CASE REPORT

Thyroid Transcription Factor-1 (TTF-1) expression in lungs metastatic adenocarcinoma from sigmoid primary: A diagnostic pitfall in a 63-year-old man

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Abstract

Thyroid transcription factor 1 (TTF-1), a very sensitive and specific marker for primary lung adenocarcinoma, has been used as a diagnostic marker for distinguishing primary pulmonary neoplasm from adeno-carcinomatous metastasis from other sites, such as the colorectal region. In a few cases, metastases have also been shown to express TTF-1. Here, we present the case of a 63-year-old man who developed metastases to the right lung from metastatic sigmoid adenocarcinoma. The pulmonary secondary lesion was strongly positive for TTF-1.

There is a paucity of existing English scientific literature to prove the non-specific nature of TTF-1 expression. This is the first documented case of its kind from Pakistan and probably the sixth case in the world. The versatile expression of IHC (Immunohistochemistry) markers influences the nature, progression and management of malignancies. Hence, histopathologists need to be aware of this extremely rare occurrence.

Keywords: (TTF-1) Thyroid Transcription Factor-1, lung adenocarcinoma, immunohistochemistry, carcinogen marker.

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Introduction

Thyroid transcription factor 1 (TTF-1) is a nuclear protein that has been documented to show limited expression in the lungs. Clara cells, type II pneumocytes and epithelial cells of the thyroid follicle usually express it.[1] It has found use in applied pathology as a diagnostic marker, and is considered to be specific and sensitive in differentiating primary lung adenocarcinoma from metastatic adenocarcinoma.[2] However, few reports in recent years have led the medical community to question the credibility of TTF-1. These cases show unequivocally TTF-1 staining in lung metastasis of adeno-rectal carcinoma.[3-5] In fact some studies have already emerged that may discourage their use when TTF-1 results are inconclusive, e.g., Napsin A and its reliability in identifying a tumour of colorectal origin.[2]

Here, we present a unique case of TTF-1 positivity in metastatic lung tumour. The origin of the tumour could not be ascertained using the conventional logarithm of funnelling. This case thus could serve as a valuable resource from which more insights into the diagnosis of such cases could be gleaned.

Case Report

A 63-year-old man with no significant medical history was diagnosed with stage IIIB (pT3N1M0) adenocarcinoma of the sigmoid colon in March 2019. An exploratory laparotomy with excision of the sigmoid mass and anastomosis was performed at Services Hospital, Lahore, followed by six sessions of adjuvant chemotherapy with oxaliplatin and capecitabine at Institute of Nuclear Medicine & Oncology, Lahore. He was regular in his follow-up visits to the primary care of facility. The colonoscopy of the patient showed a normal colon and carcino-embryonic antigen (CEA) levels were reduced to 1.64 ng/ml within a year. Further follow-up was maintained, and CEA levels were monitored for recurrence. In December 2022, the patient presented with elevated CEA levels, i.e., 11 ng/ml. Therefore, a multi-detector computed tomography (MDCT) scan of chest, abdomen and pelvis with contrast was ordered, which showed a heterogeneously enhancing, poorly marginated, soft tissue mass measuring 43 x 43 mm in size in the apico-posterior segment of the right upper lung zone.

A less invasive method of biopsy was planned by the members of multidisciplinary team (MDT). He underwent fine needle aspiration cytology (FNAC) of the right lung upper lobe mass, which showed few atypical cells. This was followed by a core biopsy of the right lung upper lobe mass that revealed tumour arranged in infiltrating glands with a prominent cribriform pattern and areas of dirty necrosis. A

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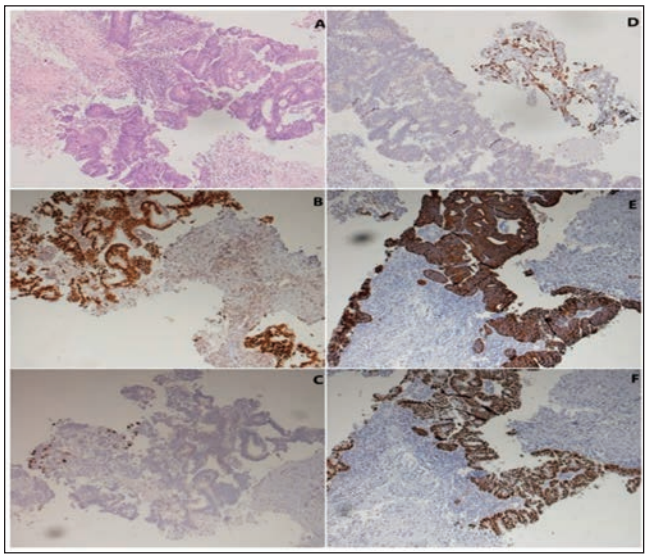

