

Expression of Thyroid Transcription Factor-1 (TTF-1) in Endometrial Carcinoma.

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Abstract: Introduction: TTF-1 is a helpful marker for primary lung adenocarcinoma and is considered as a reliable marker to distinguish between primary and secondary lung carcinoma. However, some studies showed that TTF-1 also can be expressed in extrapulmonary adenocarcinomas. The data on TTF-1 expression in endometrial cancer is limited and conflicting. The aim of this study is to evaluate the immunorexpression of TTF-1 in primary endometrial adenocarcinoma. **Material and methods:** Tissue microarrays were prepared from archival of endometrial carcinoma obtained from the Department of Pathology at King Abdulaziz University Jeddah, Saudi Arabia. Tissue sections were immunostained using monoclonal antibodies to TTF-1. The immunohistochemical stains were scored semiquantitatively from 0 to 5+. **Results:** The categories of endometrial adenocarcinoma include 78 grade I endometrioid, 17 grade II endometrioid, 12 grade III endometrioid, 7 serous, 2 clear cell. TTF-1 immunorexpression was detected only in 2 carcinoma (1 serous and one endometrioid type) and in both cases the staining score was 1+. **Conclusion:** TTF-1 is a reliable marker for lung carcinomas; however, in patient with focal TTF-1 immunorexpression, endometrial carcinomas should be considered when evaluating patients with adenocarcinoma of unknown origin and in patients with a history of endometrial adenocarcinoma.

[Jaudah Al-Maghrabi, Nisrin Anfinan, Khalid Sait, Hesham Sait, Mahmoud Al-Ahwal, Hussain Basalamah. **Expression of Thyroid Transcription Factor-1 (TTF-1) in Endometrial Carcinoma.** *Life Sci J* 2014;11(4):317-320]. (ISSN:1097-8135). <http://www.lifesciencesite.com>. 43

Key Words: Immunorexpression, thyroid transcription factor-1, TTF-1, endometrial carcinoma, metastasis.

1. Introduction

Thyroid transcription factor-1 (TTF-1) is DNA-binding protein that is encoded by a gene located on chromosome 14q13. It belongs to a family of homeodomain transcription factors. It is selectively expressed in the thyroid and lung. In the thyroid, TTF-1 is expressed in C-cells and follicular cells and it activates thyroglobulin and thyroperoxidase gene transcription (1-4). TTF-1 is useful marker for primary adenocarcinoma of the lung (1). Some studies have shown that TTF-1 also can be expressed in extrapulmonary adenocarcinomas (2-7). However the results of the expression of TTF-1 in endometrial adenocarcinoma are conflicting. The aim of this study is to provide data regarding the incidence and distribution of TTF-1 expression in endometrial carcinoma.

2. Material and methods:

Archival paraffin-embedded tissue samples from patients with endometrial carcinoma were used to construct tissue microarrays. Cases were retrieved by diagnosis search from the Department of Pathology at King Abdulaziz University Jeddah, Saudi Arabia, covering the period from January 1995 to December 2012. The study was performed in accordance with the ethics committee of Faculty of Medicine, King Abdulaziz University, Saudi Arabia,

and according to the ethical guidelines of the 1975 Declaration of Helsinki. Tissue sections from microarray blocks were immunostained using monoclonal antibodies to TTF-1, clones 8G7G3/1 (dilution 1:100, Dako North America, Inc. Carpinteria, CA). Staining was carried out by an automatic immunostainer (Ventana Bench Mark XT, Ventana Inc., Tucson, AZ). The immunohistochemical stains were scored according to the distribution of TTF-1 nuclear staining as follows: 0 = negative, 1+ = <5%, 2+ = 5% to 25%, 3+ = 26% to 50%, 4+ = 51% to 75%, and 5+ = >75%.

3. Result:

A total of 116 endometrial carcinomas were retrieved from the authors' institutions. The patient had abdominal hysterectomy with bilateral salpingo-oophorectomy. The age of the patients ranged between 25 and 80 years. The categories of endometrial adenocarcinoma include endometrioid endometrial adenocarcinomas 107 (78 grade I, 17 grade II, and 12 grade III), and 7 uterine serous carcinomas and 2 clear cell carcinoma. TTF-1 immunorexpression was detected only in 2 carcinomas (1 serous and one endometrioid type) and in both cases the staining score was 1+. Our data

demonstrated that all the other cases were completely negative.

