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HUNNER TYPE INTERSTITIAL CYSTITIS IS A DISTINCT INFLAMMATORY DISORDER CHARACTERIZED BY EPITHELIAL DENUDATION AND FREQUENT PRESENCE OF LIGHT CHAIN-RESTRICTED B-CELLS, IMPLYING INVOLVEMENT OF IMMUNE RESPONSES IN THE PATHOGENESIS

Hypothesis / aims of study

The pathological investigation of interstitial cystitis (IC) has not been performed in detail, partly due to the purported lack of characteristic pathological findings and the trend to be diagnosed only by clinical findings. In the past, inflammatory cell infiltration, predominantly composed of lymphocytes, plasma cells and denudation of epithelium had been documented as major pathological findings of IC. To investigate pathological features of IC in more detail, we scrutinized these pathological findings in a more objective and accurate manner by applying novel image-analysing software, especially regarding the presence of light chain-restricted plasma cells to explore clonal B-cell expansion.

Study design, materials and methods

Diagnosis of IC was made according to clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome (1). Patients with IC were classified into either Hunner type IC (HIC) or Non-Hunner type IC (NHIC) by the presence/absence of the Hunner lesions on cystoscopy. We performed immunohistochemical detection of infiltrating T-lymphocytes, B-lymphocytes, plasma cells and the amount of residual epithelium using CD3, CD20, CD138 and cytokeratin antibodies respectively. Bladder biopsy specimens were taken from 27 HIC patients (n = 54 in each from the Hunner lesion and background without the Hunner lesion), 39 NHIC patients (n = 39 in petechial hemorrhagic lesion after bladder distension) and 15 non-IC patients with chronic cystitis (n = 8 in noncancerous lesion of bladder cancer and n = 15 in suspicious lesion of bladder cancer, but diagnosed as no-malignancy). In situ hybridization (ISH) for kappa/lambda light chains in plasma cells was also performed in HIC and non-IC cystitis specimens. For digital quantification, density of infiltrating T-lymphocytes, B-lymphocytes, plasma cells, kappa/lambda chain expressing cells was calculated by dividing the number of CD3, CD20, CD138, and kappa/lambda-ISH positive cells by the whole tissue sample area (cells/mm^2) (Fig. 1A). The degree of the epithelial residue was evaluated by the proportion of cytokeratin-positive area to the whole tissue sample area in the same manner (%) (Fig. 1B). We also evaluated clonal B-cell expansion by assessing LCR by ISH. LCR was defined as aberrant kappa:lambda ratio (more than 5.5 or less than 0.7) (2).

Results

Demographics and characteristics of patients with IC are shown in Table 1. Substantial lymphoplasmacytic infiltration was observed in most of HIC specimens, whereas few of NHIC specimens were inflamed (Fig. 2 (A)). The amount of epithelium was smaller in HIC specimens compared with the others (Fig. 2 (B)). Plasma cell ratio in infiltrating lymphocytes was significantly higher in HIC specimens than the others (Fig. 2 (C)). Expansion of light chain-restricted plasma cells was observed in 30% of HIC cases (Table 2), whereas none of non-IC cystitis cases showed LCR in plasma cells. Degrees of either inflammation or epithelial denudation did not correlate with the degree of clinical symptom severity (data not shown).

Table 1. Demographics and characteristics in patients with interstitial cystitis (IC)

	Hunner type IC	Non-Hunner type IC	P value
No. (male / female)	27 (3 / 24)	39 (12 / 27)	1
Mean age at the time of biopsy (years)	68.4 ± 11.4 [38 – 88]‡	56.9 ± 17.6 [20 - 83]	<0.01**
Age at onset of IC (years)	65.1 ± 10.5 [38 - 80]	52.6 ± 17.3 [15 - 81]	<0.01***
OSSI†	13.1 ± 4.1 [7 - 20]	12.1 ± 3.6 [3 - 20]	0.50
OSPI†	11.4 ± 3.8 [3 - 16]	10.9 ± 3.8 [1 - 16]	0.61
VAS†	6.4 ± 2.4 [1 - 10]	6.1 ± 2.9 [0 - 10]	0.93
Urinary frequency	16.3 ± 5.7 [7 - 30]	15.4 ± 7.4 [4 - 42]	0.36
Average voided volume (mL)	106.9 ± 42.7 [40 - 220]	126.8 ± 80.5 [30 - 400]	0.58
Maximum voided volume (mL)	163.8 ± 59.6 [50 - 300]	220.4 ± 111.5 [50 - 500]	0.04*
Maximum bladder capacity at bladder distension (mL) with a pressure of 80 cmH_2O at the time of biopsy	521.2 ± 181.8 [200 - 900]	701.3 ± 179.4 [400 - 1200]	<0.001***

†OSSI / OSPI: O'Leary and Sant's symptom index and problem index, VAS: visual analogue scale (for pain) ‡mean±SD [range]