Figure: Histopathological findings of metastatic lung tumour (10x magnification). Hematoxylin-eosin staining of lung shows tumour is composed of infiltrating glands and ducts showing fusion (A). Thyroid transcription factor-1 (TTF-1) strong nuclear staining in tumour cells (B). Further results of immunohistochemistry are as follows: Napsin-A negative in tumour cells (C), Cytokeratin-7 (CK-7) negative in tumour cells (D), Cytokeratin-20 (CK-20) strong diffuse membranous staining in tumour cells (E), Caudal-related homeobox transcription factor 2 (CDX2) strong nuclear staining in tumour cells (F).

diagnosis of moderately differentiated adenocarcinoma was rendered at our set up, Aznostics – The Diagnostic Centre. TTF-1 was strongly positive in tumour cells. The tumour cells were also positive for cytokeratin 20 (CK20) and caudal type homeobox 2 (CDX2). Though the malignant cells were negative for cytokeratin 7 (CK7) and Napsin-A. The positivity for CDX2 and CK20, along with negativity for CK7 and Napsin-A, supported the diagnosis of metastasis from a colorectal primary (Figure A-F). Lobectomy for right upper lobe lung was done soon afterwards and the patient was started on adjuvant chemotherapy, six cycles have been given until date. Informed consent from the patient to publish the case report was obtained.

Discussion

TTF-1 is regarded as a highly specific (85-100% specificity) and sensitive marker (up to 84% sensitivity) to differentiate primary lung adenocarcinoma from metastatic adenocarcinoma.[2] TTF-1 is a nuclear protein, encoded by NKX2-1 (NK2 homeobox 1) gene, and it works as a transcription factor that regulates gene transcription related to the development and cellular differentiation of the forebrain, thyroid, and lungs.[4] In recent years, several studies have highlighted the fact that some cancers rising in other organs, particularly the intestinal tract, can express TTF-1 positivity.[1]

In our scientific study, TTF-1 and other additional immunohistochemical stains (CK7, Napsin A, CK20 and CDX2) were applied on only metastatic lung adenocarcinoma which is similar to a case reported by Li et al.[5] In the remaining cases, immunohistochemical staining was performed on both primary and metastatic colorectal adenocarcinoma, as shown in Table.[1-3,6] The immunohistochemical stains applied only on metastatic lung tumour are sufficient to differentiate metastatic tumour from primary lung tumour and are also cost effective.

Nordic quality control performed an assessment and concluded that SP141 and clone SPT24 are highly sensitive markers for TTF-1.[3,4] However, using more specific clones such as 8G7G3/1 or 8G7G1/1 may be beneficial in certain cases.[5] We used 8G7G3/1 as it is more specific but less sensitive as compared to SPT24 and SP141.

In our case, the histopathological findings showed cribriforming glands and dirty necrosis, while cases

Table: Reported cases of TTF-1 positive lung tumours originating from colorectal adenocarcinoma.

Case #	Study by	Age (years)	Sex	Primary Site	Secondary and Primary Site	Status of Immunohistochemistry Markers (NP: Not Performed)				
						TTF-1	Napsin A	CK7	CK20	CDX2
1	Aversa et al.[1] 2018	69	M	Rectum	Lung tumour	+	-	-	+	+
					Primary tumour	+	Unknown	Unknown	Unknown	Unknown
2	Belalcazar et al.[2] 2016	53	M	Rectum	Lung tumour	+	NP	-	+	+
					Primary tumour	+	Unknown	Unknown	Unknown	Unknown
3	Takanashi et al.[3] 2022	42	M	Rectum	Lung tumour	+	-	-	+	+
					Primary tumour	+	-	-	+	+
4	Li et al.[5] 2022	58	M	Rectum	Lung tumour	+	+	-	+	+
					Primary tumour	NP	NP	NP	NP	NP
5	Ito et al.[6] 2017	70	M	Rectum	Lung tumour	+	+	NP	NP	NP
					Primary tumour	+	+	NP	NP	NP
6	Our Case 2023	63	M	Sigmoid colon	Lung tumour	+	-	-	+	+
					Primary tumour	NP	NP	NP	NP	NP

