American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 593-598
DOI: 10.12659/AJCR.902187

Received: 2016.10.31
Accepted: 2017.03.16
Published: 2017.05.29

# IgG4-Related Disease Manifesting as Interstitial Nephritis Accompanied by Hypophysitis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E Ken Matsuda
E Ayako Saito
E Yoichi Takeuchi
E Hirotaka Fukami
E Hiroyuki Sato
E Tasuku Nagasawa

Department of Nephrology, Japanese Red Cross Ishinomaki Hospital, Ishinomaki, Miyagi, Japan

**Corresponding Author:** Ken Matsuda, e-mail: matsuda.ken.2.0.0.7@gmail.com
**Conflict of interest:** None declared

**Patient:** Male, 85
**Final Diagnosis:** IgG4-related disease
**Symptoms:** Renal failure
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Nephrology

**Objective:** Rare disease

**Background:** IgG4-related disease is a systemic disease with marked infiltration of IgG4-positive plasma cells into affected organs and elevated serum IgG4. On clinical examination, swelling, nodules, and hypertrophic lesions might appear simultaneously or metachronously in different organs.

**Case Report:** An 85-year-old man with sudden-onset polydipsia and polyuria insipidus was transported to our hospital because of hypothermia and general malaise. Laboratory tests revealed renal failure and central diabetes insipidus. According to his serum IgG4 level, the patient was diagnosed with possible IgG4-related kidney disease accompanied by IgG4-related hypophysitis. Abdominal contrast-enhanced computed tomography, hypophysis magnetic resonance imaging, and histological examination of the kidney were performed. Glucocorticoid therapy was administered and his renal function improved gradually. However, his central diabetes insipidus did not improve.

**Conclusions:** Glucocorticoid therapy showed different therapeutic effects on the kidney and posterior lobe of the hypophysis. It is possible that glucocorticoid therapy needs to be supported by other immunomodulatory therapies to have an effect on all affected organs.

**MeSH Keywords:** Diabetes Insipidus, Neurogenic • Immunoglobulin G • Kidney Diseases • Pituitary Diseases

**Full-text PDF:** http://www.amjcaserep.com/abstract/index/idArt/902187

## Background

IgG4-related disease is a systemic disease which usually accompanied by involvement of various organs with marked infiltration of IgG4-positive plasma cells into the organs and elevated serum IgG4 [1,2]. The most commonly affected organs are the pancreas, liver, gall bladder, lachrymal gland, salivary gland, kidneys, and respiratory organs; the retroperitoneum is also commonly affected. To our knowledge, the cause of this disease has not yet been determined. On clinical examination, swelling, nodules, and hypertrophic lesions might appear simultaneously or metachronously in systemic organs. Serologically, an elevated IgG4/IgG level is noted. In some cases, antinuclear antibody is identified. Histopathologically, IgG4-related disease involves infiltration of lymphocytes and IgG4-positive plasma cells into target organs and fibrosis of target organs. In this context, the consensus statement regarding the pathology of IgG4-related disease proposes the IgG4-positive cells/IgG-positive cell ratio of >40% as a comprehensive cutoff value in any organ. The consensus statement also proposes a set of cutoff points for the number of IgG4-positive plasma cells specific to each organ in the case of IgG4-related disease. If the case involves 2 or more of the 3 characteristic histological features (dense lymphoplasmacytic infiltrate; fibrosis, usually storiform in character; and obliterative phlebitis) and appropriate numbers of IgG4-positive plasma cells (for example, pancreas (biopsy) >10/HPF, liver (biopsy) >10/HPF, kidney (biopsy) >10/HPF, and salivary gland >100/HPF), then IgG4-related disease can be considered [3]. In Japan, an epidemiological survey indicated that medical treatments for IgG4-related disease are provided to 8000 individuals every year [4]. The Japanese Society of Nephrology Working Group presented epidemiology for IgG4-related kidney disease and indicated that the estimated number of patients was 130 per year [5]. Therefore, IgG4-related kidney disease with tubulointerstitial nephritis is considered rare. Inflammatory disease of the hypophysis is very rare, and adequate epidemiological studies have not been performed for this condition. Leporati et al. proposed the term "IgG4-related hypophysitis" in 2009, and there have been recent successive reports about hypophyseal stalk inflammation accompanied by IgG4-related disease [6]. In relation to IgG4-related hypophysitis, Bando et al. reported that among 170 consecutive outpatients with hypopituitarism and/or central diabetes insipidus in their hospital, 7 were diagnosed with IgG4-related hypophysitis; 2 of these 7 patients had central diabetes insipidus only [7].

