



Original Article

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A Prospective Observational Study of the Recurrence Characteristics of Hunner Lesion After Repeated Transurethral Ablation in Patients With Interstitial Cystitis/Bladder Pain Syndrome

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Purpose: The aim of this study was to investigate the rate and pattern of recurrence for patients with Hunner lesion (HL) type interstitial cystitis/bladder pain syndrome (IC/BPS) after transurethral ablation.

Methods: This prospective study included 210 patients with HL type IC/BPS. The primary outcomes were the recurrence rate according to 3 patterns of recurrence: pattern A (according to the relationship with the previous surgical site), pattern B (according to the bladder zone), and pattern C (according to the number of lesions). The secondary outcomes were recurrence-free time after treatment according to pattern A and pattern C.

Results: The pattern A recurrence rate was 50.8% in the same site (A1), 6.7% at a new site (A2), and 42.5% at mixed sites (A3). The pattern B recurrence rate was 10.5% for the anterior wall, 59.0% for the posterior wall, 69.5% for the lateral wall, and 69.0% for the dome area. Multiple lesions recurred as multiple lesions in 75.8% of cases. The pattern C recurrence rate was 10.8% for C1 (single → single), 6.7% for C2 (single → multiple), 6.7% for C3 (multiple → single), and 75.8% for C4 (multiple → multiple). The recurrence-free time in pattern A was 13 months for A1, 12.5 months for A2, and 8 months for A3, with a significant difference between A1 and A3 ($P=0.008$). There was no significant difference in recurrence-free time in pattern C, either with single or multiple HLs.

Conclusions: The distinct recurrence characteristics of HLs was not predictable despite repeated ablations. Complete remission should not be expected because the whole bladder was to have the potential to develop the HLs even after repeated transurethral ablation.

Keywords: Ablation; Interstitial cystitis; Recurrence; Therapeutics

- **Research Ethics:** This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2017-08-005).
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition that is characterized by symptoms of pain perceived to be related to the bladder and associated with lower urinary tract symptoms in the absence of other identified etiologies for the symptoms. According to the European Society for the Study of Interstitial Cystitis classification, one of the phenotypes of IC/BPS includes the presence of Hunner lesion (HL) (type 3). The prevalence of the HL type IC/BPS shows extreme variation, ranging from 3.5% to 56% [1]. The HL type IC/BPS is distinct from non-HL IC/BPS in terms of histopathology, gene expression, and clinical management. HL type IC/BPS is a bladder-centric disease with heavy inflammation, epithelial denudation, and oligoclonal B cell expansion [2].

In the case of HL type IC/BPS, several studies have reported the efficacy of transurethral ablation of HL on pain relief; however, maintenance ranged from few months to 2 years [3]. We performed a prospective observational study with long-term follow-up after transurethral ablation and found that the median recurrence-free time was 12.0 months [4]. Among the methods of endoscopic ablation, we previously investigated whether transurethral resection of HL or coagulation of HL was more effective through randomized trials and found no difference in the efficacy between the 2 treatments [5]. Although transurethral ablation is considered the optimal treatment method, high recurrence rates may still be an issue [4,6-9]. Thus, here we prospectively investigated the recurrence patterns after transurethral ablation and examined the recurrence rates in patients with HL type IC/BPS based on the recurrence patterns.

MATERIALS AND METHODS

Study Design and Patient Population

This prospective observational study was conducted on patients enrolled in the HL type IC/BPS cohort from August 2012 to September 2019. This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2017-08-005). Inclusion criteria included patients >20 years old who were diagnosed with IC with HL on cystoscopy and whose symptoms persisted for more than 6 months. At cystoscopy, HL was identified as a circumscribed, reddened mucosal area with small vessels radiating towards a central scar in the bladder. All enrolled patients with IC with HL underwent endoscopic treatment by a single surgeon. In all cases, we performed transure-

thral resection and/or coagulation with a bipolar loop under spinal or general anesthesia. Follow-up was performed at 1, 3, 6, 9, and 12 months after surgery. After 12 months, patients were advised to schedule a visit if they experienced uncomfortable symptoms. Cystoscopy was performed every 6 months or as symptoms necessitated. Recurrence included both recurrence at the previous ablation site and new lesions elsewhere in the bladder mucosa. The location and number of lesions were examined in cases of recurrence.

