



ORIGINAL ARTICLE

The size of palatine tonsils cannot be used to decide the indication of tonsillectomy for IgA nephropathy

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Abstract

Background. Tonsillectomy is one of the treatment strategies for immunoglobulin A nephropathy (IgAN). The relationship between the indication of tonsillectomy and the size of palatine tonsils (PTs) in patients with IgAN remains controversial.

Methods. This retrospective cohort study investigated 57 patients with IgAN who underwent tonsillectomy combined with steroid pulse therapy (SPT). They were classified into two groups, the hypertrophy group and the nonhypertrophy group, according to the weight of their excised PTs. The effects of tonsillectomy combined with SPT on clinical remission (CR) and the histopathological findings of PTs were compared between the two groups.

Results. During the mean follow-up period of 45.5 (range 6–133) months, 78.9% of the patients achieved CR (79.3 versus 78.6%, $P = 0.945$) and the baseline serum creatinine doubled only in one patient in the nonhypertrophy group (0 versus 3.6%, $P = 0.491$). No significant difference was observed in the incidence of CR between the two groups by the Kaplan–Meier method ($P = 0.839$). The predictor for CR, identified in Cox proportional hazards models, was baseline proteinuria [hazard ratio 0.14 (95% CI 0.032–0.621) $P = 0.010$]. Although macroscopic pus plugs were observed on the surface of PTs in almost 60% of patients in each group, microscopic pus plugs in the crypt and the enlarged interfollicular area were observed in all patients.

Conclusions. The treatment effect of tonsillectomy combined with SPT and the pathological features of PTs in IgAN were equal, regardless of the size of the PTs. Therefore, the size of PTs should not be included as a factor when deciding the indication of tonsillectomy for IgAN.

Key words: chronic inflammation; hematuria; IgA nephropathy; proteinuria; tonsillectomy

Introduction

Immunoglobulin A nephropathy (IgAN), the most common form of glomerulonephritis worldwide, is characterized by a highly variable clinical course [1]. However, many patients

progress slowly and 30–40% of patients develop end-stage renal failure (ESRF) over a 20-year period from its onset [2].

Although a disease-specific treatment modality of IgAN has not yet been established, tonsillectomy has been considered as

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one of the treatment strategies in Asia, especially in Japan, based on the theory of focal infection [3]. However, tonsillectomy has not been considered outside Asia because of insufficient evidence.

Clinical studies of tonsillectomy for IgAN have been reported since the 1980s, but their observation periods were <10 years and their conclusions varied due to the levels of renal dysfunction and histopathological damage [4–6]. However, in the early 2000s, a retrospective cohort study with a long follow-up of 16 ± 6 years resulted in the first report of a lower incidence of ESRF in a tonsillectomy group compared with a non-tonsillectomy group [7]. Additionally, in a nonrandomized comparative study, Komatsu et al. [8] reported that the normalization rate of urinary findings was higher with tonsillectomy combined with steroid pulse therapy (SPT) compared with SPT alone. A recent randomized control trial (RCT) reported that tonsillectomy combined with SPT was more effective than SPT alone in reducing urinary protein (UP) after 1 year [9].

Despite many reports having been published about tonsillectomy for IgAN, to our knowledge, no studies to date have focused on the size of palatine tonsils (PTs). The relationship between the indication of tonsillectomy and the size of PTs in patients with IgAN has not yet been established. Because of the lack of information concerning the size of PTs in IgAN, most nephrologists tend to consider the small, nonhypertrophic tonsils as nonindicative of tonsillectomy. Therefore, we conducted a retrospective cohort study to evaluate the impact of the size of PTs on the effect of tonsillectomy combined with SPT and the histopathological findings of tonsils.

Materials and methods

Patients

We identified 347 patients with histologically proven IgAN by renal biopsy between September 2003 and November 2005. The histological diagnosis was based on light microscopy and immunohistochemistry findings. Tonsillectomies were performed for the treatment of IgAN in 307 patients by two surgeons using the same operative method between January 2004 and December 2005. We included patients who had undergone SPT within half a year of the operation and who had no immunosuppressive treatment before the surgery. Patients with systemic lupus erythematosus, chronic liver disease, diabetic nephropathy and who were <15 years old were excluded. The final analysis was performed on a group of 57 IgAN patients. According to the median weight of their excised PTs, 57 patients were categorized into two groups: (1) the hypertrophic group, PT weight ≥ 3.0 g ($n = 29$) and (2) the nonhypertrophic group, PT weight <3.0 g ($n = 28$).