Here, we report a case of possible IgG4-related kidney disease simultaneously accompanied by IgG4-related hypophysitis and central diabetes insipidus. There are few case reports of IgG4-related kidney disease and even fewer case reports of IgG4-related hypophysitis. Therefore, we think our case is extremely rare.

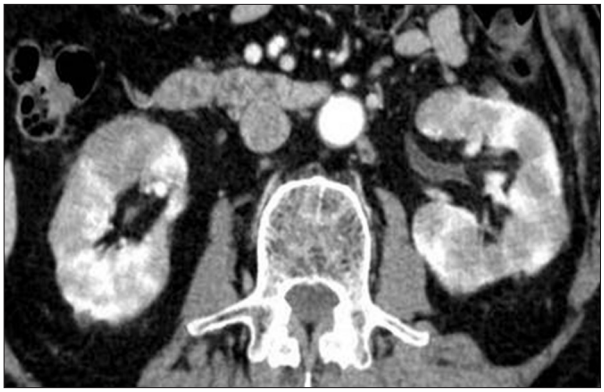

**Figure 1.** Contrast-enhanced computed tomography (CT). Contrast-enhanced CT image shows irregular findings in the kidneys and atrophy of the pancreatic parenchyma.

## Case Report

An 85-year-old man with Mallory-Weiss syndrome, cholecystitis, and ileus presented to a local hospital because of sudden polydipsia (6–10 L/day) and polyuria 13 months prior to admission to our hospital. The doctors administered desmopressin for symptomatic treatment because diabetes insipidus was suspected due to urine-specific gravity of 1.001 and hyposthenuria.

He was transferred to another general hospital because of anorexia, vomiting, headache, and weight loss 5 months prior to admission to our hospital. The doctors noted renal failure (creatinine [Cr] level, 1.65 mg/dL; estimated glomerular filtration rate [eGFR], 31.34 mL/min/1.73 $m^2$); however, urinalysis findings were negative. They noted an irregular contrast image in the bilateral kidneys on contrast-enhanced computed tomography (Figure 1) and an elevated IgG level (3226 mg/dL). On further analysis, an elevated IgG4 level (713 mg/dL) was noted. Therefore, IgG4-related kidney disease was suspected. Contrast-enhanced computed tomography showed atrophy of the pancreatic parenchyma, thereby suggesting complications of IgG4-related pancreatitis; however, there were no subjective symptoms.

The patient stopped using desmopressin 1 month prior to admission to our hospital because he experienced headache and vomiting. He experienced sore throat, fever, and general malaise. He also noted a decrease in urine volume and the amount of fluid intake 3 days prior to admission to our hospital. He was admitted to our emergency outpatient unit because of exacerbation of hypothermia and general malaise. On arrival, he was alert and conscious. His blood pressure was 150/99 mmHg, pulse rate was 51 beats/min, and temperature was 35.8°C. Tests performed by the nephrology department showed high renal function degradation (Cr level, 3.17 mg/dL; blood

