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Clinical Medicine Insights: Case Reports

A Case of IgG4-Related Hypophysitis Presented with Hypopituitarism and Diabetes Insipidus

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ABSTRACT: Immunoglobulin (Ig) G4-related systemic syndrome is a recently described entity characterized by elevated serum IgG4 and tissue infiltration of IgG4-positive plasma cells. Pituitary gland can be involved as hypophysitis. We report a case of a 72-year-old man, who presented with general fatigue and weakness. Laboratory tests revealed diabetes insipidus as well as hypopituitarism including adrenal insufficiency, hypogonadism, and hypothyroidism. His serum IgG4 was elevated. MR images showed enlargement of the pituitary stalk. Multiple nodules in bilateral kidneys were pointed out in the abdominal CT. Histological examination of the nodules showed increased IgG4-positive plasma cells. We diagnosed him with IgG4-related kidney disease and hypophysitis. After treatment with hydrocortisone, his symptoms improved. The follow-up images showed that almost all renal nodules disappeared and his pituitary stalk was shrinking. Our case appears to be very sensitive to glucocorticoid and suggests the possibility of treating IgG4-related hypophysitis successfully with a lower dose of glucocorticoid.

KEYWORDS: IgG4-related systemic syndrome, hypophysitis, diabetes insipidus

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Introduction

Immunoglobulin (Ig) G4-related systemic syndrome is a recently described entity[1] characterized by elevated serum IgG4 and tissue infiltration of IgG4-positive plasma cells. It can involve multiple organs, for example, salivary glands as Mikulicz's disease, pancreas as autoimmune pancreatitis, and thyroid gland as Riedel's thyroiditis. Pituitary gland can be involved as hypophysitis. We report a case of IgG4-related hypophysitis presented with hypopituitarism and diabetes insipidus.

Case Report

A 72-year-old Japanese man presented with 3-month history of general fatigue and weakness. After the symptoms appeared, he lost 4.5 kg of his weight and became bedridden. On admission, his height and weight were 168 cm and 43.5 kg, respectively. He denied headache, nausea, and vomiting. His physical findings were unremarkable except that he was severely dehydrated. We suspected endocrine diseases as the cause of his symptoms and assessed adrenocortical function. The results showed that his morning serum cortisol (3.39 μg/dL, normal reference: 6.2–19.4 μg/dL) and adrenocorticotropic hormone (ACTH) (5.5 pg/mL, normal reference: 7.2–63.3 pg/mL) were decreased remarkably. We suspected secondary or tertiary adrenal insufficiency and performed the anterior pituitary stimulation test, which revealed that the baseline values of the pituitary hormones were decreased and they showed delayed reactions. The thyroid antibody and antipituitary antibody were not detected. To evaluate the function of his posterior pituitary hormone, we carried out hypertonic saline infusion test, which showed that his urine osmolality did not exceed above 300 mOsm/kg during hypertonic saline infusion (8 a.m. to 10 a.m.) and his urine output was decreased and his urine osmolality was increased after the vasopressin

infusion (10 a.m.) (Fig. 1). We made the diagnosis of diabetes insipidus as well as hypopituitarism (Table 1) including adrenal insufficiency, hypogonadism, and hypothyroidism. MR images showed that the pituitary stalk (Fig. 2A) exceeded more than 2.5 mm and became thickened.

Multiple nodules in bilateral kidneys were pointed out in the abdominal CT (Figs. 2C, D, E, and F). We performed CT-guided biopsy of the nodules. Histological examination showed increased IgG4-positive plasma cells (Fig. 3). His serum IgG4 was elevated (853 mg/dL, normal reference range: 4.8–105 mg/dL). We established the final diagnosis of IgG4-related kidney disease and IgG4-related hypophysitis as the cause of the hypopituitarism and enlargement of the pituitary stalk.

He was treated with hydrocortisone 15 mg and levothyroxine 12.5 μg a day. After the treatment, his symptoms improved and the borderline values of his pituitary hormones were increased and his serum IgG4 was decreased to 337 mg/dL. The follow-up images showed that almost all renal nodules disappeared and his pituitary stalk was shrinking 3 months and 5 months after the treatment, respectively (Fig. 2B).