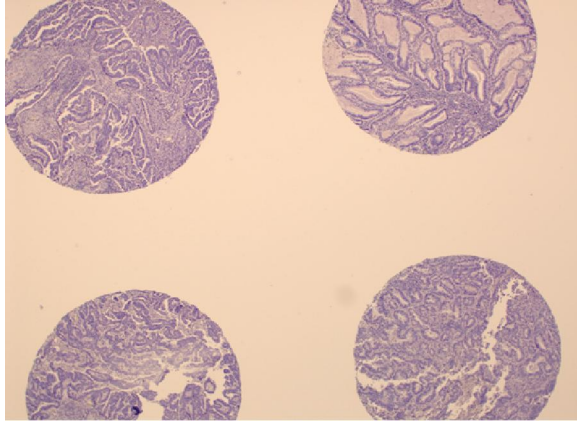


Figure 1

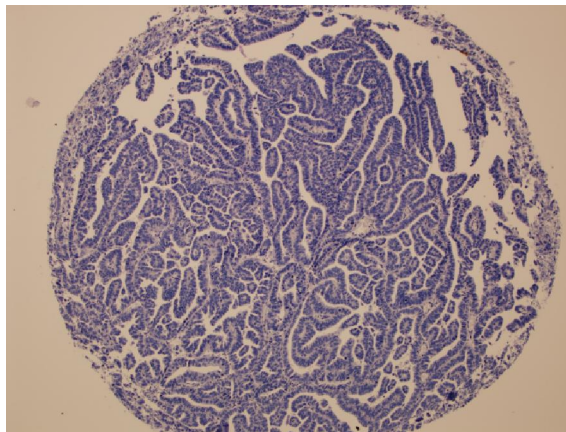


Figure 2

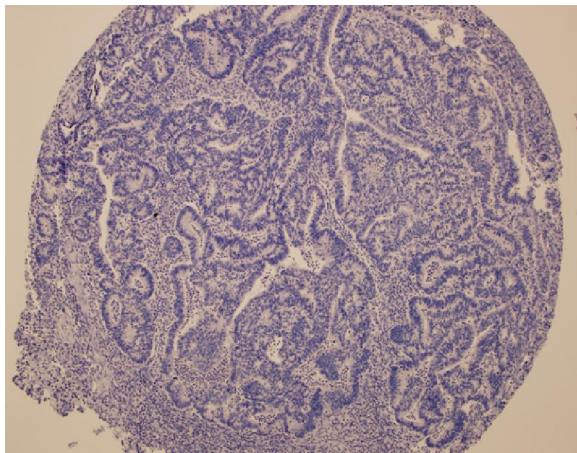


Figure 3

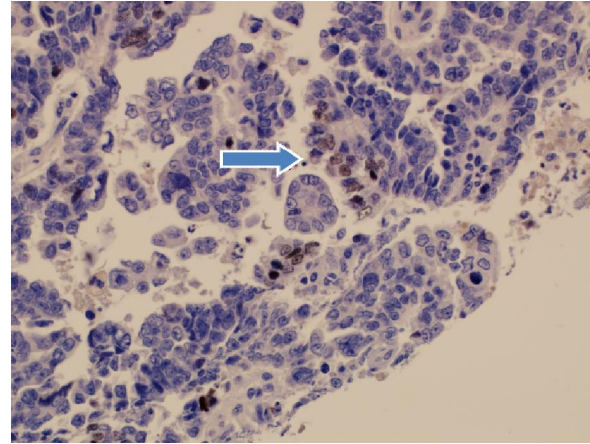


Figure 4

Figure 1: Tissue microarray reveals endometrial carcinoma cases. Each core represents a different cancer (hematoxylin-eosin, original magnification X100)

Figure 2: Immunohistochemistry stain for TTF-1 using tissue microarray reveals negative staining (original magnification X200).

Figure 3: Immunohistochemistry stain for TTF-1 using tissue microarray reveals negative staining in another case (original magnification X200).

Figure 4: higher power on another case reveal few cells that reveal nuclear staining for TTF-1 (arrow) (original magnification X400).

4. Discussion:

In normal tissue, TTF - 1 is reported to be expressed in epithelial cells of thyroid and type II pneumocytes and Clara cells in lung (8). It is unreactive with other tissues examined including prostate, pituitary, testes, adrenal gland, skin, mammary gland, kidney, colon, liver, pancreas, small intestine, brain, and stomach.

