CASE REPORT

Overlap of Post-obstructive Diuresis and Unmasked Diabetes Insipidus in a Case of IgG4-related Retroperitoneal Fibrosis and Tuberoinfundibular Hypophysitis: A Case Report and Review of the Literature

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Abstract

The clinical picture of IgG4-related disease (IgG4-RD) is diverse because various organs can be affected. We describe the case of a 56-year-old man with acute renal failure and tuberoinfundibular hypophysitis due to IgG4-RD. Steroid therapy lowered the serum IgG4 level and ameliorated renal dysfunction, bilateral hydronephrosis and retroperitoneal fibrosis. However, polyuria from post-obstructive diuresis and unmasked central diabetes insipidus ensued. The patient’s polyuria continued despite the administration of a therapeutic dose of glucocorticoid; the patient’s pituitary swelling and anterior pituitary dysfunction were partially ameliorated. The pituitary swelling recurred seven months later. In patients with IgG4-RD, the manifestation of polyuria after steroid therapy should prompt suspicion of post-obstructive diuresis and the unmasking of central diabetes insipidus.

Key words: IgG4-related disease, retroperitoneal fibrosis, pituitary, diabetes insipidus, polyuria, prednisolone

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Introduction

IgG4-related disease has been reported in over 40 different organs (1). The pathologic concept of IgG4-related disease (IgG4-RD) developed from the study of autoimmune pancreatitis cases (2), but IgG4-related sialadenitis, lymphadenopathy, cholangitis, retroperitoneal fibrosis, respiratory tract lesions and hypophysitis have also been reported. IgG4-related lesions may develop in multiple organs synchronously or metachronously (3), and the synchronous affliction of separate organ systems may complicate the clinical presentation.

Retroperitoneal fibrosis is rare in the general population, in which it affects 0.1 in every 100,000 people (4). In contrast, the incidence of retroperitoneal fibrosis among patients with systemic IgG4-RD is approximately 13% (1). Bilateral ureteral stenosis with hydronephrosis due to retroperitoneal fibrosis is a clinical presentation that is highly indicative of IgG4-RD. The first pathologically-confirmed case of IgG4-related hypophysitis was reported in 2007 (5). Since then, around 40 cases of IgG4-related hypophysitis have been reported in the literature; the incidence of hypophysitis in patients with IgG4-RD is assumed to be less than 2% (1). The clinical presentation of IgG4-related hypophysitis often includes central diabetes insipidus, and 48% of IgG4-related hypophysitis cases are reported to show both hypopituitarism and diabetes insipidus (6). In cases with hypopituitarism, diabetes insipidus may not be symptomatic and may be “masked” by adrenal insufficiency due to the vasopressin-dependent and vasopressin-independent impairment of water diuresis during glucocorticoid deficiency (7). In such cases, polyuria becomes apparent after the initiation of steroid replacement therapy.

Typical IgG4-related lesions, including retroperitoneal fibrosis, show a good response to glucocorticoid therapy, at

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least initially. In cases of IgG4-related retroperitoneal fibrosis and obstructive kidney injury, glucocorticoid therapy may resolve the obstruction and initiate a period of temporary increase in the excretion of urine, which is termed post-obstructive diuresis (8).

We herein describe the case of a patient in whom the unmasking of central diabetes insipidus due to IgG4-related infundibulo-hypophysitis occurred at the same time as post-obstructive diuresis. Steroid therapy was promptly and continuously effective in treating the patient’s renal function and initially effective in treating the patient’s anterior pituitary function; however, his pituitary swelling recurred seven months later during the tapering of prednisolone. In contrast, the patient’s central diabetes insipidus did not respond to steroid treatment.

In the present case report, we stress the importance of diagnosing unmasked diabetes insipidus and hypophysitis in IgG4-related post-acute kidney injury (AKI) cases, and also provide a review of the literature describing the recurrence and emergence of hypophysitis during the course of IgG4-RD.

