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Original Research Article

The expression of IgG4 in interstitial cystitis in a tertiary care centre- A hospital based prospective study

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Abstract

Introduction: Interstitial cystitis (IC), also known as bladder pain syndrome (BPS), is a chronic inflammatory condition of the bladder with unclear aetiology. Recent research suggests a possible link between IC and IgG4-related disease (IgG4-RD), characterized by plasma cell infiltration and fibrosis.
Aim and Objective: This study aims to assess IgG4 immunostaining in bladder biopsies of Interstitial Cystitis patients and correlate IgG4 expression with clinicopathological findings.
Materials and Methods: A total of 30 bladder biopsy samples were examined prospectively over a two-year span in the Department of Pathology at Jawaharlal Nehru Medical College and KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, KAHER, Belagavi. Immunohistochemical staining for IgG4 was performed, and its expression was correlated with clinicopathological findings.
Result: Among 30 cases, IC was the most common diagnosis (50%). Most patients were aged 31–50 years (36.7%) with a slight male predominance (53.3%). IgG4 positivity was seen in 56.7%, with 50% having elevated serum IgG4. While no strong correlations emerged, higher serum IgG4 showed a trend toward significance ($p = 0.06$).
Conclusion: This study highlights a potential IgG4-related subset of IC, warranting further research to refine diagnosis and targeted immunotherapy.

Keywords: Interstitial cystitis, IgG4, bladder pain syndrome, Inflammation, Immunohistochemistry, Chronic cystitis, Uropathology.

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1. Introduction

Interstitial cystitis (IC) or bladder pain syndrome (BPS) is characterized by persistent inflammation or damage to the bladder wall, resulting in pain, urgency, and frequency of urination.[1,2] The American Urological Association (AUA) defines Interstitial Cystitis as "an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of six weeks duration, in the absence of infection or other identifiable cause".[1,3,4] Despite its prevalence, the exact etiology remains unclear, with autoimmune, genetic, and infectious hypotheses proposed. Previously, bacterial infection was considered the primary cause of the observed changes in interstitial cystitis.[5] A vicious, self-reinforcing cycle of chronic inflammation and recurring damage to the bladder epithelium is the outcome, which is caused by a series of interconnected events.[6,7] Pain is a hallmark symptom for both men and women, including pressure or discomfort.[8,9] Physical examination findings include levator pain and spasm, suprapubic tenderness, and bladder base tenderness on pelvic examination.[8] Symptoms usually vary in intensity but rarely go away complete.[2] Cystoscopy is useful when there is uncertainty about an IC/BPS diagnosis. It helps guide treatment and rule out other conditions like bladder cancer, stones, or foreign bodies.[10] European Society for the Study of Interstitial Cystitis has outlined supportive histologic criteria, which include intrafascicular fibrosis, detrusor mastocytosis (N - 28 mast cells/mm2), formation of granulation tissue and inflammatory cell infiltration.[1,11] According to recent research, IgG4-related disease (IgG4-RD), a fibro-inflammatory systemic disorder marked by high IgG4 levels

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and an increase of IgG4-positive plasma cells in tissues, may be related to a subset of interstitial cystitis (IC) patients.[12] IgG4 is an antibody that has a unique structure and function; in healthy individuals, it makes up less than 5% of total IgG. In a healthy individual, serum IgG4 concentrations may vary by more than 100 times (reference values range from 0.01 to 1.4 mg/dL), however IgG4 levels are frequently constant between individuals. This is in contrast to IgG1, 2, and 3. Complement component (CI) and Fc receptors are faintly bound by IgG4, which is not actively involved in immune activation.[13] A gold standard method for counting IgG4 plasma cells does not exist. A conclusive diagnosis of IgG4-RD involves relationship with the clinical presentation and radiologic findings in along with the identification of histopathologic features with elevated IgG4+ plasma cells on immunohistochemical labelling.[12,14,15]

2. Materials and Methods

The present study was done from January 2023 to December 2024, over a period of two years in the Department of Pathology, Jawaharlal Nehru Medical College and KLE's Dr Prabhakar Kore Hospital and Medical Research Centre, KAHER, Belagavi. Thirty bladder biopsies were analyzed from patients who presented to the Department of Urology with complaints of dysuria, increased frequency, urgency, hematuria, and recurrent urinary tract infections. These patients underwent cystoscopy, and biopsy specimens were submitted for histopathological studies and Immunohistochemistry. The inclusion criteria comprised patients who were confirmed to have IC based on clinical and histopathological findings. However, patients with inadequate biopsy samples, benign bladder lesions, malignant or metastatic bladder conditions were excluded from the study to ensure specificity in the evaluation of IC pathology.

