CASE REPORT

A case of IgG4-related kidney disease complicated by eosinophilic lung disease

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Abstract IgG4-related disease is a systemic chronic inflammatory disorder characterized by a high blood level of IgG4 and the organ injuries by marked infiltration of IgG4-positive plasma cells and fibrosis. A 71-year-old male was hospitalized for a cough, malaise and anorexia. IgG4-related disease was suspected due to marked elevation of the serum IgG4 level. However, on lung biopsy, only eosinophil infiltration was demonstrated with no plasma cell infiltration. Otherwise abdominal contrast-enhanced CT showed mild enlargement of the bilateral kidneys and many differed contrasted areas and FDG PET-CT. Moreover, renal biopsy specimens showed typical tubulointerstitial nephritis with a large number of IgG4-positive plasma cells infiltration (the IgG4/IgG-positive cell rate, 89 %) and fibrosis. We diagnosed this patient as typical IgG4-related kidney disease. He was treated by the moderate dose of prednisolone (0.8 mg/kg/day) alone, and showed prompt response in the clinical condition, and both the lung and kidney lesions. In this case, it was useful for diagnosis of IgG4-related diseases to evaluate an image such as abdominal contrast-enhanced CT and FDG PET-CT. Our case might be one of the possible patterns of IgG4-

related lung diseases. In addition, we thought that there might be an association between hypereosinophilia and IgG4-related kidney disease.

Keywords IgG4-related kidney disease · Tubulointerstitial · Nephritis · Hypereosinophilic syndrome · Eosinophilic lung disease

Introduction

The disease concept of IgG4-related disease was proposed in association with autoimmune pancreatitis in the first. After that, similar conditions have also been reported to occur in organs other than the pancreas, which are collectively called IgG4-related diseases [1]. Takeda et al. [2] reported first that IgG4-related kidney disease is primarily tubulointerstitial nephritis (TIN). Respiratory organ lesions are observed in about 10 % of IgG4-related diseases and are often detected during the close examination of lesions in other organs [3], but patients may visit departments of respiratory disease due to initial asthma-like symptoms such as cough and wheezing. The diagnosis of organs affected by IgG4-related disease requires the demonstration of plasma cell infiltration in their tissues. Here, our case of transbronchial lung biopsy (TBLB) revealed eosinophil filtration in lung tissues, but no infiltration of lung tissues by plasma cells. We reported a case of IgG4-related kidney disease complicated by eosinophilic lung disease.

Case

A 71-year-old male developed cough 3 months ago, and was treated by a local physician. After that, an increase in

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the eosinophil count was demonstrated on a blood test, and the patient was referred to the Department of Respiratory Medicine of our hospital. Bronchial asthma was excluded based on airway reversibility and hypersensitivity tests. However, he admitted to our hospital, because of malaise and anorexia.

On admission, the blood pressure was 100/60 mmHg, heart rate was 60 beats/min, and body temperature was 36.7 °C. On urinalysis, urinary occult blood was negative, urinary protein was 1+, and the urinary protein excretion was 0.5 g/g Cr. On blood tests, the RBC was 354×10^4 cells/ μ L, Hb was 11.0 g/dl, indicating mild anemia, and WBC was 4,690/ μ L with marked eosinophilia (eosinophil count: 3,090/ μ L). The CRP was mildly elevated at 0.63 mg/dl. The IgG level was 2,713 mg/dl, and IgG4 level was markedly elevated at 941 mg/dl. The C3 level was 33 mg/dl, C4 level was 3 mg/dl, and CH50 was 10 U/ml or less, indicating hypocomplementemia. Anti-nuclear antibody, MPO-ANCA, PR3-ANCA, anti-GBM antibody, and cryoglobulins were negative (Table 1). Since a blood test during the course showed an increase in the serum Cr level to 1.40 mg/dl, IgG4-related kidney disease was suspected, and the patient was transferred to our department.

On a plain chest X-ray study, ground-glass opacity was noted, and plain chest CT showed the reticular pattern in the bilateral middle and lower lobes and bronchial dilation (Fig. 1a). Ga scintigraphy showed no accumulation in the lungs, kidneys, or other organs. Abdominal contrast-enhanced CT showed mild enlargement of the bilateral kidneys and many poorly contrasted areas (Fig. 1b). On FDG PET-CT, accumulations were observed unevenly in the bilateral kidneys, but no accumulation was noted in the lungs or other organs (Fig. 2).