The study protocol was approved by the ethical committees in our institution.

Treatment regimens

Tonsillectomies were performed according to the essential elements of the indication criteria by Akagi et al. [10]: (1) definitive diagnosis of IgAN by renal biopsy and (2) renal pathology grade [11] \leq III and serum creatinine ≤ 2 mg/dL. SPT was usually used when active lesions were present in the biopsy specimen. However, this activity is not always represented in the restricted area of a biopsy specimen. Thus, after obtaining informed consent from each patient, for those without apparent active lesions, SPT was also administered for the treatment

target of clinical remission (CR) regarding urinary findings [8], regardless of the degree of proteinuria. The regimen of SPT was intravenous methylprednisolone 0.5 g/day for 3 days for two or three courses, usually followed by oral prednisolone at an initial dose of 0.6 mg/kg on alternate days, with a decrease of 0.1 mg/kg every 2 months. Because of the retrospective nature of this study, the supportive therapy protocol, which included oral medication of renin–angiotensin system (RAS) inhibitor and antiplatelet agents (dipyridamole, diltiazem dihydrochloride), was not predetermined and depended exclusively on individual nephrologists.

Measurements

Baseline characteristics preceding tonsillectomy were collected retrospectively from patients' medical records and included age, sex, body mass index, serum concentration of creatinine, estimated glomerular filtration rate (eGFR), UP excretion, hematuria, serum IgA, systolic and diastolic blood pressure (BP), history of macroscopic hematuria and smoking status. Serum IgA after tonsillectomy was also collected to compare it with the baseline. The hematuria was scored as urinary erythrocytes of 0/high-power field (HPF) (1), 1–4/HPF (2), 5–9/HPF (3), 10–29/HPF (4), 30–49/HPF (5) or ≥ 50 /HPF (6). To determine histological severity, two nephrologists with extensive experience in the diagnosis of IgAN conducted assessments according to the Oxford classification [12, 13]: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S) and tubular atrophy/interstitial fibrosis (T). In addition, the total numbers of glomeruli and global sclerosis, tuft necrosis, cellular crescent, fibrocellular crescent and fibrous crescent were evaluated. We also collected the histopathological findings of PTs (macroscopic and microscopic pus plugs) in addition to the weight of the excised PTs and the scores of the Mackenzie scale. Microscopic pus plugs were evaluated by hematoxylin and eosin–stained sections via light microscopy. Adverse effects of corticosteroid and tonsillectomy, including hospitalization caused by infection, steroid-induced hyperglycemia, gastroduodenal bleeding, mental disorder, surgical therapy for aseptic osteonecrosis, postoperative bleeding and postoperative dysgeusia, were also collected from the medical records.

Outcome

The primary outcome was CR of urinary abnormalities defined as both hematuria and proteinuria remission: three consecutive negative results over a 6-month period in urinary sediment red blood cell count of <5/HPF (hematuria remission) and a proteinuria qualitative reaction of (–) to (\pm) (proteinuria remission) referring to the remission criteria [14]. We also analyzed a secondary outcome: a 50% increase of serum creatinine from baseline.

Statistical analyses

Variables showing a normal distribution were described as means and standard deviations and compared using the Student's *t*-test. Variables without a normal distribution were described as medians and interquartile ranges and compared using the Mann–Whitney *U* test or Wilcoxon signed-rank test. We used the chi-squared test (or Fisher's test) for data expressed as proportions.

