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Original article

ETS-1 oncoprotein expression is decreased in aggressive papillary transitional cell carcinoma of the urinary bladder: An immunohistochemical study

E.A. Ibrahim *, M.R. Hassan , S.A. Sammour

Pathology Department, Faculty of Medicine, Ain Shams University, Egypt

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KEYWORDS
Papillary transitional cell carcinoma;
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Abstract
Introduction: ETS-1 proto-oncogene is a transcription factor that plays multiple roles in the process of oncogenesis and helps in the process of tumor invasion. ETS-1 oncoprotein correlation with high grade and invasive tumors is controversial; as it is found to be upregulated with some tumors and down regulated with others. Expression of ETS-1 in urinary bladder carcinoma (UBC) and its correlation with tumor differentiation and invasiveness are still under-investigated. So far, there is no reliable prognostic marker has been proved for detection of the tumor progression and recurrence.
Objectives: To analyze the correlation between ETS-1 oncoprotein immunohistochemical expression and the different stages and grades of the primary papillary transitional cell carcinoma of the urinary bladder.
Patients and methods: This is a retrospective cross sectional study that included archival material from 150 cancer cases and 24 control biopsies.
Results: There was a decreased ETS-1 oncoprotein expression with increasing stage and grade of the tumor with a highly significant statistical correlation ($P = 0.001$). With the quantitative assessment of the immunohistochemical results and using ROC (receiver operating characteristics) curve, cut-off values were found, that were associated with high grade and muscle invasive tumors ($\leq$30% and $\leq$20%, respectively).

* Corresponding author.
E-mail addresses: emanpathology@yahoo.com (E.A. Ibrahim), imprecise@hotmail.com (M.R. Hassan), sammoursanaa@yahoo.com (S.A. Sammour).
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Conclusion: ETS-1 oncoprotein is down regulated with high grade and highly invasive urinary bladder papillary transitional cell carcinomas. This oncoprotein may be used as an independent prognostic marker to predict the aggressive papillary transitional carcinomas with high invasive potential. More studies are needed to confirm our results.

Introduction

Urinary bladder carcinoma (UBC) is one of the most prevalent malignant tumors worldwide; it is the ninth in incidence order amongst others. It is the seventh most common malignancy in adult males and the 17th among adult females [1,2].

ETS-1 proto-oncogene is a transcription factor that plays multiple roles in the process of oncogenesis. It helps the process of tumor invasion by modulating the extracellular matrix via stimulating the transcription of metalloproteinases and urokinase-type plasminogen activator [3]. Furthermore, it activates the endothelial cells proliferation and activation, thus stimulating the angiogenesis and tumor progression [4]. ETS-1 oncoprotein correlation with high grade and invasive tumors is found to be controversial; as it is found to be upregulated with some tumors [5–10] and down regulated with others [11–13]. This can be explained by the different target proteins which may result in a competitive function that may be expressed differently in various organs [13].

Expression of ETS-1 in UBC and its correlation with the tumor differentiation and invasiveness are still under-investigated.

Objectives

The present study aims to evaluate the significance of ETS-1 expression in papillary transitional cell carcinoma of the urinary bladder and determine the relationship of this oncoprotein with the histopathological parameters including tumor grade and stage.

Subjects and methods

This is a retrospective cross sectional study performed in the pathology department of Ain Shams Specialized University Hospital (ASUSH). The studied material comprised of archival paraffin blocks of urinary bladder papillary transitional cell carcinoma from patients who underwent radical cystectomy or TURT. The control cases consisted of cystoscopic biopsies for chronic cystitis, in an anonymous way, so no consent was needed from the patients. The research study was approved by the Research Ethical Committee of Ain Shams University, the rules of which were in accordance with the ethical standards laid down in 1964 Declaration of Helsinki.

Specimen and data collection

We retrieved 157 cases of primary papillary transitional cell carcinoma of the urinary bladder and 24 control biopsies. Paraffin blocks were retrieved from the pathology departments of ASUSH and Aldemerdash Hospital in the period from January 2010 to December 2014. Archival files of the cases were also retrieved and all available clinical data were registered (age, sex and stage of the tumor). Inclusion criteria included a diagnosis of primary urinary bladder papillary transitional cell carcinoma, with availability of adequate clinical data and the presence of, furthermore, adequately presented muscularis propria for proper assessment of the tumor invasion. Exclusion criteria included inadequate clinical data, tumors with much tissue necrosis and absence of muscularis propria in the examined sections.

We excluded five cases due to inadequate clinical history and another two cases due to extensive tumor tissue necrosis. Of the remaining were 150 cases, for the study; there were 81 cases had undergone radical cystectomy and the remaining 69 were transurethral biopsies.

Histopathological examination

The slides of the selected cases were reviewed under light microscopy. The tumors were graded according to the World Health Organization 2004 system [14] and staged into: stages 0 and I (early bladder cancer), stages II and III (invasive bladder cancer) and stage IV (advanced bladder cancer) [15].

Immunohistochemical staining and scoring

Four micron-thick sections were cut from the selected paraffin blocks and stained immunohistochemically by using ETS-1 antibody (mouse monoclonal antibody) (Clone 1G11: Cat. #MS-1762-R7) (7.0 ml) (Thermo Fisher Scientific Inc, MA, USA). It was a ready-to-use reagent; the manufacturer's staining protocol was followed. For positive control we used human tonsillar tissue and omitting the use of primary antibody was done for negative controls to ensure correct staining procedure [16].

ETS-1 expression was assessed semi-quantitatively into 3 categories according to the percentage of cells with positive nuclear staining; the results were expressed as follows: score 0 = 0–10% positive cells; score 1 = 10–50% positive cells; score 2 = >50% positive cells [17].

Statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc., Chicago, IL, 2001). Data was presented and suitable analysis was done; Mean, Standard deviation (±SD) and range for parametric numerical data, Student's *t*-test to assess the statistical significance of the difference between two study group means, ANOVA test was used to assess the statistical significance of the difference between more than two study group means. Chi-square test was used to examine the relationship between two qualitative variables. Fisher's exact test was done to examine the