Discussion

Hypophysitis is defined as an inflammatory disorder of the pituitary gland and has been classified from various viewpoints, histological findings, anatomical locations, and the cause. Based on the histological findings, it is classified as lymphocytic, granulomatous, necrotizing, and xanthomatous. In addition to these types of hypophysitis, IgG4-related hypophysitis is thought to be a novel classification of hypophysitis.[2] Leporati et al. devised the following five criteria to establish a diagnosis of IgG4-related hypophysitis[3] (Table 2). Based on their criteria, the swelled pituitary stalk was observed in pituitary MRI, and IgG4-positive plasma cells were proven in the biopsy of renal nodules. Furthermore, his serum IgG4 was elevated above 140 mg/dL. Based on these findings, we established a diagnosis of IgG4-related hypophysitis.

Depending on whether the clinical symptoms and MR images involve the anterior lobe or the pituitary stalk and posterior lobe or both, hypophysitis has also been classified into adenohypophysitis, infundibulo-neurohypophysitis, and panhypophysitis. Adenohypophysitis tends to develop hypopituitarism and pituitary mass, whereas the clinical presentations of infundibulo-neurohypophysitis often include diabetes insipidus accompanied by pituitary stalk swelling. According to the past case reports, the images in IgG4-related hypophysitis might present as thickening and mass of pituitary stalk or pituitary gland.[4–6] In our case, both hypopituitarism and diabetes insipidus coexisted. It has been suggested that autoimmune inflammation can cause adenohypophysitis and infundibulo-neurohypophysitis simultaneously. In lymphocytic hypophysitis, they usually occur separately. Recent studies suggest that IgG4-related hypophysitis may affect both the adenohypophysitis and the infundibulo-neurohypophysitis structure like our case.[7–9] On the other hand, Hattori et al. reported a case of IgG4-related hypophysitis without pituitary insufficiency.[10] The pathogenesis of IgG4-related hypophysitis might be different from traditional hypophysitis and warrants further discussion.

Our case appears to be very sensitive to glucocorticoid treatment. We used hydrocortisone 15 mg a day to compensate for adrenocortical insufficiency. Though the standard dose of glucocorticoid to treat IgG4-related hypophysitis is controversial, quite a high-dose glucocorticoid such as prednisolone (0.6 mg/kg) is usually used at first and gradually tapered.[11–13] However, there are some case reports of the IgG4-related hypophysitis that were successfully treated with a low dose of glucocorticoid.[14] Shimatsu et al. reported that almost all cases of IgG4-related hypophysitis occurred in middle-aged to elderly men[15] From the standpoint of the side effects, an

