



ORIGINAL ARTICLE

Study of the apoptotic effect of urine as a diagnostic biomarker in patients with interstitial cystitis[☆]

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KEYWORDS

Interstitial cystitis;
Biomarker;
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Abstract

Introduction: The main objective of the study was to assess the apoptotic effect of urine from patients with interstitial cystitis (IC) in cell cultures and to study its value as a diagnostic biomarker for IC.

Material and methods: A prospective study was conducted between January 2010 and January 2015 and included 57 patients diagnosed with IC and 50 healthy patients from the Hospital Clinic of Barcelona and the La Paz University Hospital. The urine of these patients was exposed to cell cultures, and its ability to induce apoptosis in the cultures was analyzed. Using flow cytometry, we then measured the degree of apoptosis, quantified by the percentage of cells of the cell cycle in phase sub G0.

Results: The cell cultures exposed to the urine of patients with IC had a sub G1 peak and a G2 phase, which was significantly greater than that of the control group, and a significantly lower percentage in the S phase than the control group. The mean apoptosis values in the urine cultures from patients with IC were significantly higher than those of the control group. Using a value >10% of the apoptosis test as a positive result, we observed a specificity of 96% and a positive predictive value of 92%.

Conclusions: The urine of patients with IC exerts an apoptotic effect on tumor cell cultures that is significantly greater than that exerted by the urine of healthy control patients.

A $\geq 10\%$ cutoff for the apoptosis test presented very low sensitivity (40%) but had a very high specificity (96%), thereby able to confirm the diagnosis of IC when positive.

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PALABRAS CLAVE

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Biomarcador;
Diagnóstico
intersticial

Estudio del efecto apoptótico de la orina de pacientes con cistitis intersticial como biomarcador diagnóstico

Resumen

Introducción: El principal objetivo es valorar el efecto apoptótico de la orina de pacientes con cistitis intersticial (CI) en cultivos celulares y estudiar su valor como biomarcador diagnóstico para la CI.

Material y métodos: Estudio prospectivo entre enero de 2010 y enero de 2015, en el que se incluyeron 57 pacientes diagnosticadas de CI y 50 pacientes sanas del Hospital Clínic de Barcelona y del Hospital Universitario la Fe. Se expuso la orina de dichas pacientes a cultivos celulares y se analizó su capacidad para inducir apoptosis en ellos y posteriormente, mediante citometría de flujo, se midió el grado de apoptosis, cuantificado por el porcentaje de células del ciclo celular en fase sub G0.

Resultados: Los cultivos celulares expuestos a orina de pacientes con CI presentan un pico sub G1 y una fase G2, significativamente mayor que el grupo control, y en la fase S presentan un porcentaje significativamente menor al grupo control. Los valores medios de apoptosis en los cultivos de orina de pacientes con CI son significativamente muy superiores a los del grupo control. Para un valor > 10% de la prueba de apoptosis como resultado positivo, se observa una especificidad (96%) y un valor predictivo positivo (92%).

Conclusiones: La orina de pacientes con CI ejerce un efecto apoptótico sobre cultivos celulares tumorales significativamente superior al que ejercen orinas de pacientes controles sanos.

Un punto de corte $\geq 10\%$ para la prueba de apoptosis presenta una sensibilidad muy baja (40%), pero tiene una especificidad muy alta (96%) pudiendo confirmar el diagnóstico de CI cuando es positiva.

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Introduction

The diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) is performed by elimination. Another way of diagnose it is by following the criteria proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1997.^{1,2} However, many patients do not meet NIDDK strict criteria and are finally diagnosed with IC.

Various diagnostic tools and markers have been studied for the diagnosis of IC today. There are urinary markers with higher diagnostic performance which provide better distinction between patients with IC and healthy patients. Those markers are: glycoprotein 51, antiproliferative factor (APF), insulin-like growth factor binding protein 3, epidermal growth factor and heparin-binding epidermal growth factor-like growth factor.³⁻⁷

The regenerative capacity of the bladder epithelium is impaired as a result of the presence of APF in the urine of patients with IC. That would prevent a proper regeneration of bladder epithelium after an attack.⁸ This is because the APF activates protein p53, which is responsible for cell apoptosis. Then, a shutdown of the cell cycle in sub-G1 phase would occur, preventing the epithelial cells to enter G1 phase to divide.

Our study is based on the principle that cell cycle shut down produces a change in the percentage distribution of cells in each cell phase. Specifically, as a cluster of cells at sub-G1 phase level, which is easily quantified by flow cytometry.

The main objective of this study is to assess the apoptotic effect of urine from patients with IC in cell cultures and study its value as a diagnostic biomarker for IC.

Material and methods

A prospective study was conducted between January 2010 and January 2015. This study included 107 patients from the Hospital Clinic of Barcelona and the La Fe University Hospital. Of those, 57 patients were diagnosed with IC and the other 50 were healthy patients.

The inclusion criteria for patients with IC were: women older than 18 and diagnosed according to the NIDDKD criteria (symptoms of pain and/or urinary urgency and cystoscopy demonstration of glomerulations and/or presence of classical Hunner's ulcer). All of them had a diagnosis de novo without having received any treatment. For the healthy control group, the inclusion criteria were: women older than 18 years, asymptomatic without urinary symptoms and with negative urine cultures.

All patients completed the Genitourinary Pain Index (GUPI) questionnaire to quantify objectively the signs and symptoms of patients⁹ (Fig. 1).

The study of the apoptotic effect of urine on cell cultures was conducted in the cytomics department of the Principe Felipe Research Center in Valencia.

The urine of patients with IC and the control group was exposed to neoplastic cell cultures, and its ability to induce apoptosis in the cultures was analyzed. Using flow

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