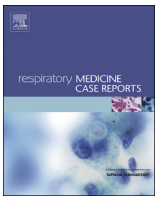
Respiratory Medicine Case Reports 42 (2023) 101812

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Thyroid transcription factor-1 expression in rectal adenocarcinoma metastatic to the lung

Yusuke Takanashi [a], Kiyotaka Kurachi [b], Mayu Fujihiro [c], Keigo Sekihara [a], Kakeru Torii [a], Akikazu Kawase [a], Yuta Matsubayashi [a], Takamitsu Hayakawa [a], Satoshi Baba [c], Haruhiko Sugimura [d], Toshihide Iwashita [e], Kazuhito Funai [a, *]

[a] *First Department of Surgery, Hamamatsu University School of Medicine, Hamamatsu city, Shizuoka prefecture, Japan*
[b] *Second Department of Surgery, Hamamatsu University School of Medicine, Hamamatsu city, Shizuoka prefecture, Japan*
[c] *Department of Diagnostic Pathology, Hamamatsu University School of Medicine Hospital, Hamamatsu city, Shizuoka prefecture, Japan*
[d] *Department of Tumor Pathology, Hamamatsu University School of Medicine, Hamamatsu city, Shizuoka prefecture, Japan*
[e] *Department of Regenerative and Infectious Pathology, Hamamatsu University School of Medicine, Hamamatsu city, Shizuoka prefecture, Japan*

ARTICLE INFO

Keywords:
Colorectal adenocarcinoma
Metastatic lung tumor
Thyroid transcription factor-1

ABSTRACT

Distinguishing metastatic lung tumors from primary lung cancer is essential for planning the appropriate treatment strategy. Thyroid transcription factor-1 (TTF-1) is a reliable immunohistochemistry (IHC) marker for differentiating between primary lung adenocarcinomas and metastatic lung tumors originating from colorectal adenocarcinomas. Herein, we report a rare case of TTF-1 expression in both the metastatic lung tumor and primary rectal adenocarcinoma. Aside from the similar histological characteristics of both tumors when stained with hematoxylin–eosin, the IHC patterns, including negative results for alveolar epithelium markers (napsin A and CK7) and positive results for intestinal markers (CK20, CDX2, SATB2, and β-catenin), of the lung tumor and the primary rectal adenocarcinoma strongly supported the final diagnosis. Considering the non-negligible frequency of TTF-1 positivity in colorectal adenocarcinomas, applying the IHC panel including multiple markers for alveolar epithelium and intestinal differentiation, would be helpful to support the diagnosis of metastatic lung tumor from a rectal adenocarcinoma.

Abbreviations

CDX2	*caudal*-related homeobox transcription factor 2
CK20	cytokeratin 20
CK7	cytokeratin 7
IHC	immunohistochemistry
SATB2	special AT-rich sequence binding protein 2
S6	superior segment

* Corresponding author. First Department of Surgery, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka, 431-3192, Japan.
E-mail address: kfunai@hama-med.ac.jp (K. Funai).

https://doi.org/10.1016/j.rmcr.2023.101812
Received 13 November 2022; Received in revised form 16 December 2022; Accepted 5 January 2023
Available online 5 January 2023

TTF-1	thyroid transcription factor-1

1. Introduction

Distinguishing metastatic lung tumors from primary lung cancer is essential for planning the appropriate treatment strategy. Thyroid transcription factor-1 (TTF-1) is an immunohistochemistry (IHC) marker with a high sensitivity and specificity and is the gold-standard for distinguishing primary lung adenocarcinomas from metastatic colorectal adenocarcinoma [1]. Herein, we report a rare case of TTF-1 expression in a metastatic lung tumor originating from a rectal adenocarcinoma. The consistent IHC patterns, including the alveolar epithelium and positive intestinal markers, between the lung tumor and primary rectal adenocarcinoma were decisive factors for arriving at a definitive diagnosis.

