

Treatment Response to Idiopathic Retroperitoneal Fibrosis-associated Hydronephrosis With a Focus on IgG4/IgG3 Serum Concentration Ratio

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Objective. Hydronephrosis, a common complication of idiopathic retroperitoneal fibrosis (iRPF), may lead to poor renal outcomes unless resolved in a timely manner. IgG4-related diseases characterized by elevated serum IgG4 levels are responsible for a few iRPF cases. However, the underlying immunologic features of most iRPF cases have not been clearly defined, and these cases exhibit varied responses to medical treatment. Thus, we investigated the predictive factors for hydronephrosis-associated outcomes among iRPF patients. **Methods.** We retrospectively included 18 iRPF patients with hydronephrosis in a tertiary referral hospital from 2012 to 2019. Hydronephrosis improvement was assessed on images taken 6 months after diagnosis. Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were compared using Mann-Whitney U-test. **Results.** On follow-up images, 8 patients (44.4%) showed an improvement in hydronephrosis. Patients with improvement more frequently had reverse serum IgG4/IgG3 ratio (87.5% vs. 30%, $p=0.025$), abdominal aorta involvement (87.5% vs. 30%, $p=0.025$) and glucocorticoid treatment administration (87.5% vs. 30%, $p=0.025$) than those without improvement. The proportion of elevated serum IgG4 level did not differ between the two groups. Even in the 14 cases with normal serum IgG4 levels, reverse serum IgG4/IgG3 ratio was more frequently observed in patients with improvement than in those without improvement (83.3% vs. 12.5%, $p=0.026$). **Conclusion.** The reverse serum IgG4/IgG3 ratio was associated with hydronephrosis improvement in iRPF patients, suggesting it to be a suitable serologic marker for predicting favourable responses to glucocorticoid treatment. (*J Rheum Dis* 2021;28:38-44)

Key Words. Immunoglobulins, Retroperitoneal fibrosis, Hydronephrosis, Glucocorticoids

INTRODUCTION

Retroperitoneal fibrosis (RPF) is a rare fibro-inflammatory disease in which inflammation occurs and fibrous tissues develop around the abdominal aorta and other retroperitoneal structures [1]. Ureteral involvement has been reported in 80%~100% of the cases at presentation, occasionally causing hydronephrosis [2]. To prevent the progression to a chronic renal complication, early resolution of hydronephrosis is essential.

RPF is categorized as secondary or idiopathic causes [3]. Secondary causes of RPF include infection, drug use, malignancy, radiation therapy and abdominal operation. Idiopathic RPF (iRPF) accounts for two-thirds of the reported RPF cases and can be divided into two groups: IgG4-related RPF and non-IgG4-related RPF [4]. Pathological confirmation can help identify IgG4-related RPF and determine the treatment strategy. However, in many cases, it is difficult to obtain sufficient tissues owing to the location of fibrosis and high risks associated with open

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biopsy. Furthermore, to date, there are no validated clinical tools for assessing the characteristics and outcomes of iRPF [5-8].

Serum IgG4 concentration is one of the criteria for classifying IgG4-related diseases [9,10]. Considering that iRPF and IgG4-related diseases share some histopathological features including irregular fibrosis and lymphoplasmacytic infiltration, the utility of serum IgG subclasses can also be investigated in iRPF [11,12]. IgG is a major antibody in humoral immune response and it consists of four subclasses: IgG1, IgG2, IgG3 and IgG4 [13]. Among healthy adults, the concentrations of IgG subclasses in serum decreases according to their sequential order, i.e., IgG1 comprises 60%~70% of the total IgG content; IgG2, 20%~30%; IgG3, 5%~8% and IgG4, 1%~4% [14,15]. A reverse serum IgG4/IgG3 ratio has been suggested to be one of the characteristics of IgG4-related diseases that distinguishes it from primary sclerosing cholangitis [16]. However, there was no data regarding the association between serum IgG subclasses and iRPF. Here, we aimed to investigate the tools for predicting hydronephrosis-related outcomes in non-IgG4-related iRPF using clinical features and serum IgG subclasses.