Endpoints

The primary outcomes were the recurrence rate according to the following 3 patterns of recurrence. (1) Recurrence pattern A, which was based on the relationship with the previous surgical site: A1 (at the same site): HL occurs on the previous surgical site, A2 (at a new site): HL occurs at a new site, A3 (mixed): HL occurs simultaneously at the same site and at a new site. (2) Recurrence pattern B, which was based on the bladder zone: B1 (anterior wall), B2 (posterior wall), B3 (lateral wall), and B-4 (dome). (3) Recurrence pattern C, which was based on the number of lesions: C1 (single → single): recurrence occurs at a single site after HL ablation of a single site, C2 (single → multiple): recurrence occurs at more than one site after HL ablation of a single site, C3 (multiple → single): recurrence occurs at a single site after HL ablation of more than one site, C4 (multiple → multiple): recurrence occurs at more than one site after HL ablation of more than one site. The recurrence rate in each pattern was assessed at the first recurrence and the second recurrence. The secondary outcomes were recurrence-free time after treatment according to recurrence pattern A and pattern C.

Statistical Analyses

Descriptive statistics for continuous variables and categorical variables are presented as median (interquartile range, IQR) and frequency (%), respectively. For secondary outcomes, continuous variables between the 2 groups were tested by the 2 sample t-test or Wilcoxon rank sum test according to normality, and categorical variables were tested by chi-square test or Fisher exact test. For each point of change compared with baseline, paired t-test or Wilcoxon signed-rank test with Bonferroni correction was performed according to normality of the change. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). All inferences and descriptive P-values are based on 2-tailed tests.

RESULTS

A total of 210 patients enrolled in the study who underwent surgery were subjected to follow-up observation for a median of 31.9 months (IQR, 15.0–49.7 months). The mean patient age was 63.2 years, and the proportion of women was 70.5% (n = 148). In the initial assessment, patients with a single HL accounted for 16.7% (n = 35) while 2 or more HLs were observed in 83.3% of patients (n = 175). The mean number of HLs was 3.0 ± 1.5. After surgery, 57.1% (n = 120) of patients showed recurrence and underwent a second ablation, of which 30.0% (n = 36) had a second recurrence.

For the patients with a first recurrence, the proportion of patients with recurrence pattern A was 50.8% (n = 61) for A1 (at same site), 6.7% (n = 8) for A2 (at new site), and 42.5% (n = 51) for A3 (at mixed site). The proportion of patients with recurrence pattern B was 10.5% (n = 22) for B1 (anterior wall), 59.0% (n = 124) for B2 (posterior wall), 69.5% (n = 146) for B3 (lateral wall) and 69.0% (n = 145) for B4 (dome). The proportion of pa-

tients with recurrence pattern C was 10.8% (n = 13) for C1 (single → single), 6.7% (n = 8) for C2 (single → multiple), 6.7% (n = 8) for C3 (multiple → single) and 75.8% (n = 91) for C4 (multiple → multiple). The recurrence rate according to the 3 recurrence patterns in the patients with a second recurrence are shown in Table 1.

In patients with a first recurrence, the median recurrence time according to recurrence pattern A was 13.0 months in group A1 (IQR, 8.0–21.0 months), 12.5 months in group A2 (IQR, 9.25–20.25 months), and 8.0 months in group A3 (IQR, 7.0–13.0 months). A significant difference was found only between the group A1 and A3 (P = 0.008). Among patients with recurrence pattern C, the median recurrence time was 14.0 months in group C1 (IQR, 11.0–28.0 months), 13.0 months in group C2 (IQR 6.8–26.5 months), 10.5 months in group C3 (IQR 7.0–14.5 months), and 10.0 months in group C4 (IQR 7.0–16.0 months), and there was no statistical difference between groups (P = 0.493) (Table 1).

