

ELECTRON MICROSCOPIC INVESTIGATION OF INTERSTITIAL CYSTITIS AND KC: ULCER VS NON-ULCER IC AND THEIR CLINICAL CORRELATION

Hypothesis / aims of study

Early studies had revealed some electron microscopic (EM) characteristics of interstitial cystitis (IC) and ketamine cystitis (KC). However, the clinical association is still lacking. The EM urothelium difference between ulcer and non-ulcer IC was also unknown. The aim of current study is to investigate the human IC and KC urothelium characteristics in EM, and further analyze the association between the EM urothelium findings and clinical symptoms severity.

Study design, materials and methods

IC and KC patients who were admission for hydrodistention were enrolled. The IC patients were classified to ulcer and non-ulcer IC according to the cystoscopic finding of Hunner's lesion. The cold-cup biopsy bladder specimens were taken during hydrodistention for transmission EM (TEM) and scanning EM (SEM). In TEM, the urothelium cell layers number, integrity of umbrella cells and tight junction complexes were investigated. In the SEM, the umbrella cell intact, uniform and deep folding were evaluated. All of these EM findings were grading with a 4 point scale (0: normal, 1: mild defect, 2: moderate defect, 3: severe defect). Visual Analogue Scale (VAS) pain score, cystometric bladder capacity (CBC) and maximal bladder capacity under general anesthesia (MBC) in these patients were recorded. Chi-square test was used to evaluate the association between symptoms severity and EM findings. Bladder biopsies were also taken from the patients with stress urinary incontinence and were considered as normal control.

Results

A total of 9 KC and 9 IC patients were enrolled. In the IC patients, the EM revealed inconsistency of umbrella cells size, flattening of umbrella cell folding, decreased urothelium cell layers and tight junctional complexes (figure 1). Widening cell junctions with interdigitation, and red blood cells extravasation from the capillary even before hydrodistention were also found in the IC patients (figure 2). In the KC patients, the EM showed almost totally denuded urothelium and exposure collagen, only little residual urothelial cell could be found. (Figure 1 A and B). In TEM, the KC patients with higher VAS pain score have more severe defect of urothelium cell layers and integrity of umbrella cells ($p=0.018$). The IC patients with more severe VAS pain score have more severe defect of tight junctional complexes in TEM (Table 1.) The CBC and MBC in KC and IC patients were not significantly associated with EM findings. In comparison to non-ulcer IC, the patients with ulcer IC had more microvilli in the umbrella cells (figure 2). The urothelium in ulcer IC have significantly more severe defect in the integrity of umbrella cells and tight junction complexes than that in non-ulcer IC.

Interpretation of results

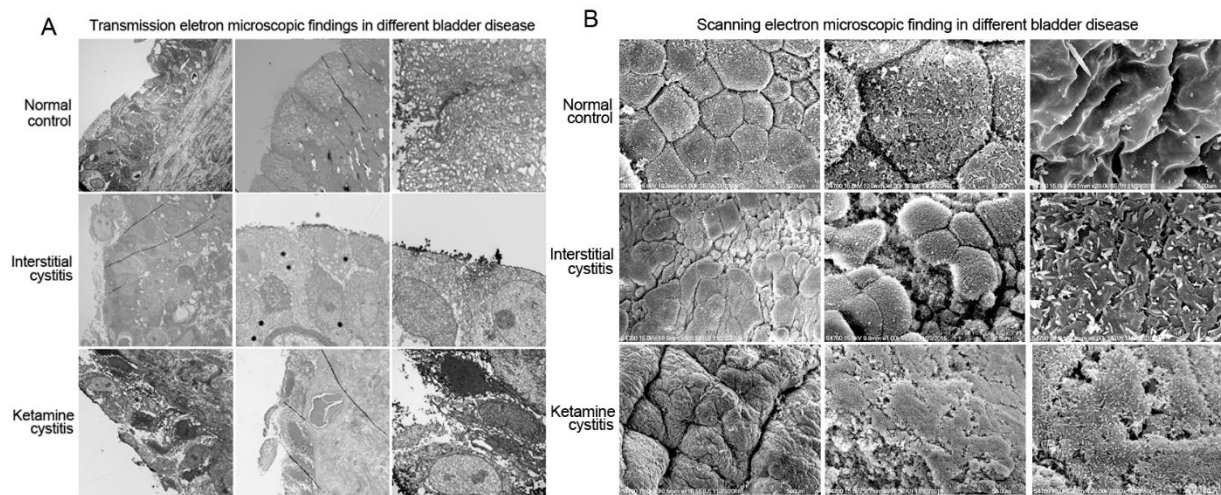
Our EM findings revealed urothelium barrier function defect in the IC patients, including decreased urothelium cell layers and widening of cell junctions. The inconsistency of umbrella cells size and flattening of umbrella cells folding in SEM also suggested an immature urothelium in the IC patients. Patients with ulcer IC had more severe urothelium defect than that in non-ulcer IC. The microvilli in ulcer IC but not in non-ulcer IC suggests more severe inflammation in the umbrella cells. In the patients with KC, almost totally lost of the urothelium and collagen exposure were found in EM. The severity of urothelium defects in TEM but not SEM are significantly correlated with bladder pain in IC and KC patients. But the bladder capacity was not correlated. It suggested the barrier function defect may be direct associated bladder pain, but the bladder capacity may be mainly affected by the pathological change below the urothelium.

