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Case report

A case of pulmonary pleomorphic carcinoma with malignant phenotypes induced by ZEB1-associated epithelial-mesenchymal transition

Mayo Kondo[a], Hirokazu Ogino[a], Hirohisa Ogawa[b], Tania Afroj[a], Yuko Toyoda[a], Satoshi Sakaguchi[a], Miki Tsuboi[a], Yoshimi Bando[c], Hisatsugu Goto[a], Koichi Tsuneyama[b], Yasuhiko Nishioka[a,*]

[a] Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, Japan
[b] Department of Pathology and Laboratory Medicine, Graduate School of Biomedical Sciences, Tokushima University, Japan
[c] Division of Pathology, Tokushima University Hospital, Japan

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ABSTRACT

A 60-year-old man was admitted to our hospital with non-small cell lung cancer (NSCLC). Imaging and pathological studies revealed NSCLC, not otherwise specified (NOS), at clinical stage T3N1M0 stage IIIA. We started radiotherapy alone because of obstructive pneumonia and end-stage renal disease, but the tumors progressed rapidly and resulted in death due to air obstruction by pharyngeal metastasis. The cancer was diagnosed as pleomorphic carcinoma in an autopsy. Viable lung tumor cells, which were resistant to radiotherapy, and the pharyngeal metastasis had mesenchymal phenotypes and expressed ZEB1 but not SNAI1. These observations indicated that ZEB1-associated epithelial-mesenchymal transition has malignant features including resistance to radiotherapy and aggressive metastatic potential. ZEB1-associated EMT may be an important mechanism to understand the pathophysiology of pleomorphic carcinoma.

1. Introduction

Pleomorphic carcinoma is defined as a poorly differentiated non-small cell carcinoma (NSCC) that contains at least 10% spindle and/or giant cells with squamous cell carcinoma, adenocarcinoma, or undifferentiated NSCC, or a carcinoma consisting only of spindle and giant cells [1]. These sarcomatoid components are derived from epithelial components by epithelial-mesenchymal transition (EMT) [2]. Pulmonary pleomorphic carcinoma has a more aggressive clinical course compared to that of other non-small cell lung cancer (NSCLC) [3,4]. However, the nature of pleomorphic carcinoma and optimal treatment remain uncertain because of its rarity.

Pulmonary pleomorphic carcinoma frequently exhibits distant organ metastasis. The progression to metastatic tumor is particularly rapid, resulting in a poor prognosis. Moreover, the cancer sometimes expands into minor organs, such as the gastrointestinal tract, thyroid gland, peritoneum, or lymph nodes of the abdomen, which cannot be observed by clinical examination before death [5].

Here, we report a case of pulmonary pleomorphic carcinoma with a severe malignant phenotype induced by ZEB1-associated EMT.

2. Case report

A 60-year-old man visited the hospital with a complaint of right-side chest pain. He was diagnosed with NSCLC in the upper right lobe by trans-bronchial biopsy and admitted. He had chronic kidney disease due to glomerulonephritis and a smoking history of 70 pack-years.

Blood tests revealed an elevated inflammatory reaction, and marked disturbance of renal function. Tumor markers, such as cytokeratin subunit 19 fragment (CYFRA) and pro-gastrin releasing peptide (Pro GRP), were slightly elevated. Imaging studies revealed a marked enlargement of the tumor shadow in the upper right lung, with no evidence of distant metastases.

He coughed up a tumor clot, and we performed a pathological examination with that clot, which consisted of malignant tumor cells with a high nuclear-to-cytoplasmic ratio (N/C ratio) and acidophilic cytoplasm. Pan-cytokeratin was partially positive, but thyroid transcription factor-1 (TTF-1) and p40 were negative. Therefore, we diagnosed him with poorly differentiated NSCLC, not otherwise specified (NOS), at clinical stage T3N1M0 stage IIIA.

He had obstructive pneumonia and exacerbation of renal

* Corresponding author. Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan.
E-mail address: yasuhiko@tokushima-u.ac.jp (Y. Nishioka).

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dysfunction, which required hemodialysis. These complications necessitated radiotherapy (RT) alone, but the right submandibular lymph nodes metastasis, pharyngeal metastasis, and brain metastasis with hemorrhage rapidly grew in a few weeks. We discontinued RT and initiated chemotherapy with carboplatin (AUC = 2, day 1, 8, 15) and paclitaxel (40 mg/m^2, day 1, 8, 15) every 21 days with local palliative RT to the cervical and brain metastasis. However, the tumor further progressed; the pharynx tumor enlargement caused airway obstruction repeatedly, and the brain metastasis caused symptomatic epilepsy. He died on day 82 after admission.

We performed an autopsy with his family's consent. We found a primary lung tumor on the upper right lobe, and metastasis in the brain, pharynx, larynx, and small intestine macroscopically. Microscopically, we observed pleomorphic tumor cell proliferations, which contained both spindle and giant cells. Immunohistochemistry (IHC) revealed tumor cells that were mostly negative for cytokeratin but strongly positive for vimentin. Therefore, we diagnosed him with pulmonary pleomorphic carcinoma.