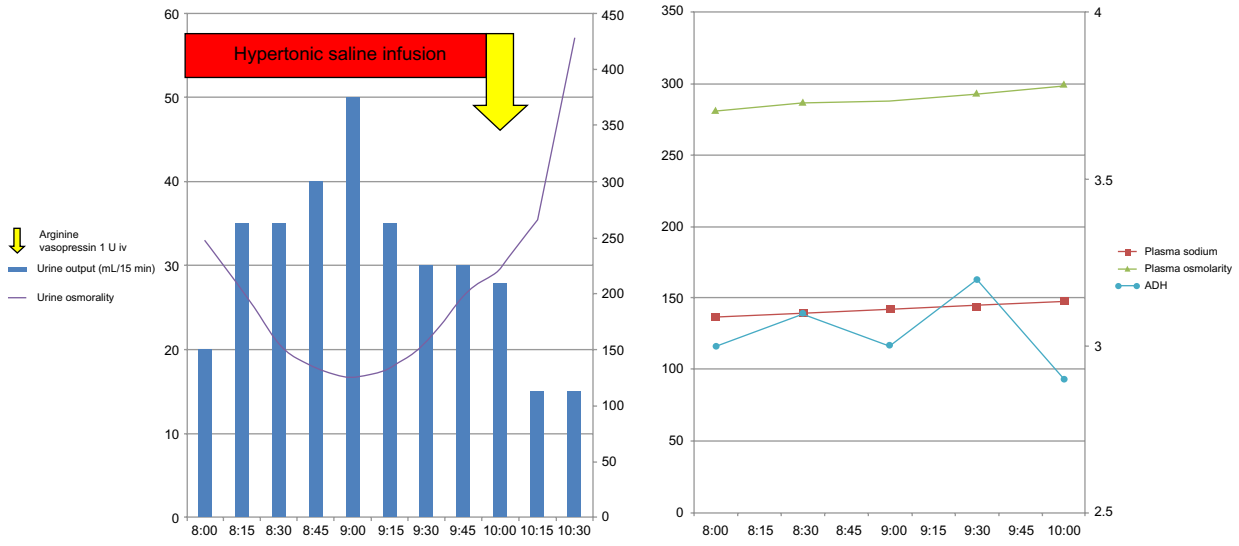

Figure 1. Hypertonic saline infusion test. 5% hypertonic saline was infused at 5 mL/kg/min for 2 hours (8 am to 10 am). At 10 a.m., 1 unit of vasopressin was infused. During the infusion, urine output and osmolality and plasma sodium were measured every 15 min.

Table 1. Endocrinological findings. Basal endocrinological value and responses of pituitary hormones to intravenous injection of 100 μg corticotropin-releasing hormone, 100 μg growth hormone (GH)-releasing factor, 100 μg luteinizing hormone (LH)-releasing hormone, and 200 μg thyrotropin-releasing hormone.

	BASAL	30 MIN	60 MIN	90 MIN	120 MIN	NORMAL RANGE
TSH (μIU/ml)	0.660	6.770	9.210	8.940	7.910	0.45–4.95
Free T4 (ng/ml)	0.42					1.0–1.64
Free T3 (pg/ml)	1.0					2.3–4.3
ACTH (pg/dl)	5.5	43.2	38.6	28.8	31.7	7.2–63.3
Serum cortisol (μg/dl)	3.39	17.35	18.43	17.67	16.95	6.2–19.4
FSH (mIU/ml)	0.31	0.42	0.63	0.79	0.88	2.0–8.30
LH (mIU/ml)	<0.1	<0.1	0.16	0.22	0.26	0.79–5.72
PRL (ng/ml)	15.99	31.25	27.05	24.33	22.44	3.58–12.8
GH (ng/ml)	0.398	2.357	2.145	1.745	1.124	0.003–0.971
Somatomedin C (ng/ml)	18					52–185

Abbreviations: TSH, thyroid stimulating hormone; FSH, Follicle stimulating hormone; PRL, Prolactin.

excessive dose of glucocorticoid should be refrained for elderly patients and the appropriate dose of glucocorticoid should be established. In our case, in addition to the symptoms, both the swelling of the pituitary stalk and multiple nodules of the bilateral kidneys were improved by the lower dose of hydrocortisone, compared with the past case reports. Our case suggests the possibility of treating IgG4-related hypophysitis successfully with the lower dose of glucocorticoid.

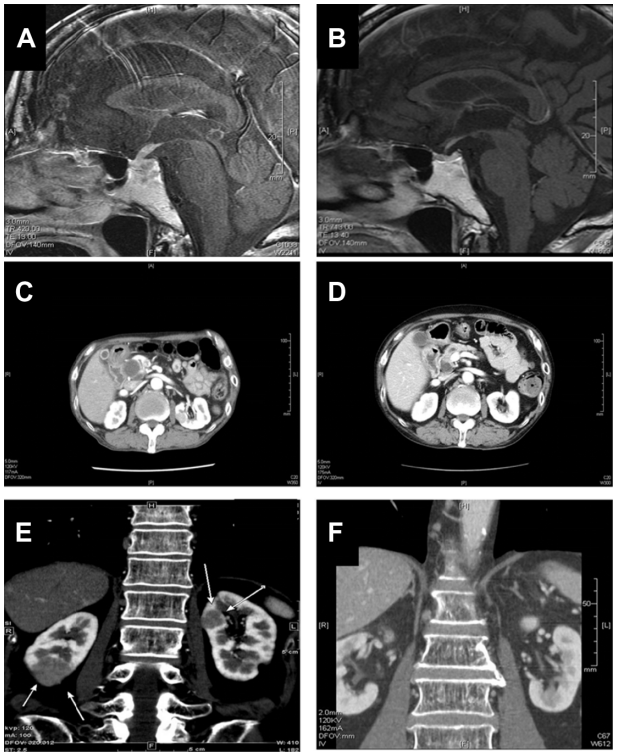

Figure 2. Pituitary MRI and abdominal CT pre- (**A**, **C**, **E**) and post- (**B**, **D**, **F**) replacement of hydrocortisone. After the treatment, almost all renal nodules (white arrows) disappeared and the pituitary stalk was shrinking.

