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Immunohistochemical pattern analysis of squamous cell carcinoma: Lung primary and metastatic tumors of head and neck☆

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ABSTRACT

Objectives: This study aimed to develop an immunohistochemical (IHC) diagnostic algorithm for primary lung squamous cell carcinoma (LSCC) and pulmonary metastasis of head and neck SCC (HNSCC).
Materials and methods: We selected three antibodies (CK19, MMP3, and PI3) from a web-based gene expression database and an IHC analysis available online. We developed an IHC diagnostic algorithm using tissue microarrays from 39 LSCCs and 48 HNSCCs as the training set. It was validated using whole tumor sections of 32 LSCCs and 23 HNSCCs. The algorithm was applied to 28 cases with a history of HNSCC and who underwent resection of pulmonary squamous cell tumors.
Results: The sensitivity, specificity, and accuracy of the algorithm were 90%, 62%, and 77%, respectively, in the training set and 96%, 44%, and 65%, respectively, in the validation set. Twenty-three of 28 SCCs were diagnosed as metastasis of HNSCC; the remaining five tumors were diagnosed as LSCC. Among the patients in the HNSCC group, 18 developed postoperative recurrence and 11 died of the disease, whereas only one patient in the LSCC group had recurrence. Compared with the LSCC group, the HNSCC group had poorer prognosis (P = 0.07). IHC diagnosis coincided with the retrospective diagnosis in 22 (79%) of the 28 patients (sensitivity, 95%; specificity, 44%).
Conclusion: The IHC diagnostic algorithm may be clinically useful for distinguishing between LSCC and pulmonary metastasis of HNSCC.

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1. Introduction

Distinguishing between a primary lung cancer and a solitary pulmonary metastasis is sometimes difficult. In particular, the presence of squamous cell carcinoma (SCC) in the lungs of patients with a history of head and neck SCC (HNSCC) frequently presents a confounding problem. Primary lung SCC (LSCC) in patients with HNSCC is not uncommon because patients with HNSCC have a high risk of developing lung cancer [1–5]. Numerous risk factors, such as tobacco exposure, are shared by LSCC and HNSCC. However, 5%–15% of patients with HNSCC develop pulmonary metastasis [6–8].

An accurate definitive diagnosis is clinically important for treating patients. The prognosis and therapeutic options for patients with metastatic HNSCC are considerably different from patients with localized primary LSCC. However, the clinical, pathological and immunohistochemical (IHC) diagnostic methods have not yet been completely established. Various molecular methods have been developed; however, these have not yet been practically applied [9].

This study aimed to develop a new diagnostic algorithm for primary LSCC and pulmonary metastasis from HNSCC on the basis of the IHC pattern

Abbreviations: FFPE, formalin-fixed paraffin-embedded; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemical; LSCC, lung squamous cell carcinoma; NPV, negative predictive value; PPV, positive predictive value; RFP, recurrence-free probability; SCC, squamous cell carcinoma.

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Table 1
Details of the selected antibodies and staining conditions.

Antibody	Source	Clone	Staining	Activation	Dilution	Localization
CK19	Dako	RCK108	Autostainer	CC1 60 min	1:100	Cytoplasm, Cell membrane
MMP3	Santa Cruz Biotechnology	1B4	Manual	Autoclave pH6.0	1:50	Cytoplasm, Cell membrane
PI3	Atlas Antibodies AB	Polyclonal	Autostainer	CC1 60 min	1:500	Cytoplasm

CK19, keratin 19, type I; MMP3, matrix metallopeptidase 3; PI3, peptidase inhibitor 3; CC1, cell conditioning solution (Ventana, Tucson, AZ).

