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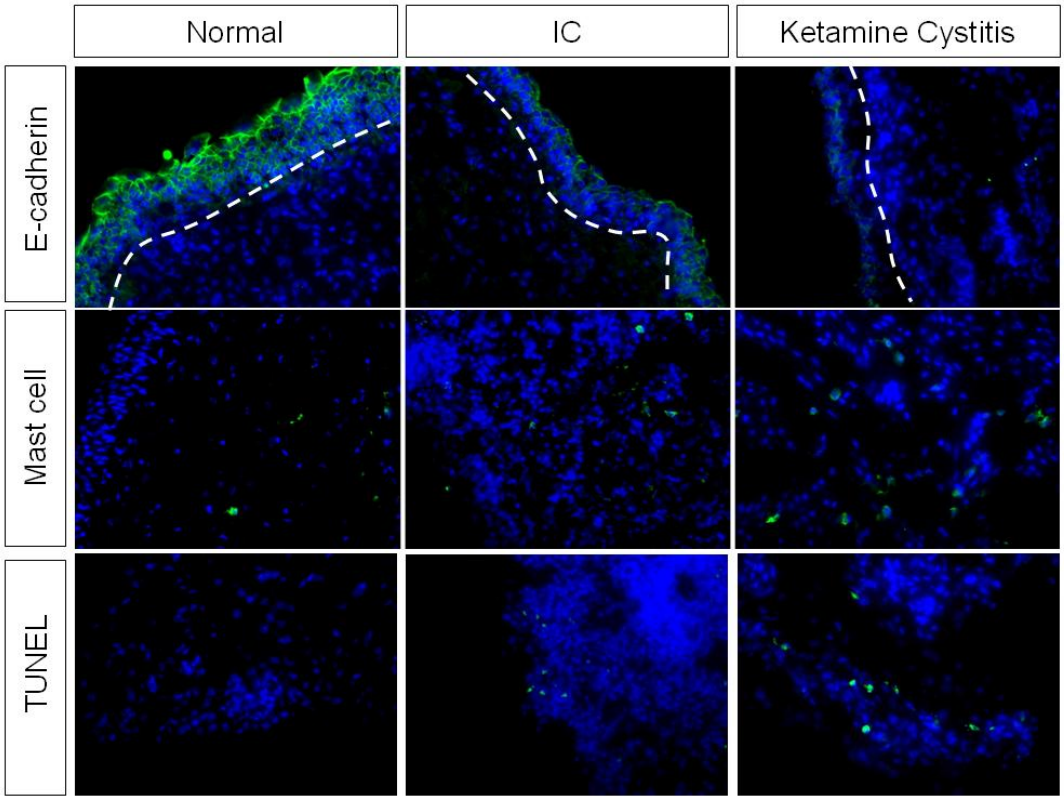
Jiang Y[1], Shie J[1], Chen J[1], Kuo H[1]
1. *Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan*

INCREASED APOPTOSIS AND SUBUROTHELIAL INFLAMMATION IN PATIENTS WITH KETAMINE RELATED CYSTITIS – COMPARISON WITH INTERSTITIAL CYSTITIS AND CONTROLS

Hypothesis / aims of study
Altered urothelial homeostasis and activation of mast cells have been found to be the possible causes of interstitial cystitis/painful bladder syndrome (IC/PBS). Ketamine is an emerging drug abused by Asian youth for recreation. The symptoms of ketamine-related cystitis (KC) included dysuria, urinary frequency, urgency, hematuria, and severe bladder pain with investigations commonly revealing epithelial inflammation, neovascularization, and petechial hemorrhage of the bladder. This study investigated the suburothelial inflammation and urothelial dysfunction in KC and IC/PBS and tried to explore the underlying pathophysiology of KC.

Study design, materials and methods
Bladder tissues from 16 patients of KC, 17 patients of IC/PBS, and 10 female controls were analyzed in this study. Immunofluorescence (IF) staining of junction protein E-cadherin, tryptase (indicating mast cell activation) and TUNEL (indicating urothelial apoptosis) were performed. The fluorescence intensity of E-cadherin was measured using an Image J method. The percentage of activated mast cells and apoptotic cells were measured and quantified as positive cells per area unit (4 μm2).

Fig.1. The differences of E-cadherin expression, mast cell count and apoptotic cell count among the normal controls (normal), patients with IC/PBS (IC) and patients with ketamine related cystitis (KC). KC had a significantly decreased expression of E-cadherin, a significant increase of apoptotic cells, and a non-significantly increased tryptase signal than IC.



Results
The mean age was 25.0 ± 3.8, 41.3 ± 13.7, and 50.5 ± 9.6 years in KC, IC/PBS and controls, respectively ($p<0.05$). In IF staining, both the distribution of E-cadherin in KC (10.1±11.2) and IC/PBS (25.1±16.3) were significantly reduced compared to controls (42.4±16.7) (both $p<0.05$). The fluorescence tryptase signal in KC (6.5±3.7) and IC/PBS (4.6±3.0) were both significantly increased compared to controls (1.3±1.12) (both $p<0.05$). TUNEL staining revealed a significant increase of apoptotic cells in KC (4.4±2.5) and IC/PBS (2.4±1.7) compared to controls (0.1±0.3) (both $p<0.05$). In addition, KC had a significantly decreased expression of E-cadherin ($p= 0.024$), a significant increase of apoptotic cell ($p=0.02$), and a non-significantly increased tryptase signal ($p=0.199$) than IC/PBS. Increased apoptotic cells and decreased expression of E-cadherin were significantly correlated with increased visual analog pain score in overall patients ($p<0.05$). (Fig.1)

Interpretation of results
Defective junction protein of urothelium with urothelial dysfunction, activation of mast cells with suburothelial inflammation, and the increase of apoptosis in the bladder mucosa have been observed and though to be the possible causes of IC/PBS. KC has

the similar histological findings of IC/PBS qualitatively but with more severe urothelial dysfunction and increased apoptosis, which correlated with more severe clinical symptoms. KC was thought to be a more severe form of cystitis, and some progressed into the end-stage bladder manifested with contracted bladder and bilateral obstructive uropathy which were rarely observed in IC/PBS. The pathophysiology of KC and IC/PBS seemed to be different, although they shared the similar qualitative findings in histological and immunofluorescent analysis.

Concluding message

KC and IC/PBS shared the similar findings of defective junctional protein, increased suburothelial inflammation, and increased urothelial cell apoptosis. Decreased expression of E-cadherin and increase of apoptosis were more severe in KC bladders than IC/PBS. These findings correlated with clinical symptoms between KC and IC/PBS, and the pathophysiology of KC and IC/PBS seemed to be different.

Disclosures

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