2. Case report

A 42-year-old man was diagnosed with rectal cancer (cT2N2bMx [UICC 8th edition]) with a solid nodule measuring 21 × 20 mm in diameter at the superior segment (S6) of the left lower lobe on the chest computed tomography (Fig. 1). The lung nodule was considered to be either primary lung cancer or metastatic lung tumor originating from the rectal cancer. Firstly, the patient underwent laparoscopic ultralow anterior resection with lateral lymph node dissection for the rectal cancer (moderately differentiated tubular adenocarcinoma, pT4aN2bMx). Six weeks after rectal surgery, we performed robotic-assisted thoracoscopic S6 segmentectomy to both diagnose and treat the tumor. As the intraoperative pathological diagnosis of the lung nodule was metastatic tubular adenocarcinoma resembling rectal adenocarcinoma, we did not perform further resection. The patient had an uneventful postoperative course and was discharged on the 4th postoperative day.

We conducted detailed pathological examinations of the obtained tumor samples, including IHC analysis of markers for differentiating metastatic and primary lung adenocarcinoma. Hematoxylin–eosin staining of the lung tumor demonstrated columnar epithelial cancer cells consisting of tubular structures (Fig. 2a); these morphologies resembled rectal adenocarcinoma (Fig. 2i). However, contrary to our expectations, TTF-1 (clone: SPT24, Novocastra, San Ramon, CA, USA) was positive in the lung tumor sample (Fig. 2b), prompting us to retrospectively review the rectal adenocarcinoma specimen. Surprisingly, TTF-1 was also positive in the rectal adenocarcinoma specimen (Fig. 2j). Further results of IHC were as follows: the lung tumor sample was napsin A (−) (clone: IP64, Novocastra, San Ramon, CA, USA), cytokeratin 7 (CK7) (−) (clone: SP52, Ventana, Tucson, AZ, USA), cytokeratin 20 (CK20) (+) (clone: SP33, Ventana, Tucson, AZ, USA), *Caudal*-related homeobox transcription factor 2 (CDX2) (weakly +) (clone: CDX2-88, Biocare Medical, Pacheco, CA, USA), special AT-rich sequence binding protein 2 (SATB2) (+) (clone: EPNCIR130A, abcam, Cambridge, UK), and β-catenin (+) (clone: 17C2, Leica Biosystems Newcastle Ltd, Newcastle, UK) (Fig. 2c–h); the rectal adenocarcinoma sample was napsin A (−), CK7 (−), CK20 (partly +), CDX2 (weakly +), SATB2 (+), and β-catenin (+) (Fig. 2k-p). Hence, we diagnosed the lung tumor as metastatic rectal adenocarcinoma based on the histological findings and the IHC results. We applied MEBGEN RASKET™-B kit (RASKET-B) (Medical & Biological Laboratories Co., Tokyo, Japan) for the pulmonary lesion and confirmed BRAF wild and KRAS mu-

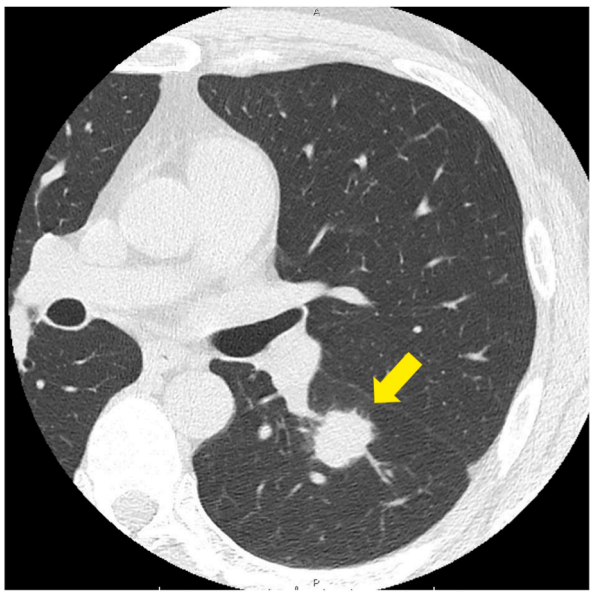


Fig. 1. Chest computed tomography image demonstrating a solid nodule (arrow) measuring 21 × 20 mm in diameter in the superior segment (S6) of the left lower lobe.