Most of the lung tumor had necrosis, which was thought to be induced by RT, but we also observed some viable areas. Viable cells has non-cohesive growth with mesenchymal properties (Fig. 1A). Tumor cells in the pharynx and small intestine had viable cells similar to the lung tumor (Fig. 1B and C) and strongly expressed vimentin (Fig. 1E–G) but not cytokeratin (Fig. 1I–K). On the other hand, tumor cells in the brain had cohesive proliferation and epithelial properties (Fig. 1D). Tumor cells in the necrotic area of the lung tumor and in the brain partially expressed vimentin (Fig. 1H) and cytokeratin (Fig. 1L). These results suggested that mesenchymal components of pleomorphic carcinoma are resistant to RT and induce unusual distant organ metastases, such as in the pharynx or small intestine.

We analyzed the role of EMT in the patient's tumor because mesenchymal tumor cells are derived from epithelial cells by EMT in several types of sarcomatoid carcinoma [2]. IHC showed that ZEB1, which is a representative EMT marker, was strongly positive (Fig. 2A), but SNAI1 and E-cadherin were negative (Fig. 2B and C), which suggests that EMT associated with ZEB1 contributes to malignant phenotypes of pleomorphic carcinoma.

3. Discussion

In general, it is difficult to diagnose pleomorphic carcinoma using small specimens because of tumor heterogeneity. Although we used a tumor clot 3 cm in diameter for pathological analysis, the tumor was poorly differentiated NSCLC (NOS). Because tumor cells were slightly positive for cytokeratin but not TTF-1 and p40, we did not initially analyze mesenchymal expression. This case study suggests that pleomorphic carcinoma is associated with poorly differentiated carcinoma with negative or slightly positive epithelial markers.

Metastasis to minor organs is frequently found on autopsies of patients with pleomorphic carcinoma, but these metastases are difficult to identify before death. In particular, metastasis to the small intestine is detrimental because of intestine perforation in some patients [5]. In our patient, metastasis to the pharynx was the major cause of death because of airway obstruction. These findings suggest that metastases, especially to minor organs, is a major factor for patient prognosis. Positron emission tomography may be useful for investigating metastases to minor organs, but could not be performed in our patient.