Since purpura was noted during the course, skin biopsy was performed. While inflammatory cell infiltration consisting primarily of eosinophils and neutrophils was demonstrated, necrotizing vasculitis, granulomatous change, or malignant cells were not detected. On bronchoalveolar lavage, the volume of the sample obtained was insufficient, but an increase in the eosinophil count was confirmed. On TBLB, no infiltration of lung tissues by lymphocytes or plasma cells was observed, eosinophil infiltration was marked, and no vasculitis or granuloma was noted (Fig. 3a). On IgG4 staining, no positive plasma cells were observed (Fig. 3b). Bone marrow centesis showed an increase in eosinophilic cells but no increase in plasma cells. Also, no blast proliferation was noted, and atypism of eosinophilic cells was also unclear. On renal biopsy, no clear mesangial cell proliferation or doubling of the glomerular basement membrane was noted. Lymphocyte, plasma cell, eosinophil infiltration, and obliterative phlebitis was observed, and fibrosis was noted in about 50 % of

the interstitium (Fig. 4a). Also, the affected and non-affected areas were clearly bordered (Fig. 4b). No sign of vasculitis or granuloma was observed. On IgG4 staining, the IgG4/IgG-positive cell rate was 89 % (Fig. 4c). A diagnosis of IgG4-related kidney disease was made, because a high blood IgG4 level, many poorly contrasted areas observed in both kidneys, renal biopsy findings consistent with tubulointerstitial nephritis, and the IgG4-positive plasma cell rate of 89 % fulfilled the Comprehensive diagnostic criteria for IgG4-related disease, 2011 [4]. However, we classified our case as probable in the diagnostic criteria of the Japanese Society of Nephrology [5]. In this case, we could not find the typical storiform fibrosis, because we started steroid therapy early before fibrosis became strong.

The clinical course is shown in Fig. 5. Treatment was initiated by administering prednisolone (PSL) at 40 mg/day (0.8 mg/kg/day), followed by prompt alleviation of the cough, malaise, and anorexia. On blood tests at discharge, the IgG4 level was improved to 92 mg/dl, eosinophil count to 108/ μ L, and serum Cr level to 0.80 mg/dl. Eventually, on blood tests at 1 month after PSL therapy, the serum Cr level was 0.75 mg/dl, and the eGFR was 77.9 ml/min, showing stabilization. On chest CT, the interstitial pattern had nearly disappeared (Fig. 1c), and abdominal contrast-enhanced CT showed improvements in the poorly contrasted areas observed before treatment (Fig. 1d). In the renal biopsy specimens after treatment, the interstitial infiltration of lymphocytes, plasma cells, and eosinophils had been markedly alleviated, and the IgG4-positive plasma cell rate improved to 55.4 %.

Discussion

IgG4-related diseases must be differentiated from diseases caused by excessive IL-6 production, such as multicentric Castleman's disease and autoimmune diseases, i.e., hyper IL-6 syndrome [6]. In hyper IL-6 syndrome, the infiltration of a large number of IgG4-positive cells in the lesion and elevation of the blood IgG4 level are often observed, and some patients histologically fulfill the diagnostic criteria for IgG4-related diseases [7, 8]. In the present case, the serum IgG4 level was high. While the serum IL-6 level was not examined, the CRP level remained mildly positive at 0.7–2.0 mg/dl during the course, so the patient was unlikely to have hypercytokinemia, and IL-6 staining of kidney tissues was negative. Also, as the IgG4-positive plasma cell rate was high at 89 %, and as the condition improved promptly by steroid administration, Castleman's disease can be excluded. Concerning Churg–Strauss syndrome, only an increase in the eosinophil count was noted as a clinical finding, and skin biopsy or TBLB showed no sign

Table 1 Laboratory findings

Urinalysis	Blood	Chemistry	Immunological studies
Urine protein 1+	Na	142 mEq/L	IgG 2713 mg/dL
Occult blood (–)	K	3.7 mEq/L	IgG4 941 mg/dL
β 2-MG 4987 ug/L	Cl	106 mEq/L	IgA 185 mg/dL
NAG 33.2 IU/L	Ca	9.2 mg/dL	IgM 261 mg/dL
u-pro/u-cr 0.5 g/g-Cr	IP	3.5 mg/dL	IgE 850 mg/dL
	BUN	9 mg/dL	CH50 10 ⁺ U/mL
	Cr	0.77 mg/dL	C3 33 mg/dL
	UA	4.8 mg/dL	C4 3 mg/dL
	TP	7.0 g/dL	ANA (–)
Peripheral blood	Alb	2.7 g/dL	Cryoglobulin (–)
RBC $3.54 \times 10^6/\mu\text{L}$	LDH	159 U/L	P-ANCA 10 > EU
Hb 11.0 g/ μL	AST	13 U/L	C-ANCA 10 > EU
Ht 32.8 %	ALT	12 U/L	Anti-GBM antibody 10 > EU
WBC $4.69 \times 10^3/\text{MI}$	Y-GTP	17 U/L	
Neutro $0.62 \times 10^3/\mu\text{L}$	T-Chol	123 mg/dL	Serum/urinary
Lymph $0.67 \times 10^3/\mu\text{L}$	Glu	109 mg/dL	Immunofixation electrophoresis (–)
Eosin $3.09 \times 10^3/\mu\text{L}$	CRP	0.63 mg/dL	
Pit $27.9 \times 10^4/\mu\text{L}$	KL-6	125 U/mL	

Before therapy **After therapy**

Fig. 1 Before therapy, plain chest CT showed the reticular pattern and bronchial dilation in the bilateral middle and lower lung fields (a). Abdominal contrast-enhanced CT showed mild enlargement of the bilateral kidneys and multiple poorly contrasted areas (b). After

therapy, the interstitial pattern nearly disappeared from the bilateral lung fields on plain chest CT (c). Abdominal contrast-enhanced CT showed improvements in the poorly contrasted areas observed before treatment (d)