In cases with a second recurrence, the median recurrence

Table 1. The recurrence rate and recurrence time of Hunner lesions according to 3 recurrence patterns

Variable	First recurrence (n = 120)		Second recurrence (n = 36)	
	Recurrence rate	Recurrence time (mo)	Recurrence rate	Recurrence time (mo)
Recurrence pattern A (relation with previous ablation site)				
A1 (at same site)	61 (50.8)	13.0 (8.0–21.0)	15 (41.7)	26.0 (19.5–29.5)
A2 (at new site)	8 (6.7)	12.5 (9.25–20.25)	1 (2.8)	15.0 (15.0–15.0)
A3 (at mixed site)	51 (42.5)	8.0 (7.0–13.0)	20 (55.6)	12.5 (10.0–19.0)
P (overall)	-	0.008	-	0.006
P (A1 vs. A2)	-	1.000	-	1.000
P (A1 vs. A3)	-	0.008	-	1.000
P (A2 vs. A3)	-	0.397	-	0.566
Recurrence pattern B (bladder zone)				
B1 (anterior bladder wall)	12 (10.0)	-	2 (5.6)	-
B2 (posterior bladder wall)	65 (54.2)	-	18 (50.0)	-
B3 (lateral bladder wall)	87 (72.5)	-	22 (61.1)	-
B4 (bladder dome)	94 (78.3)	-	20 (55.6)	-
Recurrence pattern C (number of Hunner lesions)				
C1 (single → single)	13 (10.8)	14.0 (11.0–28.0)	1 (2.8)	27.0 (27.0–27.0)
C2 (single → multiple)	8 (6.7)	13.0 (6.8–26.5)	4 (11.1)	18.0 (16.0–18.3)
C3 (multiple → single)	8 (6.7)	10.5 (7.0–14.5)	4 (11.1)	16.0 (13.3–19.0)
C4 (multiple → multiple)	91 (75.8)	10.0 (7.0–16.0)	27 (75.0)	15.0 (11.0–26.0)
P (overall)	-	0.493	-	0.742

Values are presented as number (%) or median (interquartile range) unless otherwise indicated.

time according to pattern A was 26.0 months (IQR, 19.5–29.5 months) in group A1, 11.0 months (IQR, 9.25–20.25 months) in group A2, and 12.5 months (IQR, 10.0–19.0 months) in group A3; there was no significant difference between groups. In cases with recurrence pattern C, the median recurrence time was 27.0 months (IQR, 27.0–27.0 months) for C1, 18.0 months (IQR, 16.0–18.3 months) for C2, 26.0 months (IQR, 22.3–29.0 months) for C3, and 15.0 months (IQR, 11.0–26.0 months) for C4; no significant difference was found between groups ($P=0.436$) (Table 1).

DISCUSSION

This is the first observational study to prospectively analyze the recurrence patterns and characteristics of HL through periodic cystoscopic examination in IC/BPS patients. Recurrence of HL was found at the same site as the previous surgical site in the majority of patients including 50.8% of same site only (A1) and 42.5% of mixed site (A3), which was consistent a previous retrospective study [10]. In cases with a second recurrence, the recurrence pattern remained similar even after repeated procedures. In our experience, the area where ablation was performed remained as the central scar, but there were many cases of recurrence in the area around the scar. Since these cases were included as recurrences at the same site, it is considered that the recurrence rate at the same site was high. Although we performed ablation of the HL with sufficient margin during surgery, recurrences frequently occur in the surrounding area, so it is presumed that the tissue surrounding the HL is the site of severe inflammation. Therefore, it may be necessary to secure a wider boundary safety margin.