Concluding message

In EM, the urothelium defects were found in KC and IC bladders. In comparison the non-ulcer IC, the urothelium defects and inflammation were more severe in ulcer IC. Urothelium defect in TEM may be associated with bladder pain severity in KC and IC patients.

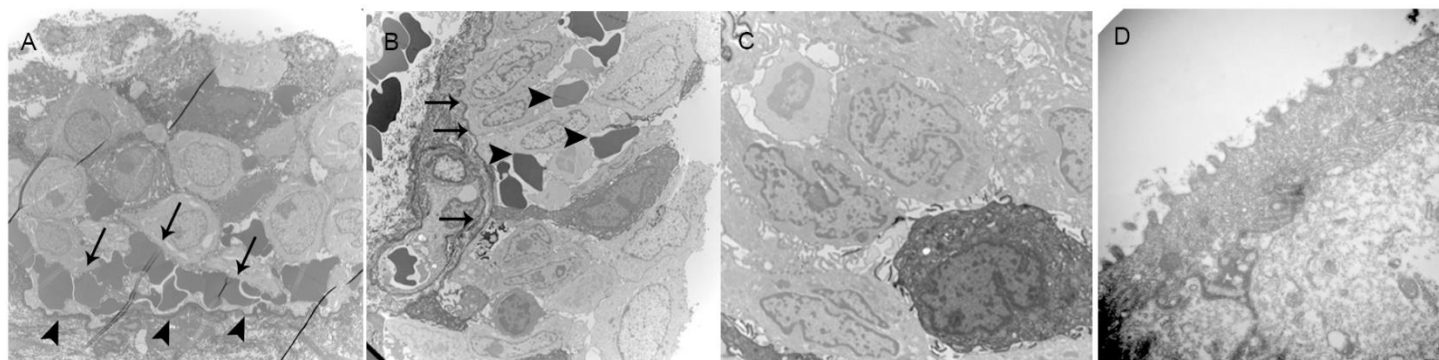
Table 1. TEM findings among patients with different bladder pain

	KC TEM	VAS<6 N=3	VAS>6 N=5	P-value	IC TEM	VAS<4 N=4	VAS>4 N=5	P-value
Urothelium layers defect	cell normal	0	0	0.018	normal	0	1	0.098
	mild	1	0		Mild	2	1	
	mod	2	0	Mod	2	0		
	severe	0	5	severe	0	3		
umbrella cells Integrity defect	normal	0	0	0.018	normal	0	0	0.058
	mild	1	0		Mild	0	0	
	mod	2	0	mod	4	2		
	severe	0	5	severe	0	3		
tight junctional complexes defect	normal	0	0	0.107	normal	1	0	0.029
	mild	0	0		mild	3	0	
	mod	2	0		mod	0	1	
	severe	1	5		severe	0	4	



In the IC patients, TEM and SEM showed inconsistency of umbrella cells size, decreased urothelium cell layers, umbrella cell folding and tight junctional complexes. In the KC patients, the TEM and SEM showed almost totally denuded urothelium and exposure collagen. In most case, only basement membrane and basal cells could be found.

Fig. 1. The urothelium TEM (A) and SEM (B) findings in different bladder diseases



The TEM of IC/BPS urothelium revealed: (A) and (B) red blood cells extravasation (arrowhead) from the capillary before hydrodistention, the location of extravasation was above the basement membrane (arrow), (C) widening cell junction with interdigitation in the urothelium (D) microvilli in the umbrella cells of ulcer IC/BPS urothelium

Fig. 2. The TEM finding of IC urothelium

Disclosures

Funding: none **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation **Helsinki:** Yes **Informed Consent:** Yes