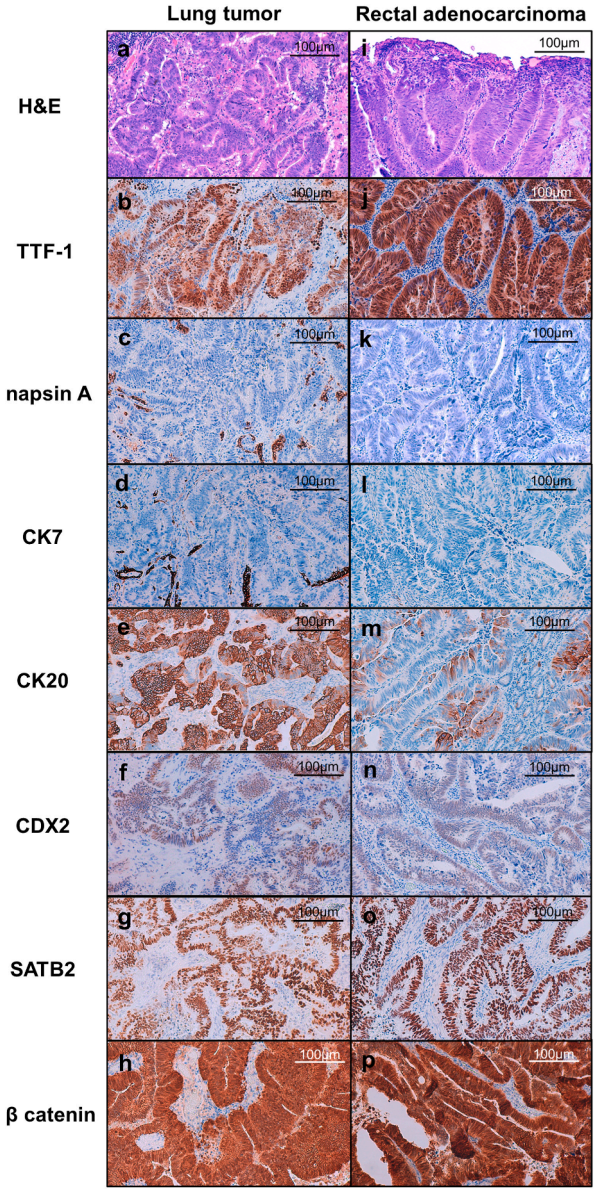


Fig. 2. Histopathological findings of the lung tumor and rectal adenocarcinoma (200 × magnification). Hematoxylin–eosin staining of the lung tumor sample demonstrated columnar epithelial cancer cells consisting of tubular structures (a) that resembled rectal adenocarcinoma (i). Thyroid transcription factor-1 (TTF-1) was positive in both the lung (b) and rectal adenocarcinoma samples (j). Further results of immunohistochemistry were as follows: the lung tumor sample was napsin A (−) (c), cytokeratin 7 (CK7) (−) (d), cytokeratin 20 (CK20) (+) (e), *Caudal*-related homeobox transcription factor 2 (CDX2) (weakly +) (f), special AT-rich sequence binding protein 2 (SATB2) (+) (g) and β-catenin (+) (h); the rectal adenocarcinoma sample was napsin A (−) (k), CK7 (−) (l), CK20 (partly +) (m), CDX2 (weakly +) (n), SATB2 (+) (o), and β-catenin (+) (p).

tation (G12R). The pathological stage of the rectal cancer was confirmed as pT4aN2bM1 stage IV (UICC 8th edition), and the patient initiated systemic chemotherapy based on the results of RASKET-B.