The cumulative probability of CR was calculated using Kaplan–Meier methods. The effectiveness of the weight of excised PTs on this outcome was compared using the log-rank test and univariate and multivariate Cox proportional hazards

Table 1. Clinical characteristics of 57 patients with IgA nephropathy

	Hypertrophic group	Nonhypertrophic group	P-value ^a
Number	29	28	
Baseline characteristics at tonsillectomy			
Weight of excised PTs, g	4.01 ± 0.80	2.20 ± 0.42	<0.01
Mackenzie scale	2 (1)	1 (1)	0.002
Age, years	29 (20)	36.5 (19.8)	0.970
Male, n (%)	19 (65.5)	10 (35.7)	0.024
Body mass index, kg/m ²	21.6 (4.7)	22.25 (2.68)	0.689
Serum creatinine, mg/dL	0.74 (0.22)	0.66 (0.26)	0.338
eGFR, mL/min/1.73 m ²	92.8 ± 21.2	81.5 ± 19.9	0.021
Proteinuria, g/day	0.34 ± 0.39	0.36 ± 0.42	0.579
Hematuria	5 (2)	4 (2)	0.074
Serum IgA, mg/dL	325 (138)	306.5 (87.5)	0.192
SBP, mmHg	125.7 ± 17.4	126.1 ± 17.7	0.532
DBP, mmHg	76.0 ± 9.9	76.6 ± 11.2	0.580
History of macroscopic hematuria, n (%)	6 (20.7)	6 (21.4)	0.945
Past/current smokers, n (%)	10 (34.5)	8 (28.6)	0.631
Therapeutic interventions			
Use of RAS inhibitor, n (%)	7 (24.1)	12 (42.9)	0.133
Use of antiplatelet agents, n (%)	14 (48.3)	11 (39.3)	0.494

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Values are given as mean ± SD, median (interquartile range) or number of patients (% of group).

^aAssessed between the two groups using a Student's t-test, Mann-Whitney's U test, chi-squared test or Fisher's test as appropriate.

models. The assumption of constant hazard rates over time was checked by plotting the logarithm of the survivor function against time. The statistical significance level was set at $P < 0.05$. All statistical analyses were performed with the statistical package SPSS for Windows (version 19.0; SPSS, Chicago, IL, USA).

Results

Baseline characteristics

The baseline characteristics of the hypertrophic ($n = 29$) and nonhypertrophic ($n = 28$) groups are described in Table 1. The hypertrophic group had a significantly higher proportion of males (65.5 versus 35.7%; $P = 0.024$) and higher eGFR (mean ± SD = 92.8 ± 21.2 versus 81.5 ± 19.9 mL/min/1.73 m²; $P = 0.021$) compared with those characteristics for the nonhypertrophic group. No statistical difference was observed between the two groups in the use of RAS inhibitor and antiplatelet agents (Table 1). There was no significant difference in the distribution of histological lesions between the two groups (Table 2). Also, no significant difference was observed between the hypertrophic and nonhypertrophic groups in the period from renal biopsy to tonsillectomy (2.75 ± 1.37 versus 2.46 ± 0.96 months; $P = 0.35$).

Outcome events

The mean observation period of the whole cohort ($n = 57$) was 45.5 months, ranging from 6 to 133 months. The frequencies of hematuria remission and proteinuria remission are indicated in Table 3. The mean time to each remission did not differ statistically between the hypertrophic and nonhypertrophic groups [hematuria remission: 7.3 versus 11.3 months ($P = 0.32$); proteinuria remission: 9.4 versus 6.3 months ($P = 0.51$)]. During the follow-up period, 45 patients (78.9%) achieved CR and baseline serum creatinine doubled in one patient (1.8%). No significant difference was observed between the two groups in the

incidence of each endpoint and the time to CR (Table 3). Among the patients achieving CR, none showed persistent reappearance of hematuria and/or proteinuria. Five patients between the 12th and the 82nd month in the hypertrophic group and six patients between the 17th and the 123rd month in the nonhypertrophic group were censored from the study before achieving outcome events. As shown in Figure 1, no significant difference was observed in the cumulative probability of CR by the Kaplan-Meier method between the two groups ($P = 0.839$). Univariate analysis showed that the factors influencing CR were proteinuria, systolic BP, use of RAS inhibitor and use of antiplatelet agents (Table 4). When these four predictors were included in the multivariate Cox proportional hazards model together with the clinically and histologically important predictors (weight of excised PTs, eGFR, diastolic BP, global sclerosis), proteinuria was the only significant predictor [Table 5; HR 0.14 (95% CI 0.032–0.621); $P = 0.010$].