MATERIALS AND METHODS

Study population

The study included 18 iRPF patients with hydronephrosis from January 2012 to June 2019 in a tertiary referral hospital in South Korea. iRPF was diagnosed by the typical presentation of clinical characteristics and imaging findings on computed tomography (CT) or magnetic resonance imaging (MRI) [17,18]. Patients with IgG4-related disease fulfilling the 2019 classification criteria or secondary causes of RPF such as a history of radiation therapy, abdominal operation, malignancy or infection were excluded [9]. Biopsy was performed in cases with atypical presentation of iRPF to exclude secondary causes of RPF. Patients with hydronephrosis caused by ureter stone, malignancy or infection were also excluded from this study. This study was conducted in accordance with the Declaration of Helsinki principles. This study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2019-1344). The requirement for informed consent was waived because of the retrospective design.

Baseline measurements and outcome

We retrospectively reviewed the baseline clinical characteristics at the time of diagnosing hydronephrosis, including age, symptoms, smoking habits and comorbidities. The laboratory findings including serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count were recorded. Serum levels of IgG subclasses such as IgG1 (reference value: 365~941 mg/dL), IgG2 (reference value: 165~545 mg/dL), IgG3 (reference value: 32~116 mg/dL) and IgG4 (reference value: 6~121 mg/dL) were also measured while diagnosing hydronephrosis.

Hydronephrosis, defined as dilatation of the drainage system of the kidney such as the calyces, infundibular and pelvis, was confirmed by assessing the images obtained via CT and MRI [19]. Medications such as glucocorticoid and methotrexate were documented. Surgical intervention included ureteral stenting, percutaneous nephrostomy and an open surgical procedure.

To assess the early outcomes of hydronephrosis, we reviewed hydronephrosis status on follow-up images taken 6 months after diagnosis. We used the Society of Fetal Urology (SFU) classification to assess the degree of hydronephrosis, and defined the improvement of hydronephrosis as a complete or partial improvement of all hydronephrosis in a patient (a reduction by at least 1 SFU grade) [20]. Patients were classified into two groups for evaluating the factors associated with the outcomes: patients with or without an improvement in hydronephrosis at 6 months.

Statistical analysis

Variables were represented as median (interquartile range [IQR]) values for continuous variables and number (%) for categorical variables. Chi-square test or Fisher's exact test were used to assess the differences among categorical variables. Continuous variables were compared using Mann-Whitney U-test. Univariate logistic regression analysis was conducted to assess odds ratio (OR) and 95% confidence interval (CI) for the improvement of hydronephrosis. p-values of <0.05 were considered to be statistically significant.

All analyses were conducted using IBM SPSS Statistics for Windows v25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical and laboratory characteristics

The clinical and laboratory characteristics of 18 iRPF patients at the time of hydronephrosis presentation are summarized in Table 1. Abdominal aorta involvement was most frequently observed, as identified in 10 patients (55.6%). Six patients (33.3%) exhibited ureter involvement alone. The median serum creatinine level was 1.07

(IQR 0.82~2.54) mg/dL; median ESR and CRP levels were 52 (IQR 21~64) mm/h and 0.63 (IQR 0.23~5.11) mg/dL; median serum IgG1, IgG2, IgG3 and IgG4 levels were 844 (IQR 734~1,001) mg/dL, 559 (IQR 497~757) mg/dL, 66 (IQR 42~86) mg/dL and 68 (IQR 39~134) mg/dL. Serum IgG4 level was elevated above upper normal limit (UNL) in 4 (22.2%) patients and no patient had a serum IgG4 level of $>5 \times$ UNL. Tissue biopsy was performed in 6 patients using ureteroscopy. Five patients

Table 1. Baseline clinical and laboratory characteristics in iRPF patients according to the short-term outcomes of hydronephrosis