In cancerous tissue, TTF-1 has been detected in pulmonary adenocarcinoma (3;8), large-cell carcinoma (8), small cell carcinoma of lung (9) and thyroid carcinoma (10). Carcinomas arising from lung show frequent TTF - 1 expression. TTF-1 is expressed in about 90% of bronchogenic adenocarcinoma. Lung also is a common site for metastases from extrapulmonary carcinomas (11). Nearly half of lung cancers are adenocarcinomas (11). Differential diagnoses of primary lung adenocarcinomas from metastatic carcinomas, particularly those with poor differentiation are challenges for practicing pathologists.

TTF-1 immunoreactivity is a very sensitive and highly specific marker in the differential diagnosis of lung adenocarcinoma and other non-pulmonary carcinoma and highly recommended to be used in

regular clinical practice for this purpose (3;12). Apart from thyroid carcinoma, all non-pulmonary adenocarcinomas classically lacked TTF-1 staining

Endometrial carcinoma is the most common cancer of the female genital cancer. Metastatic carcinomas to the lung from the endometrium, endocervix, ovary and colon have been reported to be positive for TTF-1 in rare occasion (2-7). Ye et al (14) found that fourteen (13.6%) of 103 metastatic carcinomas to the lung showed positive TTF-1 immunostaining including carcinomas from the endometrium (2), thyroid (5), colon (3), kidney (2), ovary (1), prostate (1), and salivary gland (1). Although the reported frequency of positivity is low, its misinterpretation can lead to an incorrect diagnosis. Lung metastases were found at the time of diagnosis of the primary endometrial cancer in 22%, so pulmonary metastases represent a common site of metastasis of endometrial carcinoma (13). However the results of TTF-1 expression in these tumors are conflicting.

Ervine *et al.* demonstrated that TTF-1 is expressed in a small subset of all categories of endometrial adenocarcinoma as follows: 2% low grade endometrioid, 11% grade 3 endometrioid, 9% serous and 7% clear cell and they showed that TTF-1 positivity in low grade endometrioid adenocarcinomas is a poor prognostic factor (14). Zhang *et al.* showed that TTF-1 is frequently detected in uterine malignant mixed Mullerian tumor (82%), more common in uterine tumors than ovarian tumors. When present, tumor cells can be rarely positive or diffusely positive for TTF-1 reactivity (7).

TTF-1 positivity was identified in 1 out of 48 endometrial adenocarcinoma by Turner *et al.* (15). TTF-1 has been reported in 1 of 8 endometrial adenocarcinomas by others (16). At M. D. Anderson, Deavers *et al.* studied TTF-1 expression in 31 endometrial endometrioid adenocarcinomas (11 grade I, 8 grade II, and 12 grade III), TTF-1 immunoreactivity was identified in 5 cases (16%), and ranged from focal to diffuse in distribution (17). There was no correlation between TTF-1 expression and the degree of differentiation, and no distinguishing histologic features of the positive tumors were noted (17). Recently it has been demonstrated that all primary lung adenocarcinomas were negative for PAX8, whereas all endometrial carcinoma (5/5) were positive for PAX8 and they suggested that combined use of PAX8, TTF-1 and napsin A is reliable to separate reliably lung primary from metastatic tumors including endometrial carcinoma (18). PAX 8 is expressed in the vast majority of endometrial carcinomas both of endometrioid and non-endometrioid type (19).

In this study we demonstrated that the vast majority of endometrial carcinomas are negative for TTF-1 immunoeexpression. The rare cases that expressed TTF-1 showed only focal weak expression of TTF-1. So, diffuse expression is not seen in any of the cases in this study and we think that this pattern of expression is against endometrial carcinoma origin of metastatic carcinoma. However, in patient with focal TTF-1 immunoeexpression, endometrial carcinomas should be considered when evaluating patients with adenocarcinoma of unknown origin and in patients with a history of endometrial adenocarcinoma. Additional markers such as PAX-8 to help in differentiating lung and endometrial carcinomas are recommended.

Acknowledgment:

This study was supported by a grant from the Scientific Chair of Prof. Abdullah Hussain Basalamah for Gynecological Cancer³, King Abdulaziz University, Jeddah, Saudi Arabia

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3/1/2014