**Table 1.** Laboratory data on admission.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| WBC | 8.4 | ×10⁴/μl | Na | 132 | mEq/l | IgG | 4374 | mg/dl | ACTH | 23.3 | pg/ml |
| RBC | 361 | ×10⁴/μl | K | 5.2 | mEq/l | IgA | 105 | mg/dl | Cortisol | 10.9 | μg/dl |
| PLT | 24 | ×10⁴/μl | Cl | 104 | mEq/l | IgM | 89 | mg/dl | TSH | 2.08 | μIU/ml |
| TP | 8 | g/dl | BUN | 48 | mg/dl | CH50 | 13.7 | mg/dl | FT3 | 2.48 | pg/ml |
| Alb | 2.9 | g/dl | Cr | 3.17 | mg/dl | C3 | 55 | mg/dl | FT4 | 1.41 | pg/ml |
| T-bil | 0.3 | mg/dl | UA | 6.1 | mg/dl | C4 | 4 | mg/dl | GH | 0.63 | ng/ml |
| AST | 18 | IU | | | | ANA | <40 | Times | IGF-1 | 120 | ng/ml |
| ALT | 12 | IU | Gravity | | | PR3-ANCA | <1.0 | U/ml | LH | 14.17 | mIU/ml |
| ALP | 164 | IU | Urine pH | 5.5 | | MPO-ANCA | <1.0 | U/ml | FSH | 15.42 | mIU/ml |
| γGTP | 21 | IU | Urinarysugar | – | | | | | Prolactin | 124 | ng/ml |
| LDH | 142 | IU | Urine RBC | <1/HPF | | | | | | | |
| CRP | 1.34 | mg/dl | Uric protein | 0.2 g/gCre | | | | | | | |

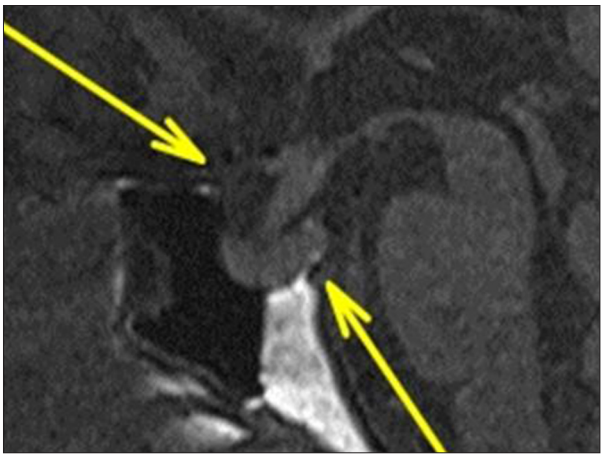

**Figure 2.** Pituitary magnetic resonance imaging (MRI). Hypophysis MRI image shows swelling of the hypophysis stalk. A T1-weighted image shows disappearance of brightness of the posterior lobe of the hypophysis.

urea nitrogen level, 48.0 mg/dL; eGFR, 15.4 mL/min/1.73 m$^2$). Other laboratory data are shown in Table 1. Abdominal computed tomography showed atrophy of the pancreatic parenchyma. Without water restrictions, we noted polydipsia, polyuria, and frequent urination. Additionally, serum osmolality shifted between –302 and 289 mOsm/kg $H_2O$ and urinary osmolality shifted between –189 and 185 mOsm/kg $H_2O$. We diagnosed this as central diabetes insipidus because we did not note secretion of antidiuretic hormones despite the elevation of serum osmolality after administration of 5% hypertonic salt solution 4 days after admission. Based on this finding, we resumed desmopressin. With a low desmopressin dose of 0.625 μg/day, we noted improvement in polydipsia and polyuria, and blood tests showed a serum Na level of 132–135 mmol/L. Serum osmolality between –293 and 286 mOsm/kg $H_2O$ was considered stable. Hypophysis magnetic resonance imaging showed swelling of the pituitary stalk, which indicated inflammatory hypophysis. Additionally, on T1-weighted imaging, brightness of the posterior lobe of the hypophysis disappeared. We considered this to be depletion of vasopressin caused by central diabetes insipidus (Figure 2). We did not observe anterior pituitary dysfunction.