Characteristics	All patients (n = 18)	With improvement (n = 8)	Without improvement (n = 10)	p-value
Clinical characteristics				
Sex, male	14 (77.8)	5 (62.5)	9 (90)	0.275
Age (yr)	62 (54~65)	62 (57~62)	61 (52~67)	0.897
Symptoms	16 (88.9)	7 (87.5)	9 (90)	1.000
Flank pain	7 (38.9)	5 (62.5)	2 (20)	0.145
Abdominal pain	6 (33.3)	1 (12.5)	5 (50)	0.152
Urinary frequency	2 (11.1)	1 (12.5)	1 (10)	1.000
Leg edema	4 (22.2)	1 (12.5)	3 (30)	0.588
Smoker	11 (61.1)	5 (62.5)	6 (60)	1.000
Diabetes mellitus	2 (11.1)	0 (0)	2 (20)	0.477
Hypertension	10 (55.6)	4 (50)	6 (60)	1.000
Hydronephrosis				
Right	17 (94.4)	7 (87.5)	10 (100)	0.444
Left	15 (83.3)	7 (87.5)	8 (80)	1.000
Bilateral	14 (77.8)	6 (75)	8 (80)	1.000
Distribution of involvement				
Ureter only	6 (33.3)	1 (12.5)	5 (50)	0.152
Abdominal aorta	10 (55.6)	7 (87.5)	3 (30)	0.025
Peritoneum	2 (11.1)	0 (0)	2 (20)	0.477
Laboratory findings				
Serum creatinine (mg/dL)	1.07 (0.82~2.54)	0.98 (0.83~3.56)	1.12 (0.72~2.54)	1.000
GFR (mL/min/1.73 m ²)	76 (23~86)	78 (18~82)	72 (26~95)	0.573
WBC ($\times 10^3/\text{mm}^3$)	7.25 (5.40~8.51)	6.20 (5.13~7.33)	7.85 (6.53~8.61)	0.146
Hemoglobin (g/dL)	11.9 (10.7~13.6)	12.4 (11.7~13.7)	11.1 (10.2~13.1)	0.173
ESR (mm/h)	52 (21~64)	56 (36~61)	32 (16~75)	0.460
CRP (mg/dL)	0.63 (0.23~5.11)	0.66 (0.22~3.05)	0.58 (0.23~10.31)	0.965
Serum IgG subclasses levels (mg/dL)				
IgG1	844 (734~1,001)	902 (798~1,027)	806 (669~951)	0.408
IgG2	559 (497~757)	559 (407~639)	656 (524~960)	0.173
IgG3	66 (42~86)	61 (28~91)	66 (45~87)	0.633
IgG4	68 (39~134)	107 (55~158)	55 (36~134)	0.408
IgG4 > UNL, n (%)	4 (22.2)	2 (25.0)	2 (20)	1.000
Serum IgG subclasses ratios				
IgG4/IgG1	0.08 (0.06~0.13)	0.10 (0.06~0.20)	0.07 (0.05~0.11)	0.315
IgG4/IgG2	0.13 (0.08~0.23)	0.19 (0.13~0.28)	0.09 (0.06~0.15)	0.027
IgG4/IgG3	1.09 (0.69~2.47)	2.06 (1.24~2.51)	0.90 (0.51~1.98)	0.122
IgG4/IgG3 > 1	10 (55.6)	7 (87.5)	3 (30)	0.025

Data are expressed as number (%) or median (interquartile range). iRPF: idiopathic retroperitoneal fibrosis, GFR: glomerular filtration rate, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, UNL: upper normal limit.

showed chronic and/or acute inflammation without meeting the immunostaining criteria. One patient had dense lymphoplasmacytic infiltration with fibrosis, but no obliterative phlebitis and storiform fibrosis, and IgG4 immunostaining was rarely observed. There was no evidence of secondary RPF in histopathology.

Among 18 iRPF patients with hydronephrosis, 8 patients (44.4%) showed an improvement in hydronephrosis 6 months after the diagnosis of hydronephrosis. Complete improvement was observed in 6 of 18 patients (33.3%), and the grade of hydronephrosis at diagnosis was bilateral grade 3 in two, bilateral grade 2 in one, unilateral grade 2 in two and bilateral grade 1 in one patient, respectively. To identify the predictive factors affecting short-term renal outcome of iRPF complicated with hydronephrosis, we compared baseline clinical and laboratory characteristics between with and without improvement patient groups. Abdominal aorta involvement was observed more frequently in the group with improvement than in group without improvement group (87.5% vs. 30%, $p=0.025$).

Median serum IgG4 level (107 [IQR 55~158] mg/dL vs. 55 [IQR 36~134] mg/dL; $p=0.408$) did not differ significantly between the two groups. With regard to the ratios of IgG subclasses, the median serum IgG4/IgG2 ratio was higher in the group with improvement than in the group without improvement (0.19 [IQR 0.13~0.28] vs. 0.09 [IQR 0.06~0.15], $p=0.027$) and the median serum IgG4/IgG3 ratio was not different between the two groups (2.06 [IQR 1.24~2.51] vs. 0.90 [IQR 0.51~1.98], $p=0.122$). However, the group with improvement

showed a higher percentage of serum IgG4/IgG3 ratio of >1 than the group without improvement (87.5% vs. 30%, $p=0.025$).