We previously reported that the median recurrence-free time of HLs after transurethral ablation tends to increase from 12.0 months after the first treatment to 18.0 months after the second procedure [4]. However, it was not possible to distinguish whether the recurrence was a newly developed HL or a recurrence of the previous ablation site. In this study, recurrence in a newly developed HL was about half, including mixed cases, but only 7% of cases where HL was found in a new site unrelated to the previous ablation site. HL type IC/BPS is a chronic and progressive disease and even if endoscopic ablation was performed for HLs that were grossly confirmed, it would not prevent newly developed HLs. There is a possibility that HLs can occur anywhere in the whole bladder mucosa and that these lesions initially appear as normal lesions. The similarity of the immuno-

histochemical characteristics between HL and non-HL in the same patient supported this possibility. This is considered a natural course of IC/BPS with HL disease with the characteristics of pancystitis [2]. In the analysis according to bladder zone, recurrence of HL was mainly observed in the lateral wall and dome area. However, these results also support that recurrence can occur anywhere in the bladder, rather than in a specific area of the bladder.

Interestingly, examination of the recurrence-free time only in cases of recurrence in the same area in this study revealed a tendency to increase from 13.0 months after the first ablation to 26.0 months after the second, so repeated endoscopic ablation may have a role in delaying the recurrence of HLs in the same area (previous ablation sites). Ultimately, we believe that there is a need for an effective intravesical treatment that can prevent recurrence of the entire bladder mucosa at the same or new site after ablation.

Multiple HL seems to have a higher risk of recurrence, but after initial treatment, the recurrence rate of patients with multiple HL was 55% and that of patients with single HL was 60%. Therefore, the extent of the initial lesion itself does not seem to affect the recurrence rate. Previous studies reported that the number of HLs did not affect recurrence [4]. One study indicated that the presence of more extensive HLs was associated with significantly worse voiding symptoms, pain index, and the O'Leary and Sant Symptom and Problem Index scales, and thus patients with multiple HL may have worse symptoms [11]. However, these observations do not indicate that the prognosis of multiple HL is poor. Although multiple HL does not appear to be a risk factor for recurrence, in this study (1) complete ablation was performed under the same conditions regardless of a single lesion or multiple lesions, (2) follow-up was performed periodically, (3) early recurrence of multiple HL was common, (4) we observed a high tendency for recurrence in the previous ablation site, and (5) the majority of patients with multiple HLs showed multiple recurrence patterns. Therefore, it is important to perform complete and thorough ablation of multiple HLs at the time of initial treatment.

The strengths of this study are that this study has a prospective design, with a relatively large sample size and over 31 months of follow-up. Additionally, almost all patients were examined by periodic cystoscopy. However, our study had some limitations. A major limitation is the inability to analyze various factors that may affect recurrence. However, given that surgery and postoperative treatment were performed under the same

protocol at a single institution, all patients received consistent treatment, so it is believed that the time of diagnosis or postoperative treatment did not affect the recurrence pattern itself. We evaluated the extent of HLs by the number of HLs, not the characteristics or distribution. Even single lesions vary in size. In addition, with multiple HLs, the severity/extent of HL was evaluated as the same in cases with the same numbers of HLs; in this case, both cases with the same numbers of focal HLs and large HLs were categorized in the same classification.

In patients with HL type IC/BPS, it was characteristics of recurrence of HL after transurethral ablation that the distinct recurrence pattern was unpredictable despite repeated ablations. Although the time of recurrence is somewhat delayed through repeated procedures, complete remission of HL type IC/BPS should not be expected. Because whole bladder was to have the potential to develop the HLs and HL type IC/BPS is a progressive disease, it is necessary to establish a treatment such as adjuvant intravesical treatment to lower the recurrence rate after transurethral ablation.

AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: *KJK, KL*
- Data curation: *KJK, HJB, SB*
- Formal analysis: *KJK, HJB, SB*
- Methodology: *SB*
- Project administration: *KL*
- Writing - original draft: *KJK, HJB*
- Writing - review & editing: *KJK, KL*

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