Renal biopsy was performed 14 days after admission, and a total of 25 glomeruli were noted without global sclerosis. Among the identified glomeruli, 8 were collapsed and the others were intact. The extent of tubular atrophy was 80% and the extent of interstitial fibrosis was 80%. Azan staining showed storiform fibrosis (Figure 3A). Hematoxylin and eosin staining showed remarkable infiltration of plasma cells (Figure 3B). CD38 immunohistochemical analysis showed remarkable CD38 positive cells (Figure 3C). IgG4 immunohistochemical analysis showed infiltration of IgG4-positive plasma cells into the tubulointerstitium (Figure 3D). The number of IgG4-positive plasma cells/HPF is 14 as a mean of the counts of 3 HPF. Regarding IgG4-positive cells/IgG-positive cells, we could not show the result because our IgG staining did not work well.

We administered 1 course of glucocorticoid pulse therapy with methylprednisolone (500 mg/day) and then reduced the dose of prednisolone to 20 mg/day. We observed that his general condition and renal function degradation improved (Cr level, 2.42 mg/dL; eGFR, 20.6 mL/min/1.73 m$^2$); therefore, he was discharged from the hospital. Desmopressin was continued and the methylprednisolone dose was gradually reduced. He was monitored as an outpatient; 21 months after admission, the

