4.5) ng/mL		
		TRACP-5b	1540 (170–590) mU/dL		

Whole PTH whole parathyroid hormone, *1–25(OH)₂D* 1–25(OH)₂ vitamin D3, *PTHrP* PTH-related peptide, *BAP* bone-specific alkaline phosphatase, *ICTP* type I collagen C-terminal telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase-5b, *ACE* angiotensin-converting enzyme, *sIL-2R* soluble interleukin-2 receptor, *IL-6* interleukin-6, *VEGF* vascular endothelial growth factor

(IL-6), lysozyme, and soluble IL-2 receptor were slightly elevated. Serum IgG was 1775 mg/dL and serum IgG4 subclass was 396.0 mg/dL. Monoclonal proteins were not detected in the serum and urine by electrophoresis. Human T-lymphotropic virus type-1 antibody, myeloperoxidase (MPO–) or proteinase 3 (PR3–) antineutrophil cytoplasmic antibodies, and antinuclear antibody were all negative.

A bone marrow examination demonstrated normocellular marrow and increased eosinophils, but no evidence of increased plasma cells or proliferation of lymphomatoid tumor cells.

Radiography revealed fracture of the left patella. Computed tomography (CT) of the head and the body showed swelling of the bilateral lacrimal glands and parotid glands, and systemic lymphadenopathy which was markedly seen in the mandibular and mediastinal lymph nodes. Diffuse centrilobular ground glass opacity of the upper lung fields and bronchial wall thickening were also observed. There were no findings of renal atrophy, hydronephrosis, and urolithiasis. No lesions suggestive of malignant disease were detected. ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) showed lymph-node uptake consistent with the findings of CT, and was also observed in the bone cortex of all extremities. $^{99\text{m}}\text{Tc}$ -hydroxymethylenediphosphonate bone scintigraphy showed increased uptake in the bone cortex of all extremities as well as ectopic uptake in the stomach, heart, lungs, and kidneys (Fig. 1). These findings suggested that metastatic calcification was developing extensively in the affected lesions.

After admission, he was treated for hypercalcemia with intravenous saline infusion, loop diuretics, elcatonin, prednisolone (60 mg/day), and denosumab (120 mg/body). Hemodialysis was performed to lower the serum Ca concentration rapidly, but the serum Ca level did not decrease below 12.0 mg/dL. After day 11, the serum Ca level was sustained more than 19 mg/dL although the therapies for hypercalcemia were continued. In addition, pathological fractures of the right tibia and fibula occurred despite cautious patient care. On the basis of lymph-node swelling and hypercalcemia, sarcoidosis and lymphoma were included in the differential diagnosis, but biopsy of the submandibular lymph node and needle aspiration of mediastinal lymph node did not show granuloma or lymphoma. In the lacrimal gland biopsy specimen, infiltration of lymphocytes, histiocytes, and plasma cells was observed with fibrosis and lymph follicle formation (Fig. 2a). Immunohistochemistry of the paraffin sections demonstrated an increased presence of IgG4-positive plasma cells ($>100/\text{high power field}$) and the IgG4+/IgG+ ratio of the plasma cells was as high as 54% (Fig. 2b, c).

On admission day 15, echocardiography showed hypotension, bradycardia, and a reduced ejection fraction, and on the next day, sudden cardiac arrest occurred. He died

Fig. 1 Anterior (left) and posterior (right) plane image of the whole body by bone scintigraphy

immediately after the cardiac arrest and an autopsy was performed after obtaining the consent of his family.

Autopsy findings

Autopsy was started approximately 6 h after his death. Systemic lymph-node swelling was observed on inspection of the whole body. The weight of the heart and the bilateral lungs was heavier than normal.