Sarcomatoid carcinoma occurs when various tumor cells,

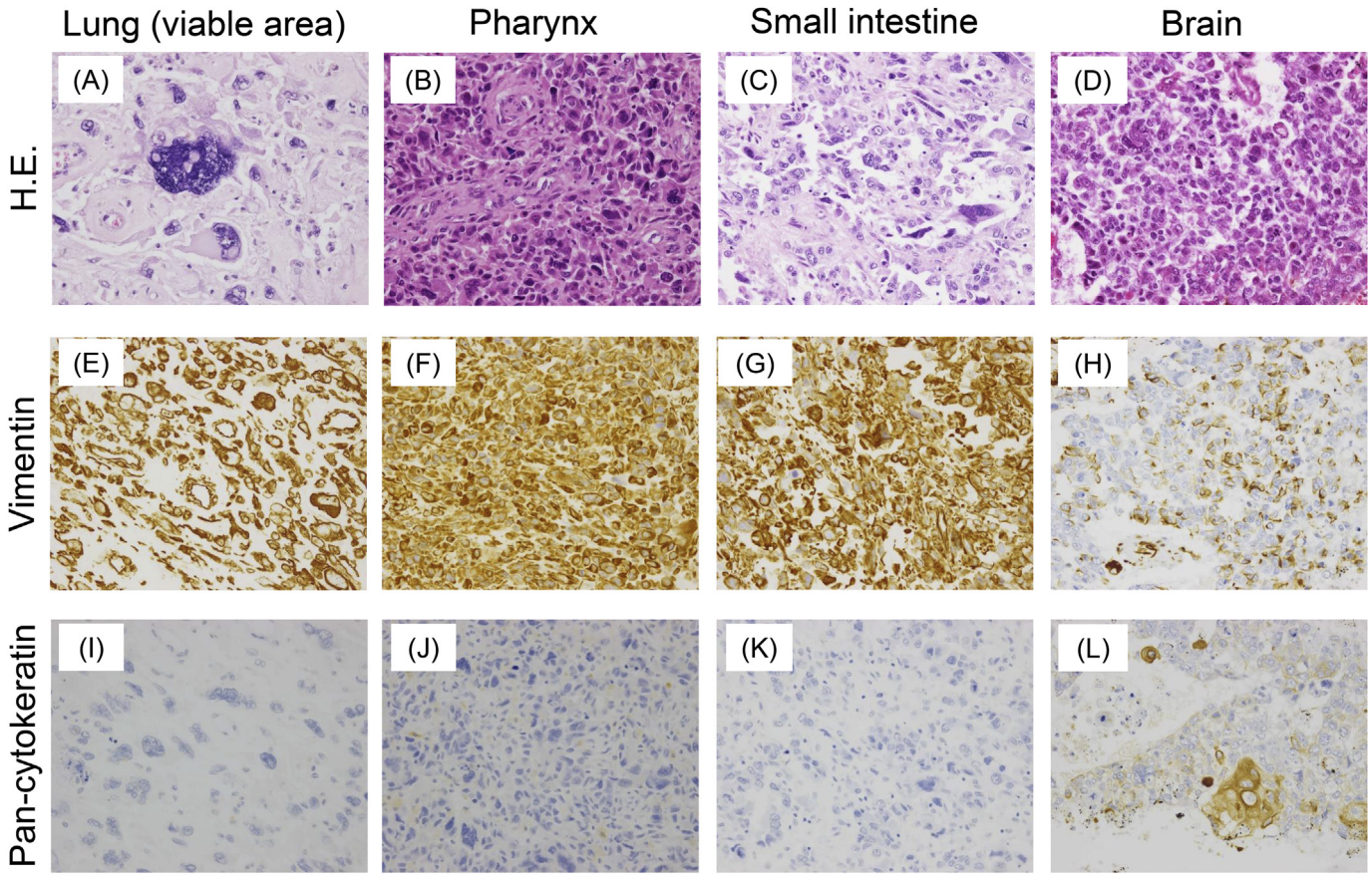

Fig. 1. Histological findings of the autopsy. Pleomorphic tumor cells had non-cohesive growth with mesenchymal properties in viable areas of the lung tumor (A) and in metastatic foci of the pharynx (B) and small intestine (C) by hematoxylin-eosin (HE) staining. These tumor cells strongly expressed vimentin (E–G) but not pan-cytokeratin (I–K). On the other hand, the tumor cells in the brain metastasis had cohesive proliferation with epithelial properties (D), and partially expressed vimentin (H) and pan-cytokeratin (L). Histological sections are shown at 200 × magnification.

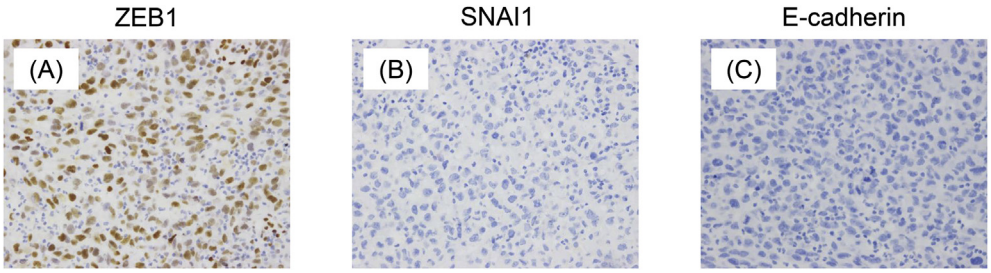

Fig. 2. The expression of epithelial-mesenchymal transition (EMT) markers in the tumor cells of the pharynx metastasis. Immunohistochemistry showed that ZEB1, which is a representative EMT marker, was strongly positive (A), but SNAI1 (B) and E-cadherin (C) were negative in the mesenchymal tumor cells. Histological sections are shown at 200 × magnification.

resembling both carcinomas and sarcomas, co-exist in a single tumor. Clonality analysis has previously shown that sarcoma-like and carcinoma-like components are derived from a common ancestor in sarcomatoid carcinoma [2]. In our case, solid proliferations of spindle and giant cells were observed in the viable area of the lung tumor, and the metastatic foci of the pharynx and small intestine (Fig. 1B and C). Moreover, ZEB1 but not SNAI1 was upregulated in these cells (Fig. 2A and B). EMT is a biological process that converts epithelial cells to mesenchymal cells, which have a higher potential for migration and invasion, and resistance to RT and chemotherapy [6]. EMT is induced by transcriptional factors, such as ZEB1 or SNAI1 [7], which are upregulated in several types of cancers including lung cancer [8]. These results suggest that ZEB1-associated EMT in pleomorphic carcinoma induces mesenchymal cells from epithelial origins, and contributes to malignancy, resistance to RT, and aggressive metastasis. However, we did not detect ZEB1-positive tumor tissues in autopsy samples possibly because of sample quality. Therefore, we could not evaluate differences in ZEB1 expression between primary and metastatic tumors.

RT may induce EMT [9], and expression of mesenchymal markers in clinical NSCLC samples was upregulated after chemoradiotherapy [10]. In our case, the right submandibular lymph nodes metastasis, pharyngeal metastasis, and brain metastasis were rapidly enlarged just after induction of RT. This suggests that RT may have triggered EMT, which resulted in an aggressive clinical course.

In summary, we observed a rare case of pulmonary pleomorphic carcinoma with malignant features possibly induced by ZEB1-associated EMT. This case highlights the importance of histological analysis for considering the possibility of pleomorphic carcinoma, and the effect of metastasis to minor sites. To further understand the role of EMT in the progression of pleomorphic carcinoma, IHC analysis of more tumor tissues is needed.

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