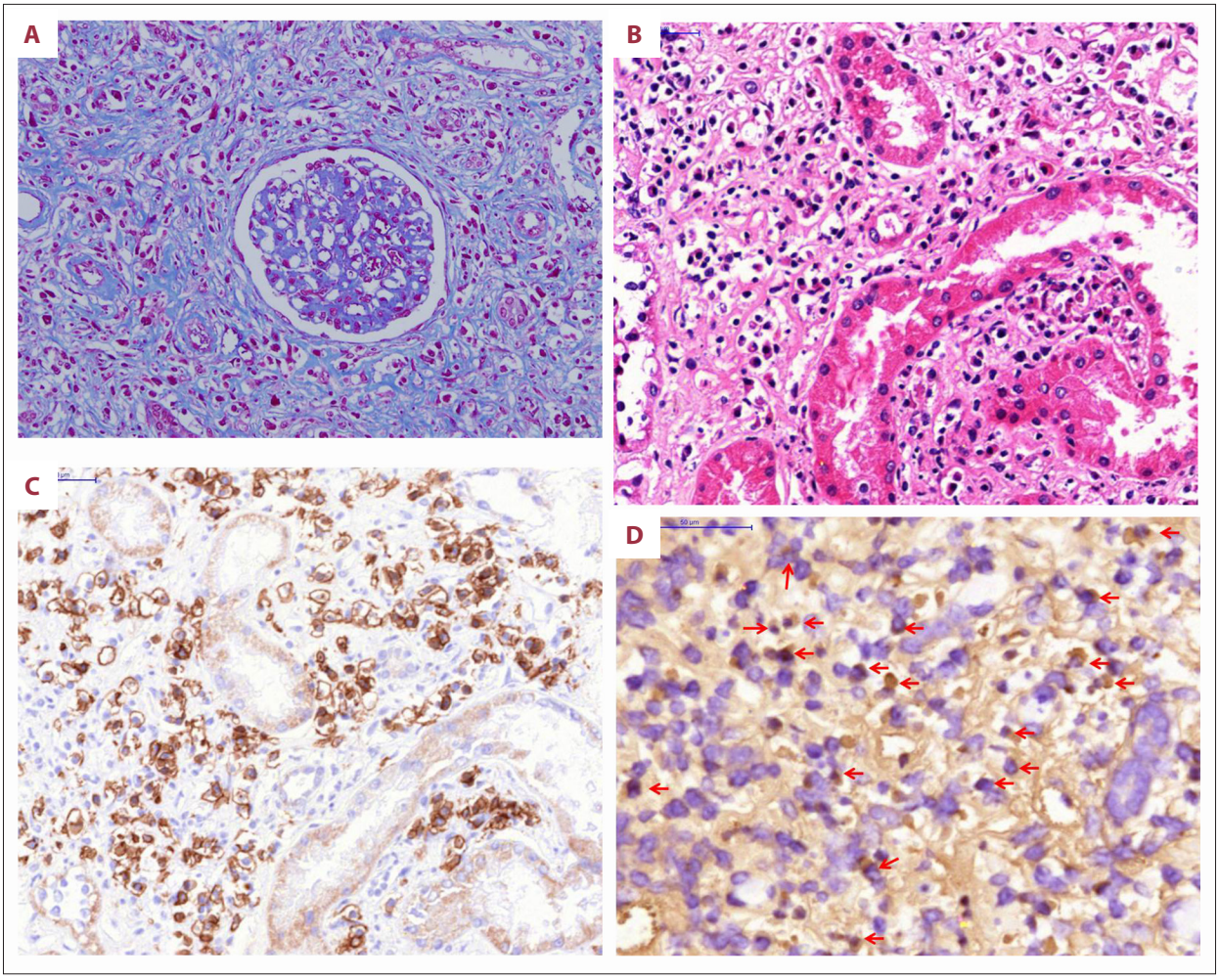


**Figure 3.** (**A**) Azan staining. Storiform fibrosis can be seen. (**B**) Hematoxylin and eosin staining. Remarkable infiltration of plasma cells is observed. (**C**) CD38 immunohistochemical analysis. Remarkable CD38 positive cells are observed. (**D**) IgG4 immunohistochemical analysis. IgG4-positive plasma cells are observed infiltrating the tubulointerstitium. The number of IgG4-positive plasma cells/HPF is 14 as a mean of the counts of 3 HPF.

methylprednisolone dose was reduced to 5 mg/day (maintenance dose) and his kidney function showed further improvement (Cr level, 1.89 mg/dL; eGFR, 26.8 mL/min/1.73 $m^2$). Other laboratory data are shown in Table 2. Additionally, swelling of the hypophyseal stalk decreased and brightness of the posterior lobe of the hypophysis was absent.

## Discussion

IgG4-related disease is a chronic inflammatory disease. We were able to establish a fundamental diagnosis based on the presence of clinical diffuse or focal swelling, a tumor mass, a nodule, a hypertrophic lesion, a high serological IgG4 level, and histological IgG4-positive plasma cells [8].

In the present case, we were able to establish a possible diagnosis of IgG4-related kidney disease based on criteria 1, 2, 3 and 4b presented by the Japanese Society of Nephrology (Figure 4) [9]. In addition, we were able to diagnose IgG4-related hypophysitis based on criteria 2, 4, and 5 presented by Leporati et al. (Figure 5) [6]. Therefore, we believe that the present case involved IgG4-related hypophysitis and IgG4-related kidney disease.

IgG4-related kidney disease with tubulointerstitial nephritis is considered rare. Inflammatory disease of the hypophysis is also very rare. Furthermore, the incidence of IgG4-related hypophysitis among primary inflammatory diseases of the hypophysis occurs even less often. Therefore, we believe that our case involving both IgG4-related hypophysitis and IgG4-related kidney disease is extremely rare.

**Table 2.** Laboratory data 21 months after admission (the IgG4 data presented here were obtained 23 months after admission).

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| WBC | 11.9 | ×10⁴/μl | Na | 134 | mEq/l | Urinespecific gravity | 1.015 | IgG | 2043 | mg/dl |
| RBC | 386 | ×10⁴/μl | K | 4.6 | mEq/l | Urine pH | 6 | IgG4 | 434 | mg/dl |
| PLT | 26.6 | ×10⁴/μl | Cl | 99 | mEq/l | Urinarysugar | – | IgA | 144 | mg/dl |
| TP | 7.1 | g/dl | BUN | 21 | mg/dl | Urine RBC | <1/HPF | IgM | 117 | mg/dl |
| Alb | 3.6 | g/dl | Cr | 1.89 | mg/dl | Uric protein | 0.1 g/gCre | | | |
| T-bil | 0.3 | mg/dl | UA | 5.2 | mg/dl | | | | | |
| AST | 30 | IU | | | | | | | | |
| ALT | 21 | IU | | | | | | | | |
| ALP | 203 | IU | | | | | | | | |
| γGTP | 21 | IU | | | | | | | | |
| LDH | 160 | IU | | | | | | | | |

**Diagnostic criteria of IgG4-related kidney disease**

1) Abnormal findings on urinary analysis or renal function tests and presence of hyper IgG, hypocomplementemia, or hyper IgG.