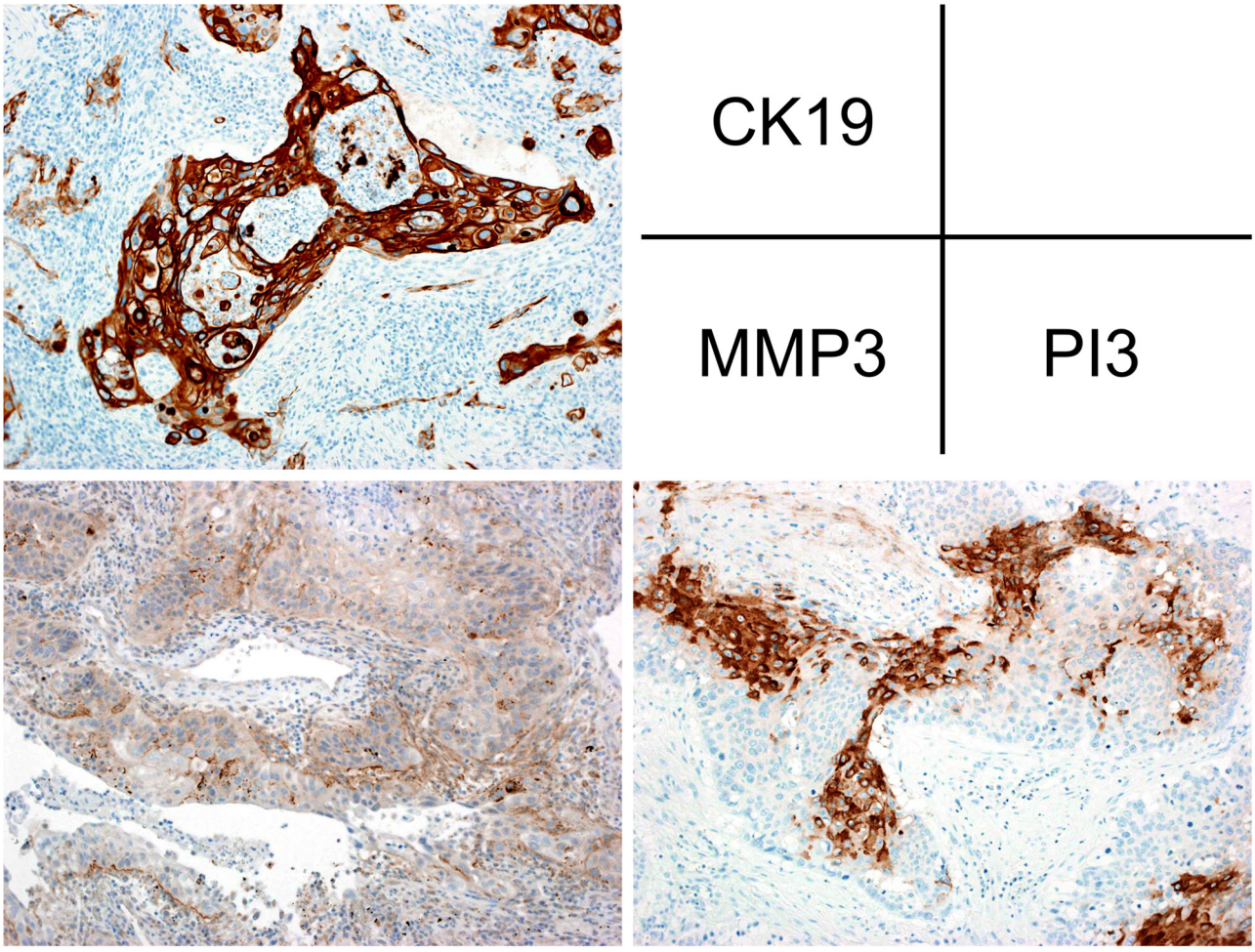

Fig. 1. Representative results of IHC staining with CK19, MMP3, and PI3. The image of CK19 staining shows that >95% of tumor cells were positive. The images of MMP3 and PI3 staining show that 50%–95% of tumor cells were positive.

2. Materials and methods

2.1. Antibody selection and IHC staining

To select useful antibodies, we extracted the top 50 genes that were markedly and differently expressed between LSCC and HNSCC from the analysis of Vachani et al. [10] comparing the expression profiles between 10 LSCCs and 18 HNSCCs using Affymetrix U133A GeneChips. Then, we selected three antibodies that had IHC results available in the Human Protein Atlas (http://www.proteinatlas.org) and that were distinguishable between LSCC and HNSCC: these were M088801 (Dako, Glostrup, Denmark) to keratin 19, type I (CK19), SC-21732 (Santa Cruz Biotechnology, Santa Cruz, CA) to matrix metallopeptidase 3 (MMP3), and HPA017737 (Atlas Antibodies AB, Stockholm, Sweden) to peptidase inhibitor 3 (PI3). The details of the selected antibodies and IHC staining conditions are shown in Table 1. Automated IHC staining was performed using the Ventana Benchmark automated staining system (Ventana Medical Systems, Tucson, AZ). IHC staining was evaluated by four grades according to the percentage of positive tumor cells: >95%, 50–95%, 5–50%, and <5%. The representative results of IHC staining are shown in Fig. 1.

2.2. Establishing and validating the IHC diagnostic algorithm

We prepared tissue microarrays using archived formalin-fixed paraffin-embedded (FFPE) specimens of 39 LSCCs from patients without a history of HNSCC and 48 HNSCCs at the primary site (two cores for each case) as the training set; the staining positivity of the three antibodies was evaluated using these FFPE specimens. We developed the IHC diagnostic algorithm (Fig. 3) on the basis of the IHC pattern analysis. Staining was defined as negative when <5% of tumor cells were positive; otherwise, the staining was regarded as positive.

The algorithm was validated using the FFPE whole tumor sections of 32 LSCCs from patients without a history of HNSCC and 23

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