*Turkish Journal of Pathology 2008;24(2):84-87*

# The value of Thyroid Transcription Factor-1 (TTF-1) in differential diagnosis of metastatic pulmonary and extrapulmonary carcinomas in pleural effusions

# Plevral efüzyonlarda metastatik pulmoner ve ekstrapulmoner karsinomların ayırıcı tanısında Tiroid Transkripsiyon Faktör-1'in (TTF-1) değeri

**Ali VERAL, Deniz NART, İrem PAKER, Banu YAMAN, Yeşim ERTAN**

*Ege Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı, İZMİR*

**ABSTRACT**

Metastasis of unknown primary site in serous pleural effusion is common and cytopathological analysis may have important therapeutic implications. Primary lung and metastatic tumors may share similar cytopathological features with difficulties in differential diagnosis especially in routine cytology practice. TTF-1 is highly specific and sensitive in the diagnosis of certain types of primary lung carcinomas, especially adenocarcinoma and small cell carcinoma in histological sections. In this study, we determined the usefulness of TTF-1 in pleural fluids for the differential diagnosis of carcinomas of pulmonary and extrapulmonary origin.

Cytological materials from 36 patients with malign pleural effusion were evaluated. The diagnosis of primary site was identified for all cases by clinical, radiological, cytological and/or histological correlation. Twenty-five out of 36 cases were primary lung carcinomas and 11 were metastatic. Immunohistochemical study was performed on the cell block sections or unstained effusion cytology specimens. Among 25 metastatic pulmonary carcinomas, 19 cases showed strong nuclear positivity with TTF-1 (15 adenocarcinoma, 3 nonsmall cell carcinoma and 1 small cell carcinoma) (sensitivity %76) and 6 cases were negative (2 nonsmall cell carcinoma, 1 adenocarcinoma, 1 squamous cell carcinoma, 1 large cell carcinoma, 1 small cell carcinoma). None of the 11 metastatic extrapulmonary carcinomas stained for TTF-1 (6 breast, 2 gastric, 1 kidney, 1 ovary, 1 oesophagus) (specificity %100).

Our results show that, TTF-1 is sensitive and also highly specific marker in discriminating between metastatic pulmonary and extrapulmonary carcinomas in effusion cytology specimens.

**Key words:** TTF-1, effusion cytology, pulmonary carcinomas, immunohistochemistry

**ÖZET**

Seröz plevral effüzyonlarda primeri belirsiz tümörlerin metastazlarının görülmesi sık karşılaşılan bir durumdur ve sitopatolojik tanının tedavi açısından önemi büyüktür. Akciğer tümörleri ile nonpulmoner metastatik tümörler özellikle sitolojik örneklerde benzer morfolojik özellikler sergileyebilirler; bu nedenle ayırıcı tanıda güçlük yaşanır. TTF-1, özellikle adenokarsinom ve küçük hücreli karsinomda olmak üzere primer akciğer karsinomlarının tanısında histolojik kesitlerde yüksek duyarlılık ve özgünlüğe sahip bir belirleyicidir. Bu çalışmada malign plevral effüzyonlarda TTF-1'in pulmoner ve ekstrapulmoner karsinomların ayırıcı tanısındaki yerini araştırdık.

Malign plevral effüzyonlu 36 olgu çalışmaya alındı. Olguların primer tümörleri klinik, radyolojik, sitolojik ve/veya histopatolojik korelasyonla belirlendi. 36 olgunun 25'i primer akciğer karsinomu, 11'i metastatik karsinom idi. İmmünhistokimyasal inceleme hücre bloklarına ya da boyasız-tespitli yayma preparatlarına uygulandı. 25 akciğer karsinomu metastazı olgusunun 19'unda (15 adenokarsinom, 3 küçük hücreli dışı karsinom ve 1 küçük hücreli karsinom) TTF-1 ile güçlü nükleer pozitivite saptandı (duyarlılık %76). 6 olgu ise (2 küçük hücreli dışı karsinom, 1 adenokarsinom, 1 skuamöz hücreli karsinom, 1 büyük hücreli karsinom, 1 küçük hücreli karsinom) TTF-1 negatifti. 11 metastatik ekstrapulmoner karsinomun tümünde (6 meme, 2 mide, 1 böbrek, 1 over, 1 özofagus karsinomu) TTF-1 negatifti (özgünlük %100).

Çalışmamızın sonuçları TTF-1'in effüzyon sitolojisinde pulmoner ve ekstrapulmoner karsinomların ayırıcı tanısında yüksek özgünlük ve duyarlılığa sahip bir belirleyici olduğunu göstermektedir.