3. Discussion

TTF-1 is expressed in alveolar type II cells and Clara cells of the lungs, and follicular cells of the thyroid gland [2]. Three commercial monoclonal antibodies against TTF-1 (clones SPT24, SP414, and 8G7G3/1) with varying diagnostic attribution are available for IHC use: SPT24 and SP141, which have superior sensitivity over 8G7G3/1 [3]. In our case, SPT24 was used for IHC studies. Although TTF-1 expression in other organs is rare, 5% of metastatic lung tumors originating from colorectal adenocarcinomas are TTF-1-positive [3]. In such cases, the differential diagnosis between primary and metastatic lung cancer needs further validation by IHC markers.

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

Case		Year	Age	Sex	Primary site		TTF-1	napsin A	CK7	CK20	CDX2	SATB2	β-catenin
1	Belalcazar et al. [4]	2016	53	M	rectum	lung tumor	+	not performed	–	+	+	not performed	not performed
						primary tumor	+	unknown	unknown	unknown	unknown	unknown	unknown
2	Ito et al. [5]	2017	70	M	rectum	lung tumor	+	+	not performed	not performed	not performed	not performed	not performed
						primary tumor	+	+	not performed	not performed	not performed	not performed	not performed
3	Aversa et al. [6]	2018	69	M	rectum	lung tumor	+	–	–	+	+	not performed	not performed
						primary tumor	+	unknown	unknown	unknown	unknown	unknown	unknown
4	Li et al. [7]	2020	58	M	rectum	lung tumor	+	+	–	+	+	not performed	not performed
						primary tumor	not performed	not performed	not performed	not performed	not performed	not performed	not performed
5	our case	2022	42	M	rectum	lung tumor	+	–	–	+	+	+	+
						primary tumor	+	–	–	+	+	+	+

The use of various IHC markers for diagnosing TTF-1-positive lung tumors originating from colorectal adenocarcinoma have been reported in five independent cases listed in Table 1 [4–7], including our case (Table 1). Except for case 4, TTF-1 positivity was observed in both the primary and metastatic lung tumors. As TTF-1 positivity was consistent between the metastatic lung and primary colorectal tumors in our case, our findings strongly supported the diagnosis of metastasis from a primary colorectal tumor. Moreover, in the four cases except for case 2, CK7 positivity and CK20 and CDX2 negativity were confirmed. In cases 2 and 4, napsin A, which is highly specific for alveolar epithelium, was positive in the lung tumor. Consistent napsin A positivity in the metastatic and primary lung tumors supported the diagnosis in case 2. In our case, a broad IHC panel, including new enteric markers (SATB2 and β-catenin) that are useful in differentiating between pulmonary enteric-type adenocarcinomas (PEA) and metastatic colorectal adenocarcinomas [8], was used for testing both lung and primary tumor samples to confirm the diagnosis of metastatic colorectal cancer. SATB2 is a known intestinal differentiation marker rarely expressed in PEAs (13%), whereas the reported positive rate of SATB2 in colorectal adenocarcinomas is 100% [8]. Meanwhile, the accumulation of β-catenin is caused by adenomatous polyposis coli gene mutation, which is common in colorectal adenocarcinomas [8]. The positive rates of β-catenin in PEAs and colorectal adenocarcinomas are 0% and 55%, respectively [8]. Thus, the differential diagnosis of PEA was excluded in our case. Additionally, the primary tumor sites in all cases were the rectum, which is consistent with a previous report stating that TTF-1 positivity in colorectal adenocarcinomas is associated with distant metastatic tumor locations [3].

Lastly, rare cases of TTF-1 expression in adenocarcinomas arising outside from the lung or thyroid are reported: 2.4% in breast carcinomas [9], 5.5–22% in serous carcinoma of the uterus and ovary [10], 5.5–22% in endometrioid carcinoma of the uterus [10], and 14% in clear cell carcinoma of the ovary [10]. Metastasis from these malignant tumors should also be raised as pitfall.