*P<0.05, **P<0.01, ***P<0.001 significant difference by Wilcoxon rank-sum test

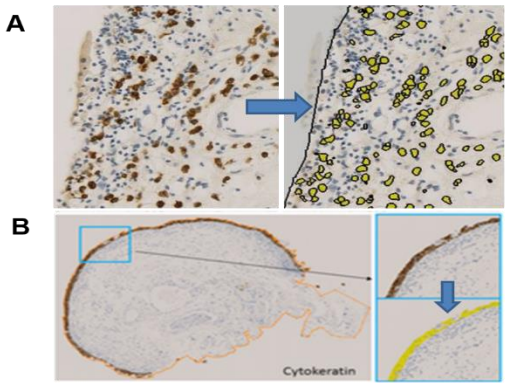
Interpretation of results

The results of this study suggest that HIC is an inflammatory disorder characterized by epithelial denudation and pancystitis, which should be distinctly distinguished from NHIC. The presence of light chain-restricted plasma cells implies clonal expansion of B-cells, which is frequently observed in a variety of inflammatory diseases, especially in association with autoimmunity or chronic infection (3). A B-cell population abnormality may be involved in the pathogenesis of HIC.

Concluding message

HIC is a distinct inflammatory disorder characterized by epithelial denudation and frequent presence of expansion of light chain-restricted B-cells, suggesting involvement of immune responses in its pathogenesis.

Figure 1: Quantification by image analysis software



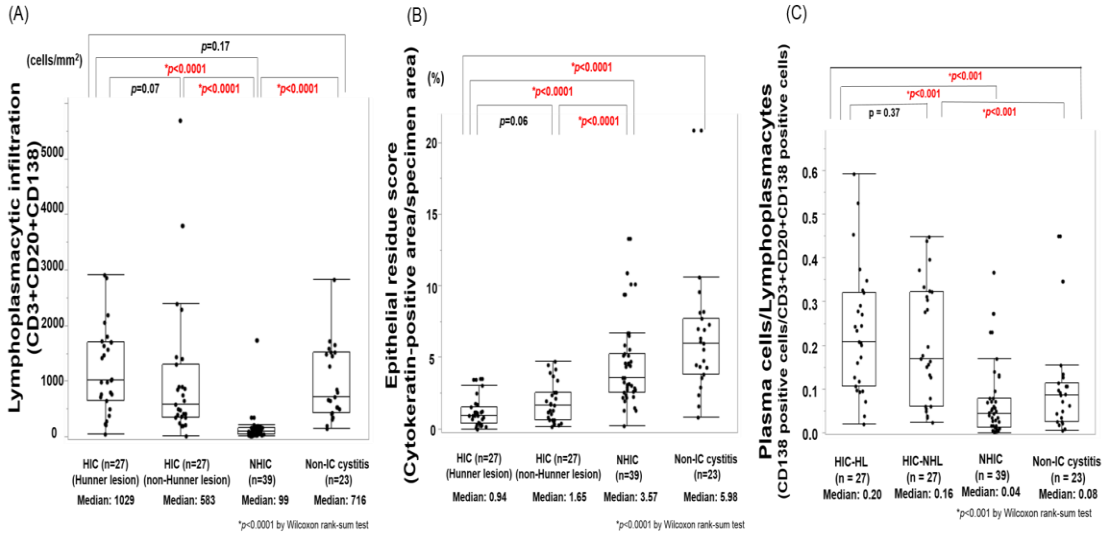
(A) Quantification of CD3-positive cells.
(Left) CD3 immunostaining (in brown)
(Right) Identification of CD3-positive cells (in yellow) by image analysis software
(B) Evaluation of epithelial residue.
(Left) Measurement of whole tissue sample area (circled in orange)
(Upper right) cytokeratin immunostaining (epithelium, in brown)
(Lower right) Identification and measurement of cytokeratin-positive area by image analysis software (in yellow)

Table 2. Light-chain restriction in cases of HIC

Case No. (Sex/Age)	Hunner lesion	Background
Case 1 (F/70)	–	+(λ)
Case 2 (M/73)	–	–
Case 3 (F/63)	–	–
Case 4 (F/80)	–	–
Case 5 (F/83)	–	–
Case 6 (F/68)	ND	–
Case 7 (F/84)	–	–
Case 8 (F/75)	–	–
Case 9 (F/65)	ND	ND
Case 10 (F/75)	–	ND
Case 11 (F/40)	ND	–
Case 12 (F/68)	–	+(κ)
Case 13 (F/81)	–	+(λ)
Case 14 (F/73)	+(κ)	ND
Case 15 (F/74)	ND	–
Case 16 (F/72)	–	–
Case 17 (F/66)	+(κ)	–
Case 18 (F/69)	+(λ)	+(λ)
Case 19 (M/64)	ND	ND
Case 20 (F/71)	–	ND
Case 21 (F/71)	ND	+(λ)
Case 22 (F/73)	–	–
Case 23 (F/88)	–	+(κ)
Case 24 (F/54)	ND	–
Case 25 (M/61)	ND	ND
Case 26 (F/64)	–	ND
Case 27 (F/38)	–	ND

ND: Not Ditected due to the failure of "Kappa and lambda in situ hybridization" or "Light-chain positive cells<50 cells"

Figure 2. Evaluation of inflammatory cell infiltration(A), residual epithelium (B), and Plasma cell ratio in infiltrating lymphocytes (C) by image analysis software



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Disclosures

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