Microscopy showed calcification in the intima of small and middle arteries, the aorta, and cardiac muscle (Fig. 3a, b). Calcification was also recognized in the alveolar walls of the lungs, liver, and digestive organs. In the lungs, infiltration of plasma cells, lymphocytes, and eosinophils was observed. In the walls of respiratory tracts from the trachea to peripheral bronchus, there was IgG4-positive plasma cell

Fig. 2 Findings of the lacrimal gland biopsy specimens. **a** Infiltration of lymphocytes, histiocytes, and plasma cells with fibrosis (arrowhead) and lymph follicles was shown by hematoxylin and Eosin

(H–E) staining (original magnification $\times 100$). **b**, **c** Immunohistochemical staining of **b** IgG-positive plasma cells and **c** IgG4-positive plasma cells (original magnification $\times 400$)

infiltration and the IgG4+/IgG+ ratio of the plasma cells was 57%. The bronchial epithelium showed diffuse squamous metaplasia. No typical change of IgG4RD was observed in the liver and pancreas. The findings of the lymph nodes were consistent with those of the prior biopsy.

In the kidney, about 2% of glomeruli exhibited global sclerosis, but the other glomeruli were shown to be intact. Interstitial fibrosis was mild. Mild cell infiltration, primarily composed of lymphocytes and partly neutrophils, was detected in the interstitium and tubular lumen. Calcification of glomerular arteriole and tubular lumen was observed, and detachment of tubular epithelial cells was shown around the calcification area (Fig. 3c). No characteristic findings of IgG4-related kidney disease such as marked lymphoplasmacytic infiltration or storiform fibrosis were observed [6].

The formation of overlaying bone was observed on the surface of trabecular bone (Fig. 4a) together with an increase of osteoclasts in the rib bone (Fig. 4b). Bone morphometric analysis of rib (Table 2) revealed that 76.8% of trabecular bone surface were covered with thin osteoid in the cancellous bone (Fig. 4c). Uncalcified osteoid was also observed in the trabecular bone, parallel to the trabecular surface

(Fig. 4d). Uncalcified osteoid thickness was $17.7\ \mu\text{m}$ and thickness from osteoid surface to trabecular surface was $29.3\ \mu\text{m}$. Bone resorption parameters were high. Marked porosity (Fig. 4c) and osteoblasts were observed in the cortical bone. From the above, high turnover bone status was indicated. Bone marrow and bone showed no finding of hematological malignancies or metastatic malignant tumors.

On the basis of the entire findings, the patient was diagnosed as having IgG4ROD with osteolytic hypercalcemia.

Discussion

In this report, we described an autopsy case of IgG4ROD who suffered from an extremely high concentration of serum calcium. This case fulfilled the diagnostic criteria of IgG4ROD as follows: (1) swelling of the lacrimal glands, (2) a serum IgG4 concentration higher than $135\ \text{mg/dL}$, (3) dense infiltration of lymphocytes and IgG4-positive plasma cells in the affected organs, and (4) a ratio of IgG4+/IgG+ plasma cells higher than 40% in the biopsy specimen [2]. The most common manifestation of IgG4RD is swelling of

Fig. 3 Findings of the autopsy specimens. **a, b** Metastatic calcification of the heart. **a** Calcified lesions are shown as purple deposits by H-E staining (original magnification $\times 40$) and **b** as dark brown deposits by von Kossa staining (original magnification $\times 100$). **c**

Microscopic finding of the kidney. Calcification of glomerular arteriole and tubular lumen was observed (original magnification $\times 200$), and detachment of tubular epithelial cells (arrowhead) was shown around the calcification area

the pancreas (60%) followed by sialadenitis (34%), nephritis (23%), and dacryoadenitis (23%) [7]. In this case, IgG4-positive plasma cell infiltration and the high IgG4+/IgG+ ratio of the plasma cells were observed in the lymph node, lacrimal gland, and the walls of respiratory tracts, but marked lymphoplasmacytic infiltration or storiform fibrosis was not observed in the kidney. In the study using autopsy kidneys of IgG4-related kidney disease, interstitial lymphoplasmacyte infiltration or fibrosis was detected around medium- and small-sized vessels and in a variety of anatomical location in all the cases [8]. Our case does not meet the diagnostic criteria [6] and is different from IgG4-related kidney disease. In addition, the age of this patient is relatively young compared to the ordinary cases of IgG4RD that were given a diagnosis in their 50–70 s, but there was a case that was diagnosed when 35 years old [7].