Case Report

A 56-year-old man with a history of brain infarction, diabetes mellitus, and dyslipidemia had suffered from appetite loss and fatigue. The onset of his symptoms occurred one month prior to his admission to our hospital. The patient was first admitted to the urology department of another hospital because a CT scan to investigate the cause of his fever revealed bilateral hydronephrosis. However, his serum creatinine level, which had been 0.81 mg/dL the previous month, increased from 2.54 to 5.94 mg/dL over a one-week period. He was then referred and transferred to our department.

Upon admission, the patient appeared weak and had lost 7 kg of body weight over the previous month. His legs showed pitting edema, and his blood pressure was 129/76.2 mmHg. Mild crackles were audible in the lower right lung. No remarkable abdominal findings or swollen lymph nodes were detected. His serum albumin level and potassium concentration were 2.3 g/dL and 4.9 mEq/L, respectively. A blood gas analysis revealed a normal pH (7.413) with an elevated anion gap (15.8), which was likely due to renal failure and respiratory alkalosis (pCO2: 30.7 mmHg, pO2: 76.2 mmHg, HCO3- 19.2 mEq/L). The serum concentrations of complements were normal, and no autoantibodies related to nephritis or vasculitis were detected. The patient displayed elevated serum concentrations of IgG (2,335 mg/dL) and IgE (617 mg/dL) and a CT image showed findings that resembled retroperitoneal fibrosis, suggesting the presence of IgG4-related disease. His serum IgG4 concentration was elevated (298 mg/dL; reference range: 4.8-105.0 mg/dL).

Furthermore, the patient had low concentrations of thyroid hormones and thyroid stimulating hormone (FT4, 0.57 ng/dL; FT3, 1.46 pg/mL; and TSH, 0.085 μU/mL), hypoglycemia (129 mEq/L) and hypoglycemia (60 mg/dL, venous plasma). The patient’s elevated HbA1c (6.7%) value and the fact that his sole antidiabetic medication was dipeptidyl peptidase-4 inhibitor suggest that the main cause of the patient’s hypoglycemia may have been adrenal insufficiency. His adrenocorticotropic hormone (ACTH) (<2.0 pg/mL) and cortisol (1.4 μg/dL) concentrations were low. The suspected central hypothyroidism and adrenal insufficiency could explain the patient’s chief complaint of appetite loss.

A CT scan on admission revealed bilateral hydronephrosis and a periaortic mass (Fig. 1A and B, respectively). The mass surrounding the aorta appeared to be soft tissue rather than lymph nodes or tumors, suggesting ureteral stenosis due to retroperitoneal fibrosis. The observation of diffuse kidney enlargement on the patient’s CT images was consistent with IgG4-related kidney disease. Contrast enhancement was not performed due to the patient’s renal insufficiency, thus we did not investigate the presence of low-intensity lesions (a typical finding of IgG4-related kidney disease) on contrast-enhanced CT. The pancreas appeared normal. Small lung nodules that could be IgG4-related inflammatory pseudotumors (9) were observed in both lobes (Fig. 1E and F).

After sufficiently ruling out infectious disease, the patient was tentatively diagnosed with IgG4-related disease and hypopituitarism and steroid therapy was initiated with prednisolone (40 mg/day) from the day after admission. Gallium-67 scintigraphy on the fifth day of steroid therapy (Fig. 1G) was negative in the retroperitoneal area and kidneys but positive in the left mandibular gland. The positivity in the mandibular gland suggested the possibility of IgG4-related sialadenitis, but was not explored further because the patient had not exhibited any symptoms that were indicative of the condition. MRI after one week of steroid therapy revealed the significant enlargement of the pituitary stalk and body, with diminished intensity of the posterior “bright spot” on a T1-weighted image (Fig. 2A).

The endocrine findings before steroid therapy revealed clear central adrenal, thyroid and gonadal insufficiency with decreased growth hormone (GH) and insulin like growth factor-1 (IGF-1) concentrations (Table 1). An elevated prolactin level suggested the impairment of dopaminergic inhibition due to the hypothalamus and/or stalk lesions.

