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病理病期IA肺腺癌におけるサブタイプと予後の関係.	吉屋智晴，宮田義浩，坪川典史，笹田伸介，見前隆洋，村上修司，伊藤宏之，中山治彦，岡田守人.	第67回日本胸部外科学会定期学術集会，ポスター，福岡.	2014年9月	国内
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小型肺癌に対する外科治療の理論と動向.	淺村尚生.	第43回頭頸部・胸部画像研究会，招請講演，東京都.	2014年5月	国内
分子病理学的背景から考える高齢者肺癌の治療戦略.	西井鉄平，伊藤宏之，今井健太郎，今村奈緒子，渡部真人，中山治彦，横瀬智之，宮城洋平，益田宗孝.	第31回日本呼吸器外科学会総会，一般ポスター，東京.	2014年5月.	国内
切除肺検体において触れなかった病変の画像的・病理学的検討.	伊坂哲哉，伊藤宏之，横瀬智之，狩野芙美，村上修司，近藤哲郎，斎藤春洋，尾下文浩，今村奈緒子，渡部真人，今井健太郎，西井鉄平，山田耕三，中山治彦，益田宗孝.	第31回日本呼吸器外科学会総会，一般口演，東京.	2014年5月	国内

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高齢者肺癌の長期治療成績—葉切に対する術前評価と認知機能に関しての検討—.	伊藤宏之，中山治彦，西井鉄平，今井健太郎，今村奈緒子，渡部真人，益田宗孝.	第114回日本外科学会定期学術集会，ポスターセッション，京都.	2014年4月	国内
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2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Tumour-to-tumour metastasis from papillary thyroid carcinoma with BRAF mutation to lung adenocarcinoma with EGFR mutation: the utility of mutation-specific antibodies.	Katsuya Y, Yoshida A, Watanabe S, Tsuta K.	Histopathology.	2015 Jan (Epub ahead of print)	国外
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（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。
（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

Ⅴ．研究成果の刊行物・別刷

Histopathology

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SHORT REPORT

Tumour-to-tumour metastasis from papillary thyroid carcinoma with *BRAF* mutation to lung adenocarcinoma with *EGFR* mutation: the utility of mutation-specific antibodies

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Tumour-to-tumour metastasis from papillary thyroid carcinoma with *BRAF* mutation to lung adenocarcinoma with *EGFR* mutation: the utility of mutation-specific antibodies

Aims: Tumour-to-tumour metastasis is a rare event. The aim of this study is to demonstrate the utility of mutation-specific antibodies to prove the occurrence of metastatic papillary thyroid cancer donor into lung adenocarcinoma recipient.

Methods and results: We report the case of an 80-year-old woman who had a papillary thyroid carcinoma with a v-raf murine sarcoma viral oncogene homologue B1 mutation that metastasized into a lung adenocarcinoma with an epidermal growth factor receptor mutation. Immunohistochemical analysis with mutation-specific antibodies not only clearly revealed two components, but also revealed their gene mutation statuses.

Conclusions: As a component of multimodal diagnostic tools, immunohistochemistry can avoid some pitfalls involved in the molecular diagnosis of complicated cases (such as our own) and can help to ensure that patients receive optimal treatments.

Keywords: gene mutation, immunohistochemistry, lung adenocarcinoma, papillary thyroid tumour, tumour-to-tumour metastasis

Introduction

Tumour-to-tumour metastasis was first reported by Berent in 1902.[1] The definition of tumour-to-tumour metastasis is the metastasis of one tumour into another, including both malignant-to-benign tumour metastasis and malignant-to-malignant metastasis. In malignant-to-malignant metastasis, the most frequent metastatic donor is lung cancer[2] and the most frequent recipient is renal cell carcinoma.[3] The incidence of cases in which lung cancer is the recipient is relatively low.[4–7] To date, only eight cases of tumour-to-tumour metastasis into the lung have been reported in the English-language literature.[3,7–13]

Driver mutations occur in genes that are crucial for tumour formation and maintenance, and cancers rely on the expression of these oncogenes for survival. Thus, anticancer agents have been developed to specifically target driver mutation genes, such as the epidermal growth factor receptor (*EGFR*) gene in lung carcinoma and v-raf murine sarcoma viral oncogene homologue B1 (*BRAF* V600E) in papillary thyroid carcinoma. Although molecular-based analyses constitute the gold standard for detecting such gene mutations, immunohistochemical tests with mutation-specific

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antibodies have the advantage of allowing the detailed visualization of protein distributions *in situ* through light microscopy.

