350

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UROTHELIAL DYSFUNCTION AND CHRONIC INFLAMMATION IN PATIENTS WITH CHRONIC INTERSTITIAL CYSTITIS WITH AND WITHOUT HUNNER'S LESION

Hypothesis / aims of study
Interstitial cystitis/bladder pain syndromes (IC/BPS) can be classified into IC with Hunner's lesion and non-ulcer IC subtypes. Cystoscopic hydrodistention usually can easily identify these two IC sybtypes. Previous studies highlighted important clinical and histopathological distinctions between the two subtypes, which have been considered different disease entities. This study was designed to investigate the suburothelial inflammation and urothelial dysfunction between the two IC subtypes.

Study design, materials and methods
Bladder mucosal tissues from 13 patients with ulcer type IC, 35 patients with non-ulcer type IC and 10 control subjects were analysed. The bladder biopsies were obtained randomly from the posterior wall in non-ulcer IC/BPS and the controls. Bladder biopsies were obtained from the margin tissue of the ulcerations in ulcer type IC/BPS. Immunofluorescence stainings of the junction protein E-cadherin, tight junction protein zonula occluden (ZO-1) were carried out. The tryptase levels and TUNEL assay were used to assess mast-cell activation and urothelial apoptosis in the bladder urothelium. The fluorescence intensity of E-cadherin and ZO-1 were measured using the Image J method. The percentages of activated mast cells and apoptotic cells were calculated as positive cells per unit area (4 μm^2).

Results
The urothelial tissues from the overall IC/PBS bladders showed significantly lower expression of E-cadherin and ZO-1. The mean distributions of E-cadherin and tight junction protein ZO-1 were significantly lower in IC/BPS groups. The mean number of activated mast cells, measured by tryptase signals was significantly higher in the IC/PBS groups. However, there was no significant difference in the E-cadherin (p=0.089), ZO-1 (p=0.570) and mast cell activities (p=0.507) between non-ulcer type and IC type IC/BPS (Table 1). TUNEL staining showed a significantly higher mean number of apoptotic cells in IC/PBS than the control groups. When we compared the TUNEL staining between ulcer and non-ulcer IC/BPS groups, ulcer type IC/BPS showed significantly greater apoptotic cells (P=0.016) (Fig.1).

Interpretation of results
This study revealed the urothelial dysfunction markers, including tight junction protein E-cadherin and ZO-1, active mast cells, and TUNEL expression for apoptosis were all significantly different compared with the control group. When we comparing the two IC/BPS subtypes, the apoptotic process was highly activated in the ulcer group. Our previous study had shown the urothelial cell apoptosis in patients with IC/BPS resulted from upregulation of inflammatory signals, including p38 mitogen-activated protein kinase and TNF-α. This study suggests the ulcer type and non-ulcer type IC/BPS might have different pathogenesis of inflammation and phenotype.

Concluding message
Bladder mucosal tissues from both ulcer type and non-ulcer type IC/BPS showed defective junction protein, increased suburothelial inflammation and increased urothelial cell apoptosis. In comparison of two IC/BPS subtypes, increased apoptotic cell was significantly higher in the ulcer type IC/BPS than non-ulcer IC/BPS group.

Table 1. The expressions of E-cadherin, mast cell activities. TUNEL, ZO-1 between the different IC/BPS and control groups

	Ulcer IC/BPS (n=13)	Non-ulcer IC/BPS (n=35)	Control (n=10)	P
E-cadherin	12.72 ± 9.77	24.25 ± 12.62	42.4 ± 16.73	P=0.000
ZO-1	5.37 ± 5.8	4.07 ± 3.55	11.02 ±5.66	P=0.002
Mast cell	5.87 ± 5.17	9.88 ± 7.68	1.25 ± 1.15	P=0.006
TUNEL	3.83 ± 3.21	2.05 ± 1.79	0.08 ± 0.26	P=0.000

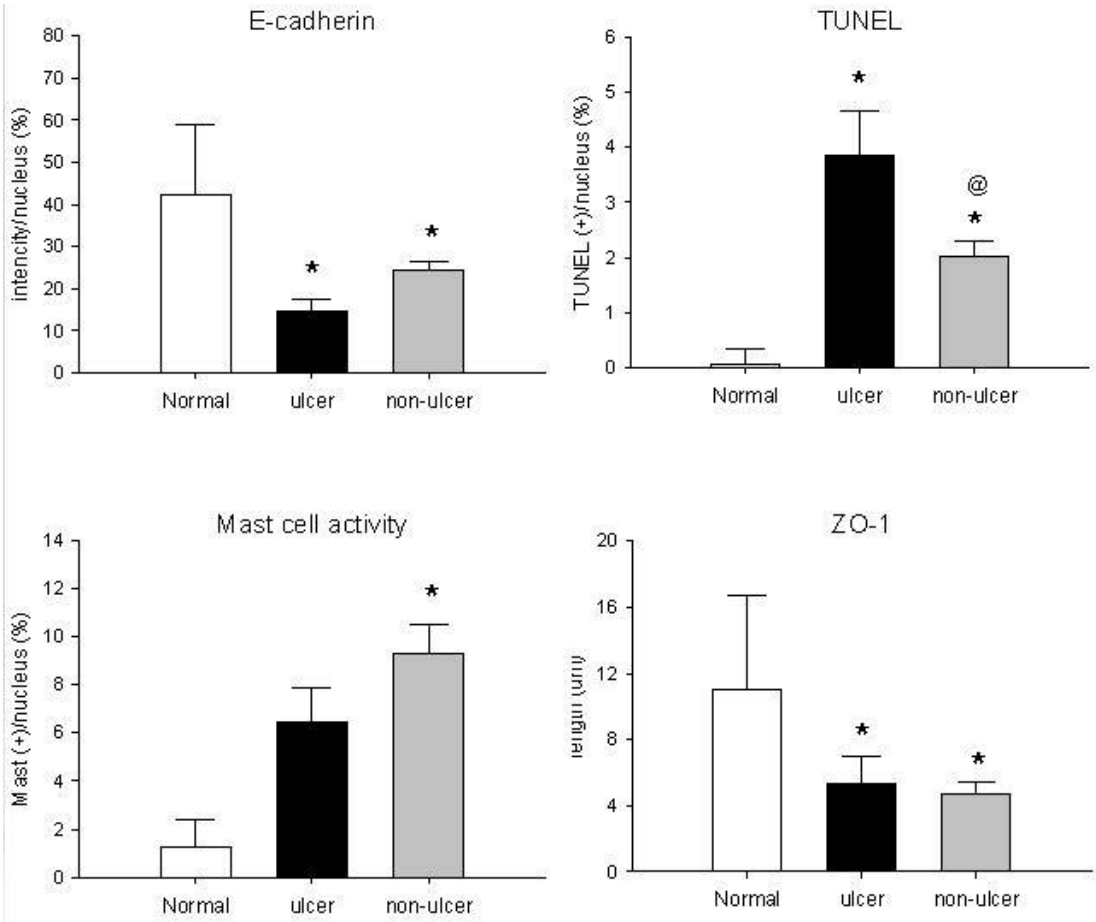

Fig.1. The difference of E-cadherin, mast cell activities. TUNEL and ZO-1 expressions among the different IC/BPS subtypes and control groups. *: indicates significant difference from the control. @: indicates significant difference between ulcer and non-ulcer IC groups.

Disclosures

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