After taking oral prednisolone, the patient quickly regained his appetite and strength. He was withdrawn from hemodialysis after only two sessions, and after two weeks of steroid therapy, his serum creatinine level decreased to 1.34 mg/dL, and his TSH and free T4 levels improved to 1.92 μU/mL and 1.13 ng/dL, respectively. Levothyroxine supplementation was not necessary at any time during the course of the patient’s treatment. His diabetes mellitus worsened after glucocorticoid use but was effectively treated with insulin and oral hypoglycemic agents.
In spite of the above-mentioned improvements to the patient’s condition, his patient’s urine volume markedly increased from approximately 2 L/day to 5-7 L/day after two weeks of prednisolone therapy (Fig. 2E). Post-AKI diuresis and the unmasking of central diabetes insipidus were presumed to be the causes of the polyuria with dilute urine. His urine volume was first observed to determine whether it would respond to steroid therapy; however, polyuria and nocturia (once/1-2 h) persisted. The low urine osmolality observed after water restriction (169 mOsm/kg H2O, with an approximately 3% body weight loss) and the increase in urine osmolality after the administration of arginine-vasopressin supported the diagnosis of central diabetes insipidus. Oral desmopressin treatment was initiated, and his urine volume was normalized.

After steroid therapy, the patient’s serum IgG4 concentration responded well, decreasing to 71.6 mg/dL by the third month, which was below the cut-off of 135 mg/dL (Fig. 2E). His TSH concentration fluctuated, with transient decreases as the steroid dose was reduced - it eventually returned to normal levels (Fig. 2E). A pituitary MR image taken after seven weeks of steroid therapy showed the clear amelioration of the pituitary and stalk swellings (Fig. 2B). By the fourth month of steroid therapy, the retroperitoneal mass had diminished (Fig. 1D), and bilateral hydronephrosis and the swelling of the kidneys were completely relieved (Fig. 1C). The patient’s pulmonary nodules had also disappeared, supporting a tentative diagnosis of IgG4-related inflammatory pseudotumor.

However, the patient experienced an asymptomatic pituitary relapse after seven months of therapy after the dose of prednisolone was tapered to 7.5 mg/day. His serum IgG4 reached its lowest level (49.4 mg/dL) in the fourth month and increased to 118 mg/dL in the eighth month. Furthermore, the TSH level also decreased to 0.72 μU/mL the eighth month; however, it remained within the normal range, and follow-up MRI showed the apparent swelling of the pituitary body and stalk (Fig. 2C). Chronological pituitary MR images were suggestive of possible “empty sella-like” atrophy of the anterior pituitary gland after steroid therapy,
while the flare-up might have been mainly on the stalk and the posterior lobe. An endocrinological re-evaluation, which was performed while substituting 0.5 mg/day dexamethasone for prednisolone, confirmed central diabetes insipidus with impaired adrenal, thyroidal, gonadal and GH axes. The patient’s prednisolone dosage was increased to 40 mg/day, and his serum IgG4, TSH, and pituitary enlargement rapidly improved (Fig. 2D).

Discussion

We experienced a case of IgG4-RD with marked polyuria after steroid therapy, which was possibly due to a combination of post-AKI diuresis and central diabetes insipidus being unmasked by glucocorticoid repletion.

The patient presented in the current report was diagnosed as having IgG4-RD and more specifically, as having IgG4-related retroperitoneal fibrosis, infundibulo-hypophysitis, pulmonary inflammatory pseudotumor, as well as possible IgG4-related kidney disease and sialadenitis. Although the current guidelines for the diagnosis of IgG4-RD require the pathological confirmation of IgG4-positive plasma cell infiltration (10), no biopsy was performed in this case due to the presence of hydronephrosis and the patient’s prompt response to treatment. However, retroperitoneal fibrosis and inflammatory pseudotumor are considered to be conditions that are highly suggestive of IgG4-RD (9); moreover, this case fulfilled the diagnostic criteria for IgG4-related hypophysitis proposed by Leporati et al. (11), which includes the response to glucocorticoid therapy as a criterion.