Data collection involved recording comprehensive clinical details of the patients, including demographics, presenting symptoms, and laboratory investigations such as serum IgG4 levels. Histopathological examination of bladder biopsy specimens was performed to assess inflammatory cell infiltration. The severity of inflammatory infiltration was classified into three grades;**Table 1**

Table 1: Grading of inflammation[1]

Grade	Severity	Histopathological description
1+	Mild	Sparse inflammatory cells present without lymphoid aggregates
2+	Moderate	Dense inflammation in less than 50% of the tissue or a single lymphoid aggregate
3+	Severe	Dense infiltration affecting over 50% of the tissue or at least two lymphoid aggregates

Immunohistochemical (IHC) analysis was carried out to detect IgG4-positive plasma cells. IgG4 positivity was identified through brown cytoplasmic staining of plasma cells. The level of IgG4 expression was quantified using a standardized scoring system based on the number of IgG4-positive plasma cells per high-power field (hpf). The scoring system was categorized as follows: Score 0 indicated no IgG4-positive plasma cells; Score 1 represented 1–5 IgG4-positive plasma cells per hpf; Score 2 included 5–30 IgG4-positive plasma cells per hpf; and score of 3 indicated that there were more than 30 IgG4-positive plasma cells observed in each high-power field (hpf).[1]

Statistical Analysis was performed using SPSS software (version 26). Descriptive statistical methods were employed for data summarization, while the chi-square test assessed associations between IgG4 expression and clinicopathological parameters, with Fisher's exact test used when necessary. IgG4 expression and inflammation severity in IC cases were considered significantly correlated when the p-value was less than 0.05.

3. Results

The age of patients ranged from 5-88 years, with the majority (36.7%) belonging to the 31-50 age group (**Table 2**). There was a slight male predominance (53.3% males, 46.7% females).

Table 2: Age wise distribution of cases

Age	Frequency (n)	Percent (%)
<10	1	3.3
10-30	5	16.7
31-50	**11**	**36.7**
51-70	9	30
>70	4	13.3
Total	**30**	**100**

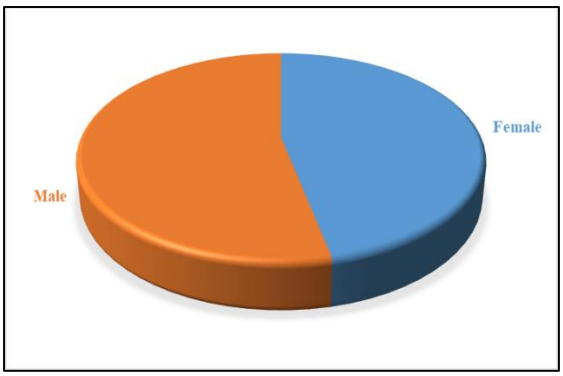

Figure 1: Distribution of cases according to gender

Clinically, lower urinary tract (LUT) symptoms were the most frequently reported complaint (53.3%), followed by hematuria (26.7%). Histopathologically, IC was the most

common diagnosis (50%), followed by chronic cystitis (33.3%) and cystitis cystica glandularis (13.4%).**Figure 3**

Inflammatory grading showed that 76.7% of cases had moderate inflammation (Grade 2+), while no cases exhibited severe inflammation. Immunohistochemically, IgG4 expression was observed in 56.7% of cases, with weak positivity in 43.3%, intermediate positivity in 13.3%, and no cases demonstrating strong positivity. Serum IgG4 levels were elevated (>135 mg/dL) in 50% of cases. **Figure 4**