**Anahtar sözcükler:** TTF-1, effüzyon sitolojisi, akciğer karsinomları, immünhistokimya

**Received:** 1.3.2008
**Accepted:** 16.4.2008
**Corresponding Author:** Dr. Ali Veral, Ege Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı, İzmir

## INTRODUCTION

Metastasis of unknown primary site in serous pleural effusion is not uncommon and cytopathologic analysis of this effusion can provide important information for the management of the patient. The identification of the organ of origin of metastatic tumors mostly has therapeutic consequences. Primary lung and metastatic tumors may share similar cytopathological features with difficulties in differential diagnosis especially in routine cytology practice. Many tumor markers have been developed in the past two decades as immunohistochemical aids in the differential diagnosis of malignant tumors (1). The availability of organ-specific markers is of major diagnostic relevance as they offer an attractive means for confirming metastatic disease in patients with known primary tumors and may assist in identifying the primary sites in patients of unknown origin. Thyroid transcription factor-1 (TTF-1) is a homeodomain nuclear transcription protein that is expressed selectively in the epithelial cells of the thyroid and lung (2,3). TTF-1 is highly specific and sensitive in the diagnosis of certain types of primary lung carcinomas, especially adenocarcinoma and small cell carcinoma in histological sections (4,5,6). Also, TTF-1 can be used to support the diagnosis of adenocarcinomas of pulmonary or of thyroid origin in patients with effusion (7).

The aim of the study is to investigate the usefulness of TTF-1 in pleural fluids for the differential diagnosis of carcinomas of pulmonary and extrapulmonary origin.

## MATERIALS and METHODS

Thirty six patients, presenting with pleural effusions, due to metastatic malignancy were included. The diagnosis of primary site was identified for all cases by cytological and/or histological correlation. Twenty-five out of 36 cases were primary lung carcinomas (16 patients with adenocarcinoma, 5 with non small cell lung carcinoma, 2 with small cell lung carcinoma, 1 with squamous cell carcinoma and 1 with large cell carcinoma) and 11 were metastatic (six patients with carcinomas of the breast, 2 of the stomach, 1 of the kidney, 1 of the ovaries and 1 of the oesophagus). Immunohistochemical study was performed on the formalin-fixed, paraffin-embedded cell-block sections or unstained smears or cytocentrifuge slides prospectively. Sections of 4-µm-thickness were cut from the paraffin blocks and placed on positively charged-polylysine coated slides. After the deparaffinization the immunostaining procedure was performed on Benchmark XT® (Ventana medical systems, USA) automated stainer using the iView DAB paraffin detection kit (Ventana,Tucson, AZ) with the TTF-1 antibody (Novocastra, NCL-L). The results of TTF-1 immunostaining were based on the nuclear staining of tumor cells.

## RESULTS

The results of TTF-1 immunostaining of carcinomas in body cavity fluids are shown in Table 1. Positive immunoreactivity for TTF-1 was characterized by a dark-brown, diffusely granular nuclear staining in tumor cells that occurred singly or in groups (Figure 1).

**Table 1. The results of TTF-1 immunostaining of carcinomas in body cavity fluids.**

| | TTF-1 (+) | TTF-1 (-) | Total | % (+) |
|---|---|---|---|---|
| Adenocarcinoma | 15 | 1 | 16 | %94 |
| NSCLC | 3 | 2 | 5 | %60 |
| SCLC | 1 | 1 | 2 | %50 |
| Squamous cell carcinoma | 0 | 1 | 1 | %0 |
| Large cell carcinoma | 0 | 1 | 1 | %0 |
| Extrapulmoner carcinomas | 0 | 11 | 11 | %0 |

*NSCLC=Nonsmall cell lung carcinoma*
*SCLC=Smail cell lung carcinoma*

Among 25 metastatic pulmonary carcinomas, 19 cases showed strong nuclear positivity with TTF-1 (15 adenocarcinoma, 3 nonsmall cell carcinoma and 1 small cell carcinoma) (sensitivity 76%, positive predictivity 100%) and 6