Tonsillar histological findings

Macroscopic pus plugs on the surfaces of PTs were observed in 17 patients (58.6%) in the hypertrophic group and 17 patients (60.7%) in the nonhypertrophic group. However, microscopic pus plugs in the crypt were observed in all patients in both groups. Moreover, an enlarged interfollicular area, considered to be a pathological finding that is specific to PTs of IgAN [15, 16], was also observed in all specimens (Figure 2).

Changes of serum IgA after tonsillectomy

The value of serum IgA after tonsillectomy was measured in 22 patients (75.9%) in the hypertrophic group and 14 patients (50.0%) in the nonhypertrophic group. The values decreased significantly in both groups (Table 6).

Table 2. Baseline histological lesions

	Hypertrophic group	Nonhypertrophic group	P- value ^a
Total number of glomeruli, mean \pm SD	42.6 \pm 14.3	45.2 \pm 14.2	0.751
Oxford classification, n (%)			
Mesangial hypercellularity (M1)	3 (10.3)	7 (25.0)	0.134
Segmental sclerosis (S1)	15 (51.7)	11 (39.3)	0.345
Endocapillary hypercellularity (E1)	6 (20.7)	7 (25.0)	0.698
Tubular atrophy/interstitial fibrosis			
T0:	21 (72.4)	23 (82.1)	
T1:	7 (24.1)	5 (17.9)	0.494
T2:	1 (3.4)	0 (0)	
Additional lesions, n (%)			
Global sclerosis	2 (3)	2.5 (3)	0.823
Tuft necrosis	4 (13.8)	1 (3.6)	0.187
Cellular crescent	2 (6.9)	4 (14.3)	0.318
Fibrocellular crescent	12 (41.4)	11 (39.3)	0.872
Fibrous crescent	9 (31.0)	4 (14.3)	0.116

^aAssessed between the two groups using a Student's t-test, Mann-Whitney's U test, chi-squared test or Fisher's test as appropriate.

Table 3. Distribution of outcome events

	Hypertrophic group	Nonhypertrophic group	P-value ^a
Clinical remission	23 (79.3)	22 (78.6)	0.945
Hematuria remission	27 (93.1)	26 (92.9)	0.681
Proteinuria remission ^b	20 (80.0)	22 (78.6)	0.898
Time to clinical remission, ^c months	11.2 \pm 15.8	12.6 \pm 20.1	0.604
50% increase in serum creatinine	0 (0)	1 (3.6)	0.491
Entire observation period, months	44.0 \pm 35.8	47.0 \pm 36.7	0.621

Values are given as mean \pm SD or number of patients (% of group).

^aAssessed between the two groups using a Student's t-test, chi-squared test or Fisher's test as appropriate.

^bExcluding four patients in the hypertrophic group who showed negative proteinuria at baseline.

^cExcluding 11 patients (5 hypertrophic group, 6 nonhypertrophic group) who were censored without remission after tonsillectomy.

Adverse effect of SPT and tonsillectomy

No significant difference was observed between the hypertrophic group and the nonhypertrophic group in hospitalization caused by infection [$n = 0$ (0%) versus $n = 1$ (3.6%); $P = 0.491$], steroid-induced hyperglycemia [$n = 2$ (6.9%) versus $n = 1$ (3.6%); $P = 0.513$] and postoperative dysgeusia [$n = 2$ (6.9%) versus $n = 0$ (0%); $P = 0.254$]. These adverse effects completely disappeared with adequate therapeutic measures. No patients in either group were diagnosed with gastroduodenal bleeding, mental disorder or postoperative bleeding, nor were surgical therapies for aseptic osteonecrosis required for any patients.

Discussion

To our knowledge, this is the first report to address the quantitative analysis of the size of PTs in IgAN. The major findings of this study are that even small, nonhypertrophic tonsils have similar pathological features to hypertrophic tonsils in IgAN and that the treatment effect of tonsillectomy combined with SPT is equal regardless of the size of PTs. Therefore, the size of PTs is not an issue when deciding the indication of tonsillectomy for IgAN.