Treatment modalities for hydronephrosis

At 6 months after diagnosis of hydronephrosis, 14 patients (77.8%) underwent medical or surgical treatment (Table 2). The remaining four patients received no treatment. Ten patients (56.6%) received medical treatment, all of which were treated with glucocorticoid. Methotrexate was administered to 2 patients (11.1%). Twelve patients (66.7%) required surgical treatment, and ureteral stenting was performing in 11 patients (61.1%), percutaneous nephrostomy in 7 patients (38.9%) and ileal ureter operation in 1 patient (5.6%). Four patients (22.2%) received surgical intervention alone without any medication.

On comparing the treatment strategies between the groups with and without improvement, the frequency of glucocorticoid administration was higher in the group with improvement than in the group without improvement (87.5% vs. 30%, $p=0.025$). There was no significant difference in the percentage of cases with surgical intervention between the two groups (75% vs. 60%, $p=0.638$).

Predictors of short-term outcomes of hydronephrosis in iRPF

In univariate logistic regression analysis (Table 3), predictors for the improvement of hydronephrosis were serum IgG4/IgG3 ratio of >1 , abdominal aorta involve-

Table 2. Medical and surgical treatments in iRPF patients according to the short-term outcomes of hydronephrosis

Treatment	All patients (n = 18)	With improvement (n = 8)	Without improvement (n = 10)	p-value
Medical treatment	10 (56.6)	7 (87.5)	3 (30)	0.025
Glucocorticoid	10 (56.6)	7 (87.5)	3 (30)	0.025
Initial dose (prednisolone, mg/d)*	40 (30~60)	40 (30~50)	60 (30~60)	0.383
Cumulative dose (prednisolone, g)*	2.42 (1.81~3.69)	2.10 (1.51~3.30)	3.67 (1.91~4.27)	0.383
Duration of treatment (mo)*	4.5 (2.3~6.0)	4.2 (2.1~5.1)	6.0 (4.5~6.0)	0.183
Methotrexate	2 (11.1)	2 (25)	0 (0)	0.183
Surgical intervention	12 (66.7)	6 (75)	6 (60)	0.638
Ureteral stenting	11 (61.1)	6 (75)	5 (50)	0.367
Percutaneous nephrostomy	7 (38.9)	3 (37.5)	4 (40)	1.000
Open surgical procedure	1 (5.6)	0 (0)	1 (10)	1.000
Surgical intervention only	4 (22.2)	1 (12.5)	3 (30)	0.588

Data are expressed as number (%) or median (interquartile range). iRPF: idiopathic retroperitoneal fibrosis. *In patients treated with glucocorticoid.

Table 3. Univariate logistic regression analysis for the predictors of hydronephrosis improvement in iRPF patients

Variables	Odds ratio	95% confidence interval	p-value
Serum IgG subclasses ratios			
IgG4/IgG1	1.91	0.0001 ~ 19,917.22	0.891
IgG4/IgG2	11,025.95	0.13 ~ 974,570,479.54	0.109
IgG4/IgG3	1.20	0.69 ~ 2.10	0.523
IgG4/IgG3 > 1	16.33	1.35 ~ 197.77	0.028
Glucocorticoid treatment	16.33	1.35 ~ 197.77	0.028
Abdominal aorta involvement	16.33	1.35 ~ 197.77	0.028

iRPF: idiopathic retroperitoneal fibrosis.

ment and glucocorticoid treatment (OR 16.33, 95% CI 1.35 ~ 197.77, $p=0.028$, respectively). However, serum IgG4/IgG2 ratio was not significantly associated with an improvement in hydronephrosis (OR 11,025.95, 95% CI 0.13 ~ 974,570,479.54, $p=0.109$).

Four patients with a serum IgG4 level above UNL showed an obvious serum IgG4/IgG3 ratio of >1 . Interestingly, when we analysed 14 patients with a normal serum IgG4 level, 6 patients (42.9%) showed an improvement in hydronephrosis and the proportion of patients with a serum IgG4/IgG3 ratio of >1 was higher in the group with improvement than in the group without improvement (83.3% vs. 12.5%, $p=0.026$). Furthermore, the median serum IgG4/IgG3 ratio was also higher in the group with improvement than in the group without improvement (1.73 [IQR 0.97 ~ 2.20] vs. 0.80 [IQR 0.43 ~ 0.96], $p=0.029$).