Common causes of hypercalcemia are primary hyperparathyroidism, cancer, granulomatous disease, administration of medication such as vitamin D and thiazide diuretics, milk-alkali syndrome, familial hypocalciuric hypercalcemia, and immobilization [9]. All of these causes were ruled

out by the laboratory and autopsy findings in our patient. A severe clinical course in patients with hypercalcemia is usually associated with malignancy, and relationship between IgG4-RD and malignancy is well known [10]. The possibility that undetectable malignancy might induce severe hypercalcemia cannot be completely denied, but the image and autopsy findings excluded from the differential diagnosis other disorders which present lymph-node swelling and hypercalcemia such as cancer, lymphoma, leukemia, bone metastasis, Castleman's disease, and sarcoidosis.

Elevation of serum markers on bone turnover and the result of bone morphological analysis on cancellous and cortical bone were consistent with the characteristics of high turnover bone. In addition, porosity that was prominent on high turnover bone state was markedly observed in the rib bone cortex [11]. Therefore, it was suggested that high turnover bone state caused hypercalcemia and pathological fracture. Interestingly, there are a few reports of IgG4RD which were associated with hypercalcemia. However, in these reports, hypercalcemia was suggested to be caused by autoantibodies which inactivated CaSR, and the laboratory

Fig. 4 Bone findings of the autopsy specimens. The findings of bone marrow of the rib. **a** Formation of overlaying bone (black arrow) and **b** increase of osteoclasts (black arrowhead) were observed (original magnification $\times 200$). The findings of rib bone by Villanueva–Gold-

ner bone staining. **c** Porosity (asterisk) was markedly shown (original magnification $\times 2$) in the cortical bone. **d** Osteoid (white arrows) was observed in the cancellous bone, parallel to the trabecular surface (original magnification $\times 10$)

Table 2 Bone morphometric analysis of rib

Cancellous bone		Cortical bone	
Total tissue area	27.270 mm ²	Cortical thickness	930.207 μ m
Bone structure parameters		Cortical area	28.159 mm ²
Bone volume	21.9 (24.7 $\pm$ 3.7) %	Cortical porosity area	6.894 mm ²
Trabecular thickness	200.1 (157.0 $\pm$ 18.1) μ m	Cortical porosity	24.483%
Trabecular number	1.1 (1.7 $\pm$ 0.4) /mm		
Trabecular separation	715 (494 $\pm$ 82) μ m		
Bone formation parameters			
Osteoid volume	5.0 (5.0 $\pm$ 1.0) %		
Osteoid surface	76.8 (30.2 $\pm$ 4.5) %		
Osteoid thickness	6.5 (11.2 $\pm$ 1.1) μ m		
Osteoblast surface	3.4 (6.0 $\pm$ 1.1) %		
Bone resorption parameters			
Eroded surface	2.1 (2.8 $\pm$ 0.5)%		
Osteoclast number	0.118/mm		
Osteoclast surface	0.3 (0.6 $\pm$ 0.4) %		
Uncalcified osteoid volume	3.238%		
Uncalcified osteoid thickness	17.696 μ m		
Thickness from uncalcified osteoid surface to trabecular surface	29.296 μ m		

Reference value when measured in the iliac bone

data including a high concentration of serum PTH were consistent with that of hypocalciuric hypercalcemia [3, 4]. In our case, serum PTH and FECa were low and hypercalcemia due to inactivation of CaSR was not likely. In hematological disorders, several factors which influence turnover of the bone are detected on investigation. In MM, the production of osteoclast-activating factors such as RANKL and IL-6 is considered to be one of the mechanisms which results in the development of bone lesions and hypercalcemia [5]. Excessive expression of RANKL was also reported in lymphoma [12], adult T cell leukemia [13], and chronic lymphocytic leukemia [14]. In IgG4RD, there are a number of reports which described an elevation of serum IL-6 [15–17]. However, an abnormality of serum Ca concentration was not reported. Although serum IL-6 was slightly elevated in our case, we were unable to identify the possible factors which activated osteoclasts.