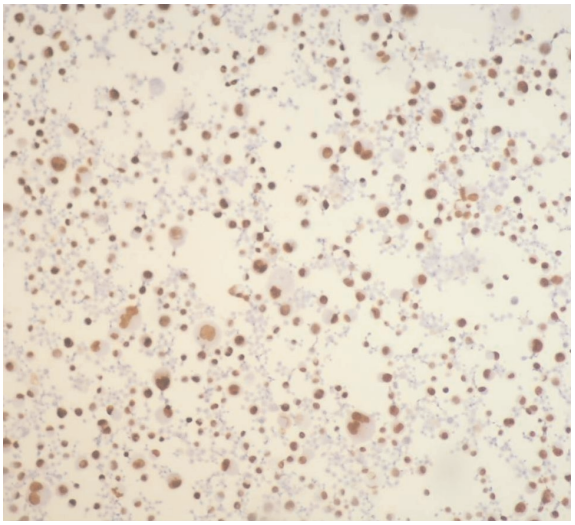

**Figure 1. Positive immunoreactivity for TTF-1 in tumor cell nuclei (Anti-TTF-1 x100).**

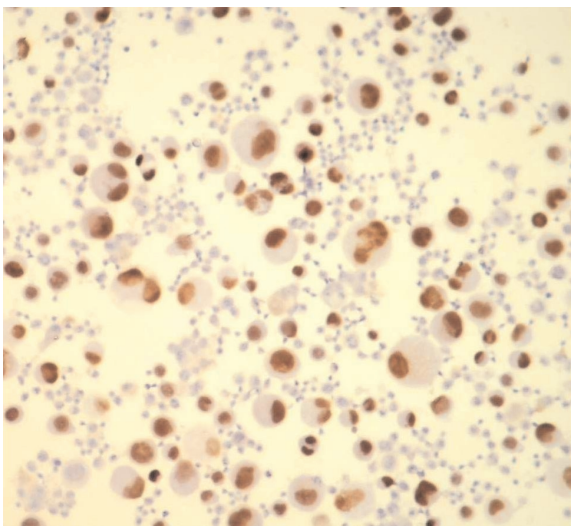

**Figure 2. TTF-1 positivity in adenocarcinoma (Anti-TTF-1 x200).**

cases were negative (2 nonsmall cell carcinoma 1 adenocarcinoma, 1 squamous cell carcinoma, 1 large cell carcinoma, 1 small cell carcinoma) (Figures 2,3). None of the 11 metastatic extrapulmonary carcinomas stained for TTF-1 (6 breast, 2 gastric, 1 kidney, 1 ovary, 1 oesophagus) (specifity 100%, negative predictivity 35%).

## DISCUSSION

The application of immunocytochemistry to routine cytologic diagnostics of serous effusi-

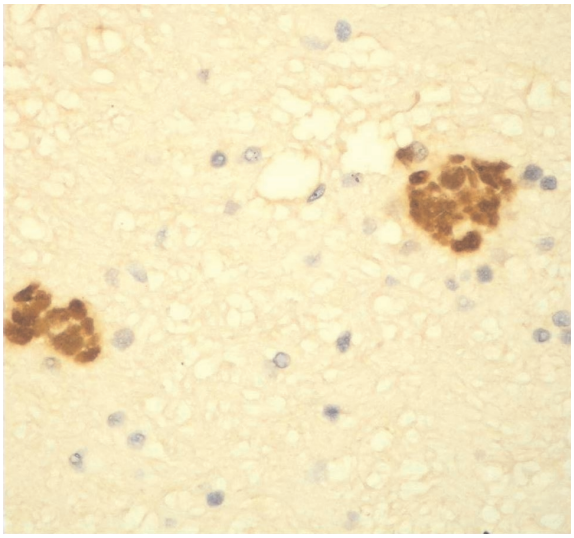

**Figure 3. Positive immunoreactivity for TTF-1 in small cell lung carcinoma (Anti-TTF-1 x200).**

ons has gained an increasing importance in the last decade (8). Organ specific markers using immunohistochemistry offer an attractive means for subclassifying carcinomas according to primary site. The immunomarker anti-TTF-1 has been shown to label pulmonary adenocarcinoma, thyroid tumors (both follicular and medullary), and small cell carcinoma (both pulmonary and extrapulmonary) with high sensitivity and specificity (4,5,6,9). Other pulmonary tumors, including carcinoid, large cell neuroendocrine carcinoma, large cell carcinoma, and squamous cell carcinoma, show less frequent expression of TTF-1 (9,10). TTF-1 is rarely expressed in tumors of extrapulmonary origin (11-14). Thus, TTF-1 is a potentially useful marker in differentiating metastatic pulmonary from extrapulmonary adenocarcinoma, provided that the possibility of thyroid origin has been excluded.