After the commencement of prednisolone treatment, we initially observed the patient’s polyuria without intervention based on the possibility that central diabetes insipidus might also respond to glucocorticoid therapy. However, we found that the glucocorticoid therapy might have little effect on the posterior pituitary function, as none of the eight previously reported cases of IgG4-related infundibulo-hypophysitis recovered from central diabetes insipidus, despite one report

![Image](https://example.com/image.png)

**Figure 2.** Upper panels: Sagittal T1-weighted images of the pituitary gland. A: After nine days of steroid therapy. B: After two months of steroid therapy. C: In the eighth month, when relapse occurred. D: Two weeks after the dose of prednisolone was increased. E: The time-course of urine volume and the serum TSH and IgG4 responses to prednisolone and oral desmopressin treatments. In the ninth month of steroid therapy, dexamethasone was temporarily used in place of PSL so that endocrinological tests could be performed.
Table 1. The Endocrinological Data.

| Day | 2   | 15  | 28   | 246  | Units | Reference range          |
|-----|-----|-----|------|------|-------|--------------------------|
| ACTH| < 2.0 | 9.2 | 3.9  | 2.9  | pg/mL | 7.2–83.3                 |
| Cortisol | 1.4 | 9.5 | 2.4  | 0.2  | μg/dL | 6.2–19.4                |
| GH  | 0.34 | 0.09 | 0.22 | 0.23 | ng/mL | ≤ 3.47                   |
| IGF-1| 27  | 101 | 82   | 62   | ng/mL | 89–237                   |
| LH  | < 0.10 | 0.77 | 3.05 | ≤ 0.10 | mIU/mL | 0.79–5.72 |
| FSH | 1.89 | 2.99 | 8.72 | 2.23 | mIU/mL | 2.00–8.30                |
| Testosterone | < 0.03 | ≤ 0.03 | 0.77 | 0.55 | ng/mL | 1.31–8.71               |
| PRL | 52.19 | 29.85 | 27.49 |        | ng/mL | 4.29–13.69              |
| TSH | 0.085 | 1.92 | 1.39 | 0.333 | μU/mL | 0.50–5.00                |
| FT4 | 0.57 | 1.13 | 0.99 | 0.96 | ng/dL | 0.99–1.70                |

The hypertonic saline loading test results in the eighth month of steroid therapy

- **Time**: 0 minutes
  - **Na**: 142 mEq/L
  - **Urine osmolality**: 292 mOsm/kgH₂O
  - **ADH**: 1.7 μg/mL

The insulin tolerance test results in the eighth month of steroid therapy

- **Time**: 0 minutes
  - **Plasma glucose**: 80 mg/dL
  - **GH**: 0.19 ng/mL
  - **ACTH**: 2.1 μg/mL
  - **cortisol**: 0.2 μg/mL

The CRH, LH-RH, and GHRP-2 loading test results in the eighth month of steroid therapy

| Pre  | Peak   |
|------|--------|
| ACTH | < 2.0  | 13.5  |
| Cortisol | 0.2 | 1.7   |
| GH  | 0.24  | 4.71  |
| LH  | < 0.1  | 0.64  |
| FSH | 2.48  | 8.39  |
| PRL | 27.17 | 33.83 |

Table 2. A Summary of the Reported Cases with a Relapse or the Emergence of IgG4-related Hypophysitis during Steroid Treatment.

| Case | Age   | Sex | 1st episode                  | 2nd episode                  |
|------|-------|-----|------------------------------|------------------------------|
| 1    | 59M   |     | Autoimmune pancreatitis      | Hyphophysitis                 |
| 2    | 75M   |     | Hypophysitis                 | Hypophysitis                 |
| 3    | 71M   |     | Inflammatory pseudotumor     | Hypophysitis                 |
| 4    | 72M   |     | Hypophysitis                 | Hyphophysitis                 |
| 5    | 47M   |     | Lymphadenopathy              | Pituitary mass                |
| 6    | 70M   |     | Retroperitoneal fibrosis     | Sialadenitis                  |
| 7    | 56M   |     | Hyphophysitis                | Retroperitoneal fibrosis     |