DISCUSSION

iRPF is generally known to have a good prognosis. However, persistent hydronephrosis may lead to poor renal outcomes including chronic kidney disease and renal atrophy [7,21]. A proper intervention, such as medical and surgical treatments, is necessary for an early relief of ureteral obstruction [22]. In the present study, hydronephrosis improved in almost half of the patients on short-term follow-up, consistent with the iRPF outcome reported in previous studies [23,24]. Besides the clinical features associated with iRPF outcomes, short-term follow-up images revealed that a reverse serum IgG4/IgG3 ratio was also associated with an improvement in hydronephrosis. This pattern was observed even in patients with a normal serum IgG4 level. Thus, our results suggested that the serum IgG4/IgG3 ratio is a marker for predicting the short-term outcomes of iRPF patients with

hydronephrosis.

We found that a quarter of the patients had a serum IgG4 level above UNL which may share the features with IgG4-related RPF. Zen et al. [25] reported that the levels of serum IgG4 and serum IgG4/IgG ratio were higher in biopsy-proven IgG4-related RPF than in non-IgG4-related RPF. Several reports suggested that a high serum IgG4 level was associated with a high disease activity and high relapse rate of IgG4-related disease [26,27]. However, we found that there was no difference in the proportion of patients with a serum IgG4 level above UNL between the groups with and without improvement. Our result was similar to a previous prospective study that failed to demonstrate a significant association between an elevated serum IgG4 level and the success of tamoxifen treatment in iRPF [28].

Little is known about the levels of serum IgG subclasses, except IgG4, in iRPF. Wallace et al. [29] found that 51% of the patients with an active IgG4-related disease had an elevated serum IgG4 level and 26% of the patients had an elevated serum IgG3 level. In our study, serum IgG3 level did not differ between the with and without improvement groups, and the median serum IgG3 levels were 54 mg/dL and 68 mg/dL in the elevated serum IgG4 and normal serum IgG4 groups, respectively. Furthermore, there were only two patients with a serum IgG3 level above UNL, which indicates that a reverse serum IgG4/IgG3 ratio may be useful for predicting renal outcomes in iRPF, especially for patients with a normal serum IgG4 level.

Medical treatment with glucocorticoid was one of the predictive factors that differed between patients with and without improvement. Glucocorticoid administration is considered to be an effective treatment strategy for achieving remission of iRPF [30,31]. Abdominal aorta involvement was also associated with an improvement in hydronephrosis. Previous studies have reported that

IgG4-related RPF tends to show more extra-retroperitoneal manifestations than non-IgG4-related RPF [4,32]. In IgG4-related diseases, patients with a high serum IgG4 level may show multiple organ involvement [27]. Ozawa et al. [33] demonstrated that patients with IgG4-related diseases who had a complication of peri-aortitis had more inflammatory characteristics, including a high serum IgG4 level, than those who did not have periaortitis. Based on these previous results, glucocorticoid response and the presence of abdominal aorta involvement in iRPF patients with ureter involvement may suggest that patients are affected by the similar mechanisms of IgG4-related RPF.

This study had several limitations. First, because of the retrospective nature of the study, clinical data available may have been limited. Second, despite the rarity of this disease, a limited number of cases was not enough for performing multivariate logistic regression analysis to verify the factors associated with the disease outcomes. Finally, tissue biopsy was not performed in all patients, which makes it difficult to define exclusion of IgG4-related RPF. However, investigating the utility of a clinical predictor is valuable in itself because of the challenges in obtaining pathological information in a real clinical setting.

CONCLUSION

Reverse serum IgG4/IgG3 ratio, glucocorticoid treatment and involvement of the abdominal aorta was associated with a favourable renal outcome in iRPF patients with hydronephrosis. With regard to the predictors related to the prognosis of iRPF with hydronephrosis, the serum IgG4/IgG3 ratio might be a useful marker.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Y.G.K. and B.S.H. were involved in conception and design of study. S.J.C. and Y.G.K. were contributed to acquisition, analysis and interpretation of data. All authors were involved in drafting and revising the manuscript critically for important intellectual content and final approval of the version to be published. J.S.O., S.H., C.K.L., and B.Y. participated in the acquisition of data.

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