Almost all cases of IgG4-related hypophysitis were successfully treated with various doses of glucocorticoid. On the other hand, Carmela et al. reported a relapse case of IgG4-related hypophysitis, in spite of their treatment with quite a high dose of prednisolone. They successfully treated the case with azathioprine.[16] Responsiveness to glucocorticoid treatment might be varied in IgG4-related hypophysitis. To establish appropriate treatment for IgG4-related hypophysitis, further case collection and discussion is warranted.

Conclusion

In our case, both hypopituitarism and partial diabetes insipidus coexisted. It has been suggested that autoimmune

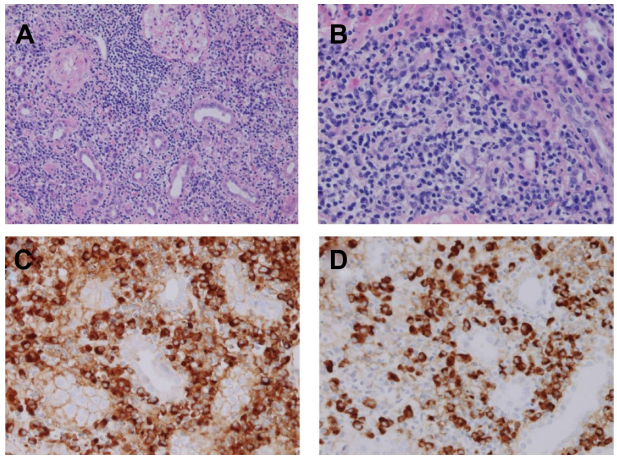

Figure 3. Histopathological features of the renal nodules specimen.
A, **B**: Hematoxylin and eosin staining showing remarkable infiltration of lymphocytes and plasma cells. Magnification: A × 40, B × 100.
C, **D**: Immunohistochemistry for IgG (C) and IgG4 (D)-positive plasma cells. The comparison revealed that the ratio of IgG4 to IgG-positive plasma cells was more than 80%. Magnification: C,D × 200.

Table 2. Diagnostic criteria for IgG4-related hypophysitis.

Criterion 1: Pituitary histopathology Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive celts per high-power field
Criterion 2: Pituitary MRI Sellar mass and/or thickened pituitary stalk
Criterion 3: Biopsy-proven involvement in other organs Association with IgG4-positive lesions in other organs
Criterion 4: Serology Increased serum IgG4 (<140 mg/dl)
Criterion 5: Response to glucocorticoids Shrinkage of the pituitary mass and symptom improvement with steroids
Diagnosis of IgG4-re!ated hypophysitis is established when any of the following is fulfilled: Criterion 1 Criteria 2 and 3 Criteria 2, 4, and 5

inflammation can cause adenohypophysitis and neurohypophysitis simultaneously in IgG4-related hypophysitis.

Our case appears to be very sensitive to glucocorticoid treatment and suggests the possibility of treating IgG4-related hypophysitis successfully with a smaller dose of glucocorticoid.

IgG4-related hypophysitis might be different from traditional hypophysitis in terms of pathogenesis and glucocorticoid treatment response. Further case collection is needed to characterize the nature of IgG4-related hypophysitis.

Author Contributions

YH conceived and designed clinical evaluations of the case. YH and KH analyzed the data. YH and HA wrote the first draft of the manuscript. YA and LK contributed to the writing of the manuscript. YA and LK agree with manuscript results and conclusions. YH, KH, and HA jointly developed the structure and arguments for the paper. YH and HA made critical revisions and approved the final version. All authors reviewed and approved the final manuscript.

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