Macroscopic pus plugs in the tonsillar lacunae are often observed in patients with IgAN [17]. Practically, macroscopic pus plugs in the tonsillar lacunae can also be observed in patients who had no sign of them 2 or 3 days before. This means that the presence of macroscopic pus plugs is variable in a

relatively short time. Thus the presence of pus plugs on the surface of PTs does not affect the treatment [17]. Even in patients without macroscopic pus plugs, microscopic pus plugs were observed in this study.

Histologically, the tissues of tonsils consist of three microcompartments: the crypt epithelium, interfollicular area and lymphoid follicle [18]. The interfollicular area is an important place where the antigen-specific T cell activation and subsequent T cell-B cell interaction takes place [19]. Kawaguchi et al. [15] and Takechi et al. [16] previously reported that enlarged interfollicular areas of tonsils were characteristic of IgAN. In this study, interfollicular areas were characteristically expanded both in the hypertrophic group and in the nonhypertrophic group. This means that even non-hypertrophic PTs may have immunoreactive power. With regard to response to treatment, no particular differences were observed in the histopathological findings of PTs between patients with and without CR in this study. We were unable to find any other reports concerning this comparison. The PTs of IgAN have specific pathological findings. However, it is still difficult to predict the prognosis after treatment intervention based on the pathological findings of PTs. This point may be a target of future study.

The efficacy of tonsillectomy for reducing the incidence of ESRF was reported by a long follow-up cohort study [7]. However, use of the size of tonsils as a factor of indication for tonsillectomy in IgAN has been controversial. Otolaryngologically, the main indication for tonsillectomy is

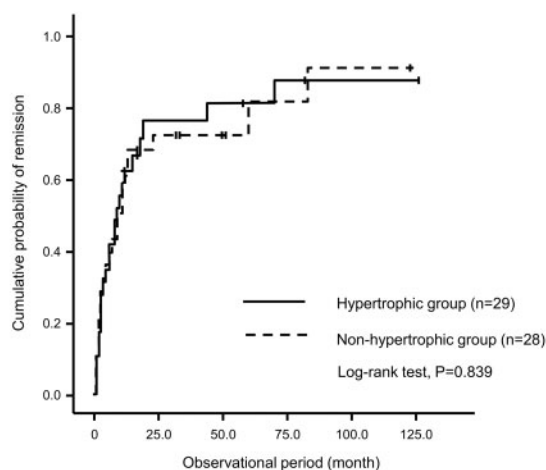


Fig. 1. Cumulative probability of clinical remission by the Kaplan–Meier analysis in the hypertrophic (n = 29, solid line) and nonhypertrophic (n = 28, dashed line) groups. See the text for the definition of each group. Probability was analyzed according to the log-rank test (P = 0.839).

Table 4. Univariate analysis of predictors of clinical remission

Predictors	HR	95% CI	P-value
Weight of excised PTs	0.929	0.701–1.231	0.608
Age	0.982	0.961–1.003	0.098
Male (versus female)	1.027	0.568–1.857	0.930
Body mass index	0.950	0.869–1.038	0.254
Serum creatinine	0.353	0.081–1.542	0.166
eGFR	1.012	0.998–1.027	0.088
Proteinuria	0.120	0.030–0.478	0.003
Hematuria	1.008	0.799–1.272	0.947
Serum IgA	1.000	0.997–1.002	0.908
SBP, mmHg	0.979	0.961–0.998	0.030
DBP, mmHg	0.971	0.943–1.000	0.050
Use of RAS inhibitor	0.339	0.165–0.696	0.003
Use of antiplatelet agents	0.462	0.248–0.861	0.015
Mesangial hypercellularity	0.824	0.367–1.850	0.638
Segmental sclerosis	1.239	0.674–2.278	0.490
Endocapillary hypercellularity	1.363	0.684–2.716	0.378
Tubular atrophy/interstitial fibrosis	0.583	0.283–1.202	0.144
Global sclerosis	0.952	0.858–1.055	0.349
Tuft necrosis	0.639	0.267–1.527	0.313
Cellular crescent	0.989	0.723–1.353	0.944
Fibrocellular crescent	0.912	0.776–1.071	0.261
Fibrous crescent	1.130	0.890–1.436	0.315

SBP, systolic blood pressure; DBP, diastolic blood pressure.

upper airway obstruction due to tonsillar hypertrophy as well as recurrent acute or chronic tonsillitis. Therefore, most nephrologists tend to consider small, non-hypertrophic tonsils as nonindicative for tonsillectomy in IgAN.