Here, we describe a case of papillary thyroid carcinoma metastasis into lung adenocarcinoma. Using immunohistochemical examinations, we demonstrate that it is possible to determine the histology and gene mutation status, each of which is helpful for treatment.

Clinical summary

An 80-year-old Japanese woman presented with hoarseness for 3 months. Her medical history included hypertension, asthma, and a history of cholecystectomy. She had never smoked, and two of her brothers had a history of lung cancer. Physical examination revealed a 30-mm nodule in the left lobe of her thyroid.

Laboratory tests showed elevated serum levels of thyroglobulin (86.8 ng/ml; normal range <35 ng/ml), whereas the levels of other thyroid hormones were within the normal ranges. No tumour marker showed remarkable elevation. A fine-needle aspiration biopsy specimen of the thyroid revealed papillary thyroid carcinoma.

During preparation for an operation, a chest radiograph revealed a ground-glass nodule (GGN) in the right upper area of the lung. Computed tomography of the chest revealed a 28-mm part-solid GGN in the right upper lobe of the lung, and multiple well-circumscribed nodules in both sides of the lung. [^{18}F] Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography showed an ^{18}F-FDG-avid nodule in the thyroid [maximum standard uptake value (SUV-max.) 10.06], the GGN in the right upper lung (SUV-max. 2.08), and multiple nodules in both sides of the lung (SUV-max. range 3.06–4.87). Furthermore, one right lateral cervical lymph node was also positive (SUV-max. 7.74). The multiple masses were considered to be metastases of thyroid carcinoma, but primary lung cancer was highly suspected in regard to the GGN in the right upper lobe. The patient declined to undergo a bronchoscopy for lung biopsy, after which lobectomy of the right upper lobe was performed.

Methods and results

HISTOPATHOLOGICAL FINDINGS

Macroscopic examination of the resected specimen showed a 25 × 15 × 15-mm solid nodule in segment 1 of the right lung. Cut sections revealed a grey–white firm mass with an irregular border and infiltration into the surrounding lung tissue, but without pleural indentation.

Microscopically, the nodule was composed of two different components of carcinoma (Figure 1A,B). Approximately 80% of the total tumour area on the maximum cutting surface consisted of lung adenocarcinoma, and the remainder consisted of papillary thyroid carcinoma. Regarding the lung adenocarcinoma, the predominant histological subtype was lepidic predominant adenocarcinoma (Figure 1C). Regarding the papillary thyroid carcinoma, two metastatic deposits were distributed in the lung adenocarcinoma. The larger deposit (22 mm in diameter) was located in the middle of the tumour area. Both of the deposits were clearly delineated, with well-circumscribed borders with the lung adenocarcinoma component. The cells of the papillary thyroid carcinoma showed intranuclear cytoplasmic inclusions and nuclear grooves (Figure 1D). The transitional zone was not observed, and the two components differed because of the destruction of elastic fibres within the papillary thyroid carcinoma component (Figure 1B). The histological diagnosis was pulmonary adenocarcinoma pT1bN0M0, stage IA, and multiple metastatic papillary thyroid carcinoma stage IV.

IMMUNOHISTOCHEMICAL FINDINGS

Four-micrometre sections from the paraffin-embedded specimen were prepared for immunohistochemistry. Immunohistochemical staining was performed with the following primary antibodies: anti-thyroid transcription factor-1 (TTF-1) (8G7G3/1, dilution × 100; Dako, Carpinteria, CA, USA), anti-napsin A (TMU-Ad02, dilution × 400; IBL, Gunma, Japan), anti-EGFR exon 19 deletion (E746-A750) (6B6, dilution × 200; Cell Signaling Technology, Danvers, MA, USA), anti-EGFR L858R (43B2, dilution × 200; Cell Signaling Technology), anti-PAX8 (ag0306, dilution × 100; Proteintech, Chicago, IL, USA), and anti BRAF V600E (VE1, dilution × 200; Spring Bioscience, Pleasanton, CA, USA). Subsequent development of antibody-bridge labelling with the EnVision/HRP system (Dako) with haematoxylin counterstaining was performed. Appropriate positive and negative controls were run simultaneously.

For EGFR L858R and BRAF V600E, double immunohistochemical staining was performed. The EGFR L858R antibody was visualized with the Liquid DAB+ Substrate Chromogen System (Dako). Subsequently, immunostaining for BRAF V600E antibody