Serum calcium regulation occurs in a narrow concentration range. Hypercalcemia damages cell function and induces various symptoms such as fatigue, confusion, anorexia, thirst, polyuria, and dehydration. Systemic calcification and renal insufficiency occur when the serum Ca level is above 13 mg/dL. Coma and cardiac arrest may occur if the Ca concentration is higher than 15 mg/dL. Surprisingly, in our case, the patient walked to the outpatient clinic of our hospital without disturbed consciousness despite a serum Ca concentration of 19.2 mg/dL. From the medical history, it might be speculated that IgG4RD had developed about a year ago or more. The serum Ca level may have elevated very slowly over a year or longer and some mechanism of physical adaptation to the extreme hypercalcemia may have occurred which resulted in a relatively mild manifestation of hypercalcemic symptoms.

Hypercalcemia can lead to renal failure through hypovolemia due to polyuria, vasoconstriction, nephrocalcinosis, nephrolithiasis, and interstitial nephritis. Fractional excretion of sodium was 0.55%, suggesting prerenal causes of kidney disease. However, the serum creatinine level did not decrease despite sufficient treatment with intravenous saline. There was no finding of hydronephrosis which suggests postrenal kidney failure. There was no renal atrophy on CT and only 2% of glomeruli exhibited global sclerosis on autopsy. Nephrocalcinosis, nephrolithiasis, and tubulointerstitial injury around the calcification area were observed, but there were no characteristic findings of IgG4-related kidney disease. It is suggested that renal failure of this patient developed acutely and hypercalcemia had a pivotal role in renal injury through metastatic calcification and tubulointerstitial injury.

Therapy of hypercalcemia is usually initiated with intravenous saline infusion, loop diuretics, elcatonin, and/or

bisphosphonates. Removal of serum Ca may be attempted by performing hemodialysis. However, these treatments were not sufficient to reduce the serum Ca level in this patient. Denosumab instead of bisphosphonate was administered for hypercalcemia because of his renal impairment [18, 19], and prednisolone was added to his therapy from admission. However, the refractory hypercalcemia was never successfully controlled. We could not examine any response in terms of lacrimal gland or lymph-node enlargement after steroid therapy because of worsening of general condition. At autopsy, uncalcified osteoid was shown in the trabecular bone, which led to speculation that osteoid remained due to mineralization impairment during the osteogenesis, and lamellar bone was formed on the surface of osteoid as the mineralization was restored by the therapy. We must reconsider effective therapies against severe and persistent hypercalcemia of this extent.

The main cause of death was cardiac dysfunction. Hypercalcemia induces shortening of QT interval and cardiac arrhythmias. In addition to the electrophysiological imbalance, it is reported that calcium deposits in the heart tissue can cause cardiac dysfunction [20]. The calcific deposits in the heart are suggested to induce the dysfunction of myocardial contraction and interruption of the conductive system. In our case, findings of bone scintigraphy showing an uptake of calcium in the heart and multiple foci of metastatic calcification in the cardiac tissue were actually demonstrated in the autopsy specimen. Bone scintigraphy offers a useful tool for the diagnosis of metastatic calcification [21] and prognosis of the affected organs may be estimated by referring to the results of scintigraphy.

In conclusion, we herein report an autopsy case of IgG4ROD with severe hypercalcemia. This case suggests that certain unknown factors may have contributed to excessive bone resorption. Although IgG4RD complicated with severe hypercalcemia is rare, it is necessary to pay attention to hypercalcemia which occurs in IgG4ROD and to start the adequate therapy promptly.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from participants included in the article.

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