Matsutani *et al.* [17] indicated that it was difficult to predict the efficacy of tonsillectomy based on the size of PTs. On the other hand, Tabata *et al.* [20] reported that urinary remission by tonsillectomy was achieved in patients with a higher degree of tonsillar hypertrophy. This inconsistent argument may be due to the subjective method used to evaluate tonsil size. Previous

Table 5. Multivariate analysis of predictors of clinical remission

Predictors	HR	95% CI	P-value
Weight of excised PTs	0.833	0.617–1.123	0.230
eGFR	1.008	0.987–1.030	0.456
Proteinuria	0.140	0.032–0.621	0.010
SBP	0.996	0.961–1.032	0.838
DBP	0.987	0.929–1.049	0.679
Use of RAS	0.552	0.189–1.611	0.277
Use of antiplatelet agents	0.648	0.326–1.292	0.218
Global sclerosis	1.011	0.874–1.170	0.885

SBP, systolic blood pressure; DBP, diastolic blood pressure.

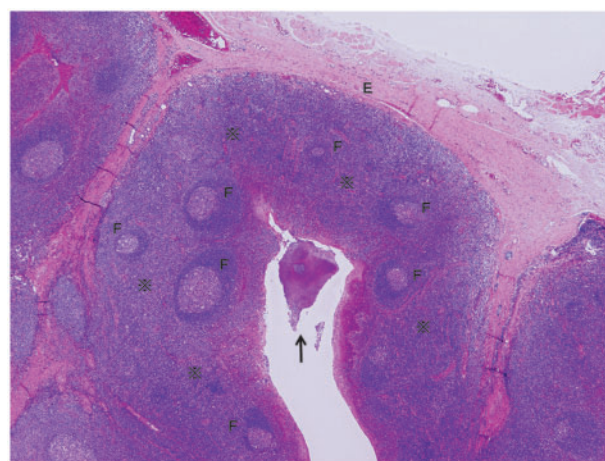


Fig. 2. Microscopic features of palatine tonsils in patients with IgAN. Original magnification $\times 40$. The pus plugs in the crypt (arrow) and the enlarged interfollicular area (asterisks) we are observed in both the hypertrophic group and in the nonhypertrophic group. F: lymphoid follicle; E: crypt epithelium.

studies macroscopically evaluated the size of tonsils using the Mackenzie scale, which is not an absolute measurement. This scale might be influenced by structural variations in the components of the lateral pharyngeal wall. Therefore, we quantitatively evaluated the size of tonsils by measuring their weight.

For evaluation of CR, we used the proposed criteria based on a nationwide opinion survey in Japan [14]. Among the items in the criteria, we used urinary sediment red blood cell count as hematuria remission and proteinuria qualitative reaction as proteinuria remission in this study. The evaluations for hematuria and proteinuria were semiquantitative and qualitative, respectively. We did not use the urine occult blood reaction by test paper and proteinuria amount (g/g creatinine), because the former may induce false positives and negatives [14] and the latter was not evaluated for every outpatient visit among our patients.

Moderate or heavy proteinuria is considered to be a prognostic factor in IgAN. It may be reasonable to assume that the patients included in this study would have a good prognosis even without any specific intervention. However, from the viewpoint of chronic kidney disease, even microalbuminuria is a risk factor of cardiovascular disease [21]. In addition, several studies have demonstrated that 7–20% of IgAN patients with hematuria alone or hematuria coexistent with mild proteinuria show a decrease in renal function over long-term observation [22, 23]. These reports indicate that not only is a larger amount of proteinuria important as a prognostic factor, but that hematuria

Table 6. Changes of serum IgA after tonsillectomy

	At baseline	After tonsillectomy [time from baseline, months]	P-value ^a
Hypertrophic group (n = 22) ^b	302 (168)	248 (138) [35.2 ± 28.8]	<0.001
Nonhypertrophic group (n = 14) ^b	318 (91)	263 (144) [28.4 ± 18.2]	0.012

Values are given as mean ± SD or median (interquartile range).