4. Conclusion

Considering the non-negligible frequency of TTF-1 positivity in colorectal adenocarcinomas [3], the application of an IHC panel including multiple markers for alveolar epithelium and intestinal differentiation, would be helpful to support the diagnosis of a metastatic lung tumor from a primary rectal adenocarcinoma.

Funding

This study was supported by Smoking Research Foundation (X 108).

Author contributions

Yusuke Takanashi drafted the manuscript. Kiyotaka Kurachi, Mayu Fujihiro, Toshihide Iwashita, Kazuhito Funai, Akikazu Kawase, Keigo Sekihara and Kakeru Torii collected clinical data, commented on and revised the manuscript. Yuta Matsubayashi, Takamitsu Hayakawa, Satoshi Baba and Haruhiko Sugimura commented and revised the drafted manuscript. All authors approved the final manuscript critically.

Ethics statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

Declaration of competing interest

None declared.

Acknowledgments

The authors would like to thank Enago (WWW.enago.jp) for the English language review.

References

[1] K. Inamura, Y. Satoh, S. Okumura, K. Nakagawa, E. Tsuchiya, M. Fukayama, et al., Pulmonary adenocarcinomas with enteric differentiation: histologic and immunohistochemical characteristics compared with metastatic colorectal cancers and usual pulmonary adenocarcinomas, Am. J. Surg. Pathol. 29 (5) (2005) 660–665.
[2] V. Boggaram, Thyroid transcription factor-1 (TTF-1/Nkx2.1/TITF1) gene regulation in the lung, Clin. Sci. (Lond.) 116 (1) (2009) 27–35.
[3] J.M. Bae, J.H. Kim, J.H. Park, H.E. Park, N.Y. Cho, G.H. Kang, Clinicopathological and molecular implications of aberrant thyroid transcription factor-1 expression in colorectal carcinomas: an immunohistochemical analysis of 1319 cases using three different antibody clones, Histopathology 72 (3) (2018) 423–432.
[4] A. Belalcazar, U. Krishnamurti, W. Shaib, TTF-1 expression in rectal adenocarcinoma: a case report and review of the literature, Case Rep. Oncol. 9 (3) (2016) 747–751.
[5] T. Ito, K. Nakanishi, H. Goto, A case of napsin A-positive metastatic lung cancer originating from the colon, Surg. Case Rep. 3 (1) (2017) 114.
[6] S. Aversa, C. Bellan, TTF1 expression in pulmonary metastatic rectal adenocarcinoma, Case Rep. Gastrointest. Med. 2018 (2018) 6405125.
[7] W. Li, M.B. Cohen, TTF-1, napsin A and CDX2 co-expression in metastatic rectal adenocarcinoma to the lung, Cytopathology 32 (1) (2021) 146–148.
[8] J. Matsushima, T. Yazawa, M. Suzuki, Y. Takahashi, S. Ota, T. Nakajima, et al., Clinicopathological, immunohistochemical, and mutational analyses of pulmonary enteric adenocarcinoma: usefulness of SATB2 and β-catenin immunostaining for differentiation from metastatic colorectal carcinoma, Hum. Pathol. 64 (2017) 179–185.
[9] R. Judith, G. Lynn, M.G. Allen, J.S. Stuart, Thyroid transcription factor-1 expression in breast carcinomas, Am. J. Surg. Pathol. 34 (12) (2010) 1881–1885.
[10] J.Z. Paul, G.G. Hong, L.P. Theresa, L. Leslie, A.L. Virginia, TTF-1 expression in ovarian and uterine epithelial neoplasia and its potential significance, an immunohistochemical assessment with multiple monoclonal antibodies and different secondary detection systems, Int. J. Gynecol. Pathol. 28 (1) (2009) 10–18.