2) Characteristics abnormal findings on imaging (diffuse renal sweeling, multiple issues in the renal parenchyma on contrast imaging, solitary renal hypovascular tumor, wall thickening of the pelvis).

3) Hyper IgG4 (>135 mg/dL) on hematological assessment.

4) Renal histopathological findings as follows: a) remarkable lymphocyte and plasma cell infiltration (ratio of IgG4-positive cells/IgG-positive cells of over 40% or more than 10 IgG-positive plasma cells per high-power field; b) characteristic fibrosis surrounded by infiltrating cells.

5) Remarkable lymphocyte and plasma cell infiltration and fibrosis in other organs, except the kidney, on histopathological analysis (ratio of IgG-positive cells/IgG-positive cells of over 40% or more than 10 IgG-positive plasma cell per high-power field).

**Difinite:** 1+3+4a, b
2+3+4a, b
2+3+5
1+3+4a+5

**Probable:** 1+4a, b
2+4a, b
2+5
3+4a, b

**Possibile:** 1+3
2+3
1+4a
2+4a

**Figure 4.** Diagnostic criteria of IgG4-related kidney disease presented by the Japanese Society of Nephrology [7].

**Diagnostic criteria of IgG4-related hypophysitis**

1) Pituitary histopathology: Mononuclear infiltration of the pituitary gland, high number of lymphocytes and plasma cells and more than 10 IgG-positive cells per high-power field.

2) Pituitary magnetic resonance imaging: Sellar mass and/or thickened pituitary stalk.

3) Biopsy proven involvement in other organs: Presence of IgG4-positive lesions in other organs.

4) Serology: High serum IgG4 level (>140 mg/dL).

5) Response to glucocorticoids: Shrinkage of the pituitary mass and symptom improvement.

**IgG4-related hypophysitis is diagnosed when any of the following is fulfilled:**
1
2+3
2+4+5

**Figure 5.** Diagnostic criteria of IgG4-related hypophysitis presented by Leporati et al. [4].

To our knowledge, only 2 reports have presented cases involving both IgG4-related kidney disease and IgG4-related hypophysitis [10,11]. Regarding IgG4-related hypophysitis, only 1 of 2 cases involved central diabetes insipidus simultaneously [10].

Our patient's renal response to glucocorticoid treatment was favorable, and such a favorable response has been mentioned in previous reports of IgG4-related kidney disease [9,12]. We noted improvement in kidney function, with the eGFR improving from 15.4 mL/min/1.73 m$^2$ during the first medical examination at our hospital to 26.8 mL/min/1.73 m$^2$ during the last follow-up examination. A previous report mentioned that recovery of renal function was only partial in cases of high renal function deficiency (eGFR ≤60 mL/min/1.73 m$^2$) before treatment [12]. Therefore, we believe that our patient's renal function might not improve further because his renal function before treatment was very low (eGFR 15.4 mL/min/1.73 m$^2$).

Regarding IgG4-related hypophysitis, we could not withdraw desmopressin administered for the treatment of central diabetes insipidus; however, glucocorticoid therapy, including glucocorticoid pulse therapy, resulted in improvement in the swelling of the hypophysis stalk. For IgG4-related kidney disease accompanied by IgG4-related hypophysitis and central diabetes insipidus, which was previously reported, glucocorticoid therapy resulted in simultaneous improvement in renal function and central diabetes insipidus [10]. However,

glucocorticoid therapy showed different effects on the kidney and hypophysis in our case.