| Case | Age   | Sex | Relapse-free interval | PSL dose at relapse | Report |
|------|-------|-----|-----------------------|---------------------|--------|
| 1    | 59M   |     | 5 years               | 5 mg/day            | 19     |
| 2    | 75M   |     | 3 months              | Less than 10 mg/day | 21     |
| 3    | 71M   |     | 2 years               | 7.5 mg/day          | 20     |
| 4    | 72M   |     | not specified          | 10 mg/day           | 21     |
| 5    | 47M   |     | 15 years              | 2 mg/day            | 22     |
| 6    | 70M   |     | 8 years               | 5 mg/day            | 23     |
| 7    | 56M   |     | 8 months              | 7.5 mg/day          | present case |

noting the improvement of a patient’s pituitary and stalk swellings (6). It may be that the posterior pituitary, which consists of neural projections, may be more sensitive to inflammatory and fibrotic changes than other organs; however, this needs to be pathologically confirmed in future studies.

It has been suggested that the anterior pituitary function responds to replacement doses of glucocorticoid hormone or remits spontaneously in some cases of IgG4-related hypophysitis (12). However, the emergence of hypophysitis and relapse has been reported to have occurred under steroid therapy in at least seven IgG4-RD cases, including the present case (Table 2). All of the reported cases involved middle-aged and elderly men, with prednisolone doses of ≤ 10 mg/d. To our knowledge, this is the first case to report the relapse of IgG4-related hypophysitis with compatible pituitary MRI alterations and documented serum IgG4 and TSH fluctuations. As for the future management of our patient, it may be preferable to taper his prednisolone dose more slowly (especially from 10 mg/d), while monitoring his IgG4 and TSH levels. In the case of a future recurrence, rituximab may be an additional therapeutic option because its efficacy in IgG4-RD has recently been reported (13).

In the diagnostic criteria of IgG4-RD, the cut-off serum concentration of IgG4 is 135 mg/dL. Serum IgG4 levels are reported to be normal in some IgG4-related disease cases, especially after the initiation of glucocorticoid therapy, even at a physiological dose (14). It has not yet been established whether serum IgG4 concentration reflects disease activity;
however, in the present case, the serum IgG4 and TSH concentrations seemed to be good markers of hypophysitis activity. Considering that the half-life of IgG4 in patients with IgG4-RD is reported to be 30 days (while that in subjects is reported to be 21 days (15)) it can be assumed that, in the present case, most of the abnormal IgG4 production stopped immediately after the initiation of steroid treatment. The measurement of serum IgG4 before steroid therapy may increase the probability of diagnosing IgG4-RD and enable the monitoring of disease activity based on the individual time-course of the serum IgG4 concentration, which has been included as a criterion in the proposed “IgG4-related disease Responder Index” (16). The accumulation of more data using these tools may help to draw a conclusion on the usefulness of the measurement of the serum IgG4 concentration in the future.

Retroperitoneal fibrosis is the most common IgG4-related manifestation among patients with IgG4-related hypophysitis; previous studies have reported incidence rates of 38% (14) and 45% (17). These may be higher than the rate of retroperitoneal fibrosis among other IgG4-related lesions, which is reported to be approximately 10% (4). Although the pathogenesis of IgG4-related disease remains unclear, environmental factors such as infectious agents are suggested to act as triggers (18), and some subtypes of IgG4-related disease may preferentially affect a certain set of organs. Because retroperitoneal fibrosis and hypophysitis patients often present non-specific symptoms, and because steroid therapy would improve the symptoms of adrenal insufficiency, IgG4-related hypophysitis may initially escape detection. Prolonged polyuria after steroid use should indicate the presence of hypophysitis in cases of IgG4-related retroperitoneal fibrosis.

In summary, we experienced a case of IgG4-RD where marked polyuria occurred due to post-obstructive diuresis and unmasked IgG4-related central diabetes insipidus. The IgG4-related central diabetes insipidus was refractory to steroid treatment. The patient’s serum concentrations of TSH and IgG4 reflected the disease activity. All previously reported cases of IgG4-RD in which hypophysitis relapsed or emerged during steroid therapy have involved men who were receiving prednisolone at doses of ≤10 mg per day at the time of relapse or emergence. As there may be a relatively high incidence of hypophysitis among patients with retroperitoneal fibrosis, central diabetes insipidus should be considered when a patient with IgG4-related disease exhibits polyuria after steroid therapy.

The authors state that they have no Conflict of Interest (COI).

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