Correlation analysis showed no significant association between IgG4 intensity and inflammation severity (p = 0.290), but serum IgG4 levels varied significantly across histopathological diagnoses (p = 0.04). The study analyzed IgG4 expression in 15 interstitial cystitis patients based on age, gender, inflammation severity, and serum IgG4 levels. IgG4 positivity was most common in the 31-50 age group, with a slight male predominance. Moderate inflammation had the highest IgG4 positivity, but no significant correlation was found. Patients with higher serum IgG4 levels (>135 mg/dL) were more frequently IgG4-positive, showing a trend toward significance (p = 0.06). Overall, while IgG4 expression varied across groups, no strong statistical associations were observed, except for a possible link with serum IgG4 level.(**Figure 2** ,**Figure 3**, **Figure 4**, **Figure 5**, **Figure 6**, **Figure 7**)

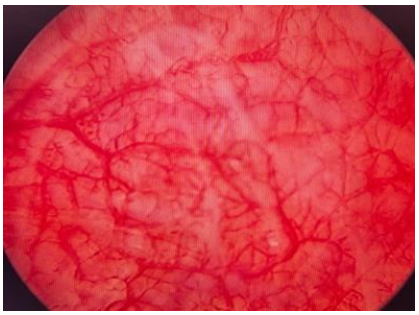

Figure 2: Cystoscopic Image of bladder showing Glomerulations with Prominent Capillaries

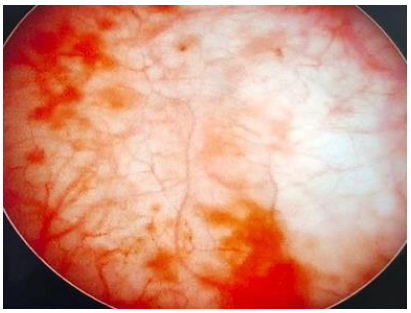

Figure 3: Cystoscopic image of bladder showing glomerulations in multiple quadrants

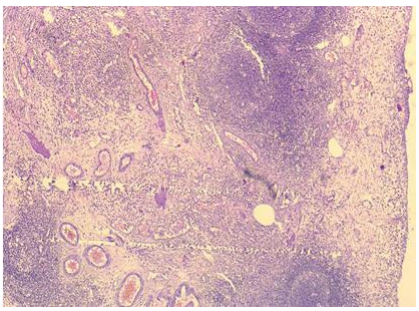

Figure 4: Interstitial cystitis: showing denuded urothelium, lymphoid aggregrates in lamina propria- (H&E; 4X)

Table 3: Cases distribution based on histopathological diagnosis

HP Diagnosis	Frequency (n)	Percent (%)
Interstitial Cystitis	15	50
Chronic Cystitis	10	33.3
Cystitis cystica et glandularis	4	13.4
Eosinophilic Cystitis	1	3.3
Total	30	100

Table 4: Clinicopathologic correlation in 15 patients with interstitial cystitis

		IgG4 Expression status		Total	P-value
		Positive	Negative		
Age	10-30	2	0	2	0.290
	31-50	6	0	6	
	51-70	4	1	5	
	>70	1	1	2	
Total		**13**	**2**	**15**	

Gender	Female	6	0	6	0.215
	Male	7	2	9	
Total		**13**	**2**	**15**	
Grading of inflammation	Mild	3	1	4	0.423
	Moderate	10	1	11	
	Severe	0	0	0	
Total		**13**	**2**	**15**	
Serum IgG4 level	<135mg/dL	10	2	6	0.06
	>135mg/dL	3	0	9	
Total		**13**	**2**	**15**	

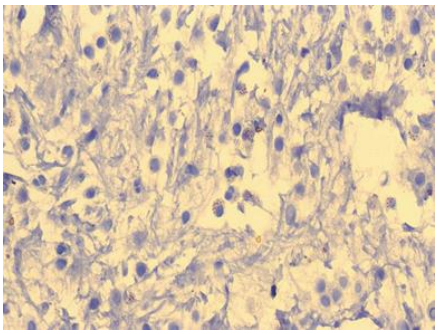

Figure 5: Showing IgG4 positivity in 7-8 plasma cells/hpf (IHC 40X)