^aAssessed between the two groups using the Wilcoxon signed-rank test.

^bExcluding 21 patients (7 hypertrophic group, 14 nonhypertrophic group) whose serum IgA was not measured after tonsillectomy.

and/or mild proteinuria are as well. Moreover, achieving CR lightens the patient's burden of regularly attending hospital and taking medicine, which may continue for life. Accordingly, we set a treatment target of 'remission of nephropathy' rather than 'slowing the progression of nephropathy'. We evaluated neither hematuria nor proteinuria alone, but rather both together as a stronger endpoint of CR.

An RCT has shown that SPT is more effective than conventional steroid therapy for long-term preservation of renal function [24]. However, the remission ratio of proteinuria was not significantly high and severe proteinuria reappeared among some of the patients after the cessation of treatment. Additionally, hematuria, which is considered to be a prognostic factor in the early stage of the disease [25], was not evaluated. On the other hand, in a nonrandomized comparative study, Komatsu et al. [8] reported that the normalization rate of urinary findings including hematuria was higher with tonsillectomy combined with SPT compared to SPT alone. Furthermore, a recent RCT reported that tonsillectomy combined with SPT was more effective than SPT alone in reducing UP [9]. IgAN has been considered to be one of the focal infections, like palmoplantar pustulosis. Consequently, the removal of infection would constitute a treatment strategy [3].

Previous studies about the efficacy of tonsillectomy for IgAN have yielded different results owing to the levels of renal dysfunction, histopathological damage and other criteria [4–6]. The follow-up period is also considered to be a such factor. Research that showed negative results in the efficacy of tonsillectomy had a follow-up period of <10 years [6, 26]. Conversely, those that showed positive results had a longer follow-up period. For example, the follow-up period of the report by Agaki et al. [27] was 13 years while that of Xie et al. [7] was 16 years. Although the report by Chen et al. [28], with a follow-up period of 11 years, showed a negative result, they mentioned in their discussion section that 'perhaps a longer follow-up might reveal a statistical significant difference'. Recently, Feehally et al. [29] reported that no significant correlation was found between tonsillectomy and a decline in renal function over a follow-up of 4.7 years in the VALIGA cohort. On the basis of the previous reports, a longer follow-up may be needed for a more proper evaluation. In the (Kidney Disease: Improving Global Outcomes clinical practice guidelines for glomerulonephritis, tonsillectomy is not recommended because no RCT has been performed for IgAN [30]. However, it is difficult to get high-level evidence concerning the efficacy of tonsillectomy with an RCT study because it takes nearly 15 years to evaluate the efficacy of tonsillectomy on the outcome of ESRF [7].

The two main pathways for the pathogenetic mechanisms of IgAN, upstream and downstream, have been proposed as an action mechanism of this combination therapy [31]. The 'upstream' pathway is continuous antigenic stimulation of the innate immune system by the tonsillar mucosa via the mucosa-bone marrow axis. In the 'downstream' pathway, the anomalously stimulated immune response in bone marrow results in

the production of aberrantly glycosylated IgA1 and its subsequent deposition within the mesangium. Such deposition leads to inflammation in renal glomeruli. From this viewpoint, a tonsillectomy may affect the upstream pathway of the pathogenic mechanism by eliminating antigenic stimuli from the tonsillar mucosa. SPT may influence the downstream pathway of the immunological mechanism by suppressing the abnormal immune response in the bone marrow, inducing inflammation in glomeruli. Therefore, tonsillectomy combined with SPT can have an improved therapeutic effect on IgAN compared with SPT alone, tonsillectomy alone, or neither.

The CR rate of urinary findings by tonsillectomy combined with SPT was 79% after a period of ~45 months. A previous analysis reported that ~60% of patients with moderate or heavy proteinuria who underwent this combination therapy achieved CR [8]. These results indicate that a higher CR rate may be expected in patients with milder proteinuria. It is possible that our results are influenced not only by tonsillectomy combined with SPT but also by combining other drugs such as RAS inhibitor and antiplatelet agents. However, the supportive therapy was not administered to all patients. Thus the main therapeutic factor for this result is tonsillectomy combined with SPT, which all patients underwent.