In previous reports, some symptoms of central diabetes insipidus did not improve with glucocorticoid therapy; however, improvement was noted in the swelling of the hypophysis stalk on imaging. Interestingly, these cases showed improvement in coexisting hypopituitarism of the anterior lobe of the hypophysis with glucocorticoid therapy [14,15]. Based on these findings, it is possible that the posterior lobe of the hypophysis is refractory to glucocorticoid therapy, whereas the anterior lobe of the hypophysis responds to glucocorticoid therapy.

It is possible that the speed of tissue fibrosis differs between organs. In organs with rapid fibrosis, improvement decreases with time, even with effective treatment. In this case, we believe that the onset of the patient's symptoms occurred more than 13 months before the renal biopsy. In addition, it is possible that other immunosuppressive agents such as rituximab and glucocorticoid therapy have a stronger effect on the organ. However, our patient was elderly, and combination therapy involving other immunosuppressive agents likely could have caused infection. Therefore, we did not use other immunosuppressive agents. Therefore, further studies of IgG4-related disease are needed to clarify these points.

## Conclusions

We present a rare case involving IgG4-related hypophysitis and possible IgG4-related kidney disease. In our case, the possibility of glucocorticoid therapy having different therapeutic effects on different organs was indicated.

### Acknowledgments

Special thanks to Yuko Itakura and Kiyomi Kisu for performing immunostaining.

### Conflict of interest

None.

## References:

1. Hamano H, Kawa S, Horiuchi A et al: High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med, 2001; 344: 732–38
2. Hamano H, Kawa S, Ochi Y et al: Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet, 2002; 359: 1403–4
3. Deshpande V, Zen Y, Chan JK et al: Consensus statement on the pathology of IgG4-related disease. Mod Pathol, 2012; 25: 1181–92
4. Uchida K, Masamune A, Shimosegawa T, Okazaki K: Prevalence of IgG4-related disease in Japan based on nationwide survey in 2009. Int J Rheumatol, 2012; 2012: 358371
5. Nakashima H, Kawano M, Saeki T et al: Estimation of the number of histological diagnosis for IgG4-related kidney disease referred to the data obtained from the Japan Renal Biopsy Registry (J-RBR) questionnaire and cases reported in the Japanese Society of Nephrology Meetings. Clin Exp Nephrol, 2017; 21(1): 97–103
6. Leporati P, Landek-Salgado MA, Lupi I et al: IgG4-related hypophysitis: A new addition to the hypophysitis spectrum. J Clin Endocrinol Metab, 2011; 96: 1971–80
7. Bando H, Iguchi G, Fukuoka H et al: The prevalence of IgG4-related hypophysitis in 170 consecutive patients with hypopituitarism and/or central diabetes insipidus and review of the literature. Eur J Endocrinol, 2013; 170: 161–72
8. Umehara H, Okazaki K, Masaki Y et al: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol, 2012; 22: 21–30
9. Kawano M, Saeki T, Nakashima H et al: Proposal for diagnostic criteria for IgG4-related kidney disease. Clin Exp Nephrol, 2011; 15: 615–26
10. Harano Y, Honda K, Akiyama Y et al: A case of IgG4-related hypophysitis presented with hypopituitarism and diabetes insipidus. Clin Med Insights Case Rep, 2015; 8: 23–26
11. Hsing MT, Hsu HT, Cheng CY, Chen CM: IgG4-related hypophysitis presenting as a pituitary adenoma with systemic disease. Asian J Surg, 2013; 36: 93–97
12. Saeki T, Nishi S, Imai N et al: Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. Kidney Int, 2010; 78: 1016–23
13. Saeki T, Kawano M, Mizushima I et al: The clinical course of patients with IgG4-related kidney disease. Kidney Int, 2013; 84: 826–33
14. Isaka Y, Yoshioka K, Nishio M et al: A case of IgG4-related multifocal fibrosclerosis complicated by central diabetes insipidus. Endocrinol J, 2008; 55: 723–28
15. Tsuboi H, Inokuma S, Setoguchi K et al: Inflammatory pseudotumors in multiple organs associated with elevated serum IgG4 level: Recovery by only a small replacement dose of steroid. Intern Med, 2008; 47: 1139–42