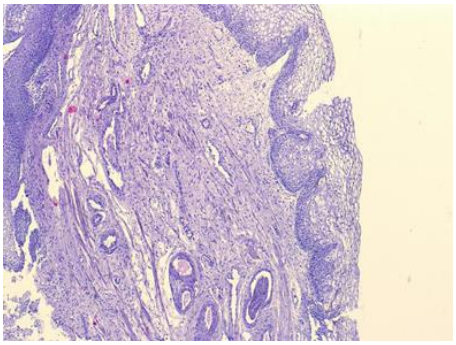

Figure 6: Interstitial cystitis: Showing reactive urothelium, lamina propria is edematous with moderate inflammatory infiltrates- (H&E; 4X)

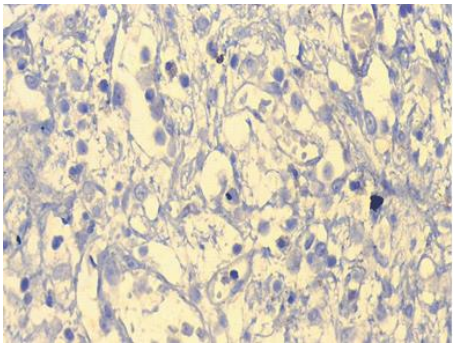

Figure 7: Weak IgG4 positivity in plasma cells (2-3/hpf) (IHC 40X)

4. Discussion

Interstitial cystitis (IC) is a long-term inflammatory bladder condition that causes symptoms such as urinary urgency, increased frequency, and pelvic pain without any underlying infection.[1] Research into the role of IgG4-related disease (IgG4-RD) in IC is gaining attention. IgG4-RD is a systemic condition marked by excessive fibroinflammation, elevated serum IgG4 levels, and infiltration of tissues by IgG4-positive plasma cells. Studies have demonstrated a potential association between IC and IgG4-related inflammation.

Crumley et al. detected IgG4-positive plasma cells in 9.1% of IC cases, whereas in the present study, 56.7% of cases exhibited IgG4 positivity. Unlike Crumley et al., who found IgG4-positive cases predominantly in older individuals(1). Our study identified the highest IgG4 positivity in the 31–50 age group. Additionally, a slight male predominance was observed, consistent with previous findings.

Berry et al. conducted a population-based study on IC prevalence, estimating that only 9.7% of symptomatic women were formally diagnosed. This highlights a gap in IC recognition, which may also apply to IgG4-related IC.[2] The present study, integrating IgG4 staining as a potential marker, could aid in better identifying underdiagnosed cases of IC with an immune-mediated component.

Kim et al. evaluated diagnostic criteria for IC/BPS but did not consider IgG4 involvement.[4] Our findings suggest that IgG4 immunostaining could serve as an additional diagnostic tool. Grover et al. described inflammation as a key factor in IC pathogenesis, correlating persistent inflammation with fibrosis.[6] However, unlike their findings, our study did not report severe fibrosis in IgG4-positive cases, suggesting a less aggressive disease course. Other studies have explored potential inflammatory markers in IC.

Montaño-Roca et al. Highlighted that IgG4-RD frequently affects the urinary system, often mimicking other urologic conditions.[13] While their study emphasized mass-forming lesions, our study found no tumor-like lesions but demonstrated significant IgG4 plasma cell infiltration, suggesting a localized inflammatory process.

Hao et al. conducted a meta-analysis on serum IgG4 levels, indicating that values above 135 mg/dL had high sensitivity for IgG4-RD.[16] In our study, 50% of IC cases exhibited serum IgG4 levels exceeding 135 mg/dL, supporting an IgG4-related immune mechanism.

According to Wallace et al., plasmablasts serve as a reliable diagnostic marker for IgG4-RD, irrespective of serum IgG4 concentrations, indicating a more refined method for diagnosis.[17] Their findings align with the present study, where IgG4 positivity was observed in a significant subset of IC cases, emphasizing its potential diagnostic value.

5. Conclusion

The present study suggest that IgG4-related inflammation play a role in a subset of IC cases. Further large-scale studies and longitudinal follow-ups are required to validate these observations. Implementing IgG4 testing in clinical practice could enhance diagnostic accuracy and guide targeted immunomodulatory therapies for IC patients with IgG4-mediated pathology.

6. Conflict of Interest

None.

7. Source of Funding

None.

8. Acknowledgement

None.

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