published by Aversa et al, Ito et al. and Takanashi et al. showed epitheliomorphic neoplasm with acinar differentiation which resembled primary rectal adenocarcinoma.[1,3,6] However, Li et al. reported adenocarcinoma without clear features that were suggestive of the site of origin.[1,3,5-7] The cribriforming glands and dirty necrosis favoured that the adenocarcinoma is colorectal in origin.

For diagnosis of TTF-1 positive lung adenocarcinoma, from a colorectal primary, a variety of immunohistochemical markers were used that have been reported in six independent cases, including our case (Table 1).[1-3,5,6] Except for our case and case 4, TTF-1 positivity was observed in both the primary and metastatic lung tumours. In our case and case 4 IHC markers were not tested on the primary tumour. Furthermore, except for case 2, all cases including ours tested positive for CK20 and CDX2, while CK7 was negative. Napsin A, a marker which is highly specific for alveolar epithelium was found positive in the lung tumours of Case 2 and case 4, while it was negative in our case and the remaining cases.

Overall, as techniques for detecting proteins in tissues continue to improve, it is likely that more cases with TTF-1 positivity will be identified. Therefore, it is necessary to understand the importance of judicious use of immunohistochemical stains for accurate diagnosis.[2] In our case, the previous history of sigmoid adenocarcinoma, histopathological features of lung metastasis (cribriforming glands and dirty necrosis) and immunohistochemistry results indicated a diagnosis of metastatic adenocarcinoma of colorectal origin. Cases of occult primary malignancies with pulmonary metastasis or recurrence with metastatic lesions may pose a diagnostic challenge.[1]

TTF-1 plays a significant role in the development and maturation of the thyroid, lung bronchi, and central nervous system. It has a well established role in differentiating pulmonary adenocarcinoma from non-pulmonary adenocarcinoma, but its function in the gastrointestinal tract (GIT) remains unclear. Its presence in the metastatic GIT tumours could be further investigated.[8,9] We recommend interpreting TTF-1 in the context of additional immunohistochemistry markers including CK20, CDX2 and CK7 and using SPT24 antibody due to it's higher sensitivity. Finally, if available, concurrent evaluation of the primary tumour pathology can be of great help in achieving the correct diagnosis and, in offering our patients the most appropriate treatment.[2] In addition to IHC markers, imaging studies also play a significant role in assessment, ^{18}F-FDG PET/CT has a higher sensitivity than conventional CT in detecting extra-hepatic metastasis, and is a more accurate, non-invasive method for detecting metastasis of CRC.[10] It is the collection of findings i.e. clinical history, histopathological features and immuno-histochemistry results of TTF-1, Napsin A, CDX2, CK7, and CK20, that leads to the most accurate diagnosis.

Conclusion

This case highlights, the non-negligible frequency of TTF-1 positivity in colorectal adenocarcinoma, it is essential to apply additional immunostains, such as Napsin A, CDX2, CK7, and CK20, as it is critical in the differential diagnosis of primary lung adenocarcinoma and metastatic colorectal adenocarcinoma on biopsy or FNAs cell blocks. The unusual presentation underscores the need for histopathologists to maintain a broad differential diagnosis and consider applying additional immunostains irrespective of TTF-1 positivity in lung adenocarcinoma particularly in patients with colorectal adenocarcinoma. It is noteworthy that other diagnostic challenges will remain, including cases of recurrence with a single metastatic lesion or new cases of occult primary malignancies with lung metastasis.

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Author Contribution:

BY & HMQ: Concept, design, drafting, revision, final approval and agreement to be accountable for all aspects of the work.

MAA & NH: Data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.