The age of the hypertrophic group was younger than that of the nonhypertrophic group, but the difference was not statistically significant. The relationship between tonsil size and age has never been elucidated in IgAN. Interestingly, Cahali et al. [32] reported that tonsil volume has a negative correlation with age in patients with obstructive sleep apnea and simple snoring [32]. It may be natural that a longer period of continuously chronic inflammation should induce more atrophy of the tonsillar tissue.

Both the proportion of males and the eGFR levels are completely inconsistent in the two groups. To our knowledge, the association between the two factors and tonsil size has never been investigated, neither in IgAN nor in the healthy population. It is difficult to clarify the reasons for these results in this small study. However, we suspect that differences in age might affect the eGFR.

We evaluated histological severity using the Oxford classification [12, 13]. However, our study included patients with proteinuria of <0.5 g/day, who were excluded in the Oxford classification. Therefore, we evaluated additional lesions due to a new histological classification of IgAN, as proposed by the Special IgAN Study Group of the Progressive Glomerular Diseases Study Committee, organized by the Ministry of Health, Labour and Welfare of Japan [33]. Although some histological lesions, such as cellular crescents and tubulointerstitial changes, are considered to be influential factors for prognosis, no lesions were detected in this study. We suspect that the crescents might respond to treatment by tonsillectomy with SPT and that the tubulointerstitial change, the degree of which was the level of T0 in >70% of patients, was not severe enough to affect prognosis. From the viewpoint of proteinuria and renal function, the

disease activities of the patients in this study look mild. Alternatively, the frequencies of some histological lesions are relatively high considering the clinically mild impression. To interpret such a sham discrepancy, we have to consider two factors: (i) a strong degree of hematuria and (ii) that almost 20% of patients did not reach proteinuria remission despite mild proteinuria. We speculate that relatively high frequencies of some histological lesions may affect these factors.

Only proteinuria was detected as a significant predictor in multivariate analysis. Proteinuria is already a factor that is well-known to influence the prognosis of IgAN [34]. This study indicates that the proteinuria had a significant impact on CR by tonsillectomy combined with SPT even in IgAN with milder proteinuria. No other covariate, such as weight of excised PTs, eGFR, systolic and diastolic BP, use of RAS inhibitor, use of antiplatelet agents and global sclerosis, had an impact. Although eGFR and global sclerosis are considered to be prognostic factors, the reason why these two covariates were not statistically significant may be that they did not range widely in value because the targeted patients in this study had only normal or mild renal dysfunction.

With respect to the limitations of this study, we must consider several issues. First, the average amount of proteinuria was mild, so the included patients are not representative of the IgAN population as a whole. In this study we included only patients who underwent a tonsillectomy before SPT to avoid the effect of steroids on histological tonsillar findings. In patients with moderate or heavy proteinuria, SPT was conducted before tonsillectomy to decrease proteinuria at an earlier time. As a result, the remaining patients who underwent tonsillectomy before SPT had relatively mild proteinuria. The second issue concerns the study population. This was a single-center study and the number of patients was small, including only patients who had undergone a tonsillectomy between January 2004 and December 2005 performed by the same two otolaryngologists, who used the same operative method to avoid technical biases by the surgery. Third, the background factors such as sex and eGFR between the two groups were not strictly equitable because of the retrospective nature of this cohort study. We performed a Cox multivariate analysis to exclude this potential bias. Fourth, treatment results did not come from tonsillectomy monotherapy but instead from tonsillectomy combined with SPT. Because even mild urinary abnormality would be a prognostic factor [21–23], we performed SPT combined with tonsillectomy for the treatment target of CR [8] at an earlier time. Because both the annual health check system and national health coverage [35] in Japan make early referral and treatment intervention possible, the treatment goal has been changing from ‘slowing the progression of nephropathy’ to ‘remission of nephropathy’.

In conclusion, although the present study is not prospective, the treatment effect of tonsillectomy combined with SPT may be equal for IgAN regardless of the size of the tonsils. In addition, nonhypertrophic tonsils have specific pathological features to PTs of IgAN that are similar to hypertrophic tonsils. Therefore, tonsil size should not be included among the factors when deciding the indication of tonsillectomy for IgAN.

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Conflicts of interest statement

None declared.

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