Fig. 2 On FDG PET-CT, accumulation was observed unevenly in the bilateral kidneys (a–c), but no clear accumulation was noted in the lung or other organs (a)

Fig. 3 Lung tissues obtained by TBLB showed no lymphocyte or plasma cell infiltration in the pulmonary interstitium, but marked eosinophil infiltration was noted. **a** H and E, $\times 200$ original magnification. No positive cell was noted on IgG4 staining. **b** Immunohistochemistry $\times 200$ original magnification

of microvascular granuloma or fibrinoid necrotizing vasculitis, so the possibility of Churg–Strauss syndrome was judged to be low.

Multiple poorly contrasted areas in the renal parenchyma, diffuse kidney enlargement, solitary masses, and hypertrophic lesions of the renal pelvic wall not accompanied by luminal irregularity have been reported as characteristics findings in imaging studies of IgG4-related

kidney disease [9]. Our case showed multiple poorly contrasted areas in the renal parenchyma and diffuse kidney enlargement. Also, about 30 % of the patients diagnosed with IgG4-related kidney disease show no abnormality on abdominal CT, with the percentage of patients showing abnormalities having been reported to be 72.1 % by Saeki et al. [10] and 70.7 % by Kawano et al. [5]. However, many patients do not undergo contrast-enhanced CT, and

Fig. 4 In kidney biopsy specimens, no clear mesangial cell proliferation or doubling of the basement membrane was observed. About 50 % of the interstitium was fibrosed, and lymphocyte, plasma cell, and eosinophil infiltration was noted. **a** H and E, $\times 200$ original

magnification. **b** Masson's trichrome stain, $\times 100$ original magnification. On IgG4 staining, the IgG4/IgG-positive plasma cell rate was 89 %. **c** immunohistochemistry $\times 200$ original magnification

Fig. 5 Clinical course treatment was initiated by administering prednisolone (PSL) at 40 mg/day (0.8 mg/kg/day), followed by prompt alleviation of the cough, malaise, and anorexia

contrast-enhanced CT is considered necessary as long as the renal function tolerates the modality. FDG PET-CT and Ga [6, 9] scintigraphy have been reported to be effective for evaluation of the sites and activities of lesions [11], but positive accumulation in the kidney on Ga [6, 9] scintigraphy was in only 11 % of patients according to Saeki et al. [12], and further evaluation is considered necessary as an imaging modality for kidney lesions.

CT findings of the lung in IgG4-related diseases have been reported to be classified into 4 types: ground-glass opacity (GGO), diffuse reticular, bronchial wall thickening, and nodular patterns [13]. Moreover, Zen et al. reported the imaging findings: when a GGO or diffuse reticular pattern was observed, lymphocytes and plasma cells infiltrated the pulmonary alveoli and interstitium, and thickening of the pulmonary alveoli and interstitium was even, similarly to non-specific interstitial pneumonia. When bronchial wall thickening was observed, plasma cells infiltrated the bronchial vascular bundles, alveoli and interstitium, interlobular septa, and pleura. When the nodular pattern was observed, nodular sclerosing inflammation of the bronchial glands and irregular plasma cell infiltration were noted. There is also a report that eosinophil infiltration was observed in 43 % [14]. However, the confirmation of IgG4-positive plasma cells is necessary for diagnosis. In the present case, as no IgG4-positive plasma cell infiltration was observed while eosinophil infiltration was noted in lung tissues.

Indeed, IgG4-related disease has been often associated with eosinophilia [15, 16]. In addition, eosinophilic diseases have been associated with TNF- α [17], IL-5 [18], IL-10 [19]. Furthermore, IL-5, TNF- α and eotaxin-3 were correlated with eosinophilia in IgG4-related disease [20]. Nakashima et al. reported that Th2 and Treg appear to play a central role in IgG4-related TIN. Treg cells can produce regulatory cytokines including IL-10 and TGF- β [21]. James et al. [22] reported that the chest X-ray of hypereosinophilic syndrome shows interstitial, non-lobe infiltrates. In this case, we thought that these cytokines were correlated with eosinophilia, therefore pulmonary lesion may be in association with secondarily to hypereosinophilic syndrome. Recently, regulatory T cells have been suggested to be involved in IgG4-related diseases, and IL-10 produced by regulatory T cells has been reported to induce fibrosis and class switch to IgG4 [23]. However, many aspects of the disease remain unclear, and reports on lung lesions are particularly scarce. Further studies are considered necessary.

In conclusion, we diagnosed this case as typical IgG4-related kidney disease with a complication of eosinophilic lung disease, showing very good response to corticosteroid mono-therapy with moderate PSL dose (0.8 mg/kg/day). On lung biopsy, only eosinophil infiltration was demonstrated

with no plasma cell infiltration. This case may be one of the possible patterns of IgG4-related lung diseases.

Conflict of interest The authors have declared that no conflict of interest exists.

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