In the current study, TTF-1 was shown to be sensitive and highly specific in diagnosing the pulmonary origin of metastatic carcinoma in effusion cytology and cell block materials, in our study group, the sensitivity and specificity were 76% and 100% respectively. The highest TTF-1 positivity was seen in the pulmonary adenocarcinoma group (15/16-93,7%). This ratio was correlated with the literature (15). There

was 60% positivity in the nonsmall cell group group. In this group TTF-1 negative cases might be undifferentiated squamous cell carcinoma or large cell carcinoma. In small cell lung carcinoma cases there was 50% TTF-1 positivity. This ratio was very low corresponding to literature (10) and probably related low case number (only two cases). In extrapulmonary carcinoma group there were no TTF-1 positive cases. Pomjanski et al. (16) used a panel including CK 5/6, CK 7, CK 20, CA 125, TTF-1, and cdx 2 in serous effusions of unknown primary cases. They put forward in 85.1% cases the primary site was determined when their broad panel was used. Furthermore, Chhieng et al. (17) were suggested TTF-1, PE-10, CK7 and CK20 may be helpful in discriminating between primary and metastatic adenocarcinomas of the lung in FNAB. Therefore, immunohistochemical study for TTF-1 performed on the effusion cytology or cell block material is an effective method to confirm pulmonary origin of metastatic carcinoma.

## REFERENCES


1. Chu P, Wu EBS, Weiss LM. Cytokeratin 7 and Cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol 2000;13:962-972.
2. Lazzaro D, Price M, De Felice M, Di Lauro R. The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the foetal brain. Development 1991;113:1093-1104.
3. Fabbro D, Di Loreto C, Stamerra O, Beltrami A, Lonigro R, Damante G. TTF-1 gene expression in human lung tumours. Eur J Cancer 1996;32A:512-517.
4. Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. Adv Anat Pathol 2000;7:123-127.
5. Ordonez NG. Value of thyroid transcription factor-1, e-cadherin, BG8, WT1, and CD44S immunostaining in distinguishing epithelial pleural mesothelioma from pulmonary and nonpulmonary adenocarcinoma. Am J Surg Pathol 2000;24:598-606.
6. Srodon M, Westra WH. Immunohistochemical staining for thyroid transcription factor-1: a helpful aid in discerning primary site of tumor origin in patients with brain metastases. Hum Pathol 2002;33:642-645.
7. Afify AM, Al-Khafaji BM. Diagnostic utility of thyroid transcription factor-1 expression in adenocarcinomas presenting in serous fluids. Acta Cytol 2002; 46:675-678.
8. Bedrossian CWW. Special stains: the old and the new: the impact of immunocytochemistry in effusion cytology. Diagn Cytopathol 1998;18:141-149.
9. Kaufmann O, Dietel M. Thyroid transcription factor-1 is the superior immunohistochemical marker for pulmonary adenocarcinomas and large cell carcinomas compared to surfactant proteins A and B. Histopathol 2000;36:8-16.
10. Folpe AL, Gown AM, Lamps LW, Garcia R, Dail DH, Zarbo RJ, et al. Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors. Mod Pathol 1999;12:5-8.
11. Reis-Filho JS, Carrilho C, Valenti C, Leitao D, Ribeiro CA, Ribeiro SG, et al. Is TTF1 a good immunohistochemical marker to distinguish primary from metastatic lung adenocarcinomas? Pathol Res Pract 2000; 196:835-840.
12. Yun JP, Zhang MF, Hou JH, Tian QH, Fu J, Liang XM, et al. Primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical features of 21 cases. BMC Cancer 2007 3;7:38.
13. Alijo Serrano F, Sánchez-Mora N, Angel Arranz J, Hernández C, Alvarez-Fernández E. Large cell and small cell neuroendocrine bladder carcinoma: immunohistochemical and outcome study in a single institution. Am J Clin Pathol 2007;128:733-739.
14. Siami K, McCluggage WG, Ordonez NG, Euscher ED, Malpica A, Sneige N, et al. Thyroid transcription factor-1 expression in endometrial and endocervical adenocarcinomas. Am J Surg Pathol 2007;31:1759-1763.
15. Hecht JL, Pinkus JL, Weinstein LJ, Pinkus GS. The value of thyroid transcription factor-1 in cytologic preparations as a marker for metastatic adenocarcinoma of lung origin. Am J Clin Pathol 2001;116:483-488.
16. Pomjanski N, Grote HJ, Doganay P, Schmiemann V, Buckstegge B, Böcking A. Immunocytochemical identification of carcinomas of unknown primary in serous effusions. Diagn Cytopathol 2005;33:309-315.
17. Chhieng DC, Cangiarella JF, Zakowski MF, Goswami S, Cohen JM, Yee HT. Use of thyroid transcription factor 1, PE-10, and cytokeratins 7 and 20 in discriminating between primary lung carcinomas and metastatic lesions in fine-needle aspiration biopsy specimens. Cancer 2001;93:330-336.