A Rare Case of Primary Pulmonary Choriocarcinoma in a Male: Immunohistochemical Detection for Human Chorionic Gonadotropin, Epidermal Growth Factor (EGF) and EGF-Receptor

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Abstract. A rare case of primary choriocarcinoma of the lung in a male is described with immunohistochemistry for human chorionic gonadotropin (hCG), epidermal growth factor (EGF) and EGF-receptor. The extragonadal trophoblastic origin of this pulmonary carcinoma was definitely confirmed by an autopsy examination, and hCG-production and hCG-positive staining of the tumor cells. Furthermore, the tumor cells clearly expressed EGF and its receptor which play an important role in the proliferation and differentiation of normal and neoplastic trophoblasts of the uterus. Our present case suggests that EGF may act in an autocrine manner in the tumor cells of primary pulmonary choriocarcinoma.

Key words: Choriocarcinoma, Lung, hCG, EGF, EGF-receptor

CHORIOCARCINOMA is a very aggressive and rapidly metastasizing tumor. The tumor is commonly intrauterine associated with gestation [1]. Extrateruterine, nongestational choriocarcinoma is very rare and most cases arise in the gonads, mediastinum, retroperitonium, brain, alimentary tract, liver, kidneys and urinary bladder [2–9]. Less than 16 cases of primary pulmonary choriocarcinoma have been reported and in males only four [10–16]. The expressions of EGF and its receptor, which change dramatically in normal trophoblasts during pregnancy and play a crucial role in the proliferation and differentiation of normal and neoplastic trophoblasts of the uterus, have not been investigated in these cases of pulmonary choriocarcinoma [17–18]. We describe herein primary pulmonary choriocarcinoma in a male with autopsy examination and immunohistochemistry for hCG, EGF and EGF-receptor.

Clinical summary

A 69-year-old male presented with hemoptysis, a 5-kg weight loss for 2 months and bilateral gynecomastia. Neither testis exhibited abnormal physical findings. The patient had a 40-pack-a-year history of cigarette smoking but no past history of any disease. A chest roentgenogram showed a large right lower lobe mass with multiple coin lesions in both lungs. Computed tomography disclosed multiple coin lesions in the liver. A lung biopsy showed necrotic and hemor-
rhagic tissue without neoplastic cells and did not result in a specific diagnosis. Serum total and β-subunit hCG were 68,920 U/L and 420 ng/ml, respectively. A diagnosis of hCG producing lung tumor was convincingly made. He died 6 weeks after admission, although he underwent chemotherapy and serum total hCG was decreased to 4,219 U/L.

Pathological findings

Autopsy showed a large (18 cm-diameter) necrotic and hemorrhagic mass in the right lower lobe of the lung, and metastatic multiple smaller nodules in both lungs (Fig. 1). Similar metastatic nodules were also found in the liver, both adrenals, and the lymph nodes of both the pulmonary hilus and abdominal paraaorta. Microscopically, the tumor with massive necrosis and hemorrhage consisted of two types of malignant cells: 1) cytotrophoblast-like single nuclear cells with ovoid nuclei, clear cytoplasm and distinct cell borders; 2) syncytiotrophoblast-like multinucleated giant cells with pleomorphic nuclei and abundant eosinophilic cytoplasm (Fig. 2a). This tumor had no histologic evidence of squamous cell carcinoma or adenocarcinoma. Furthermore, serial sectioning with careful histological examination of both testes did not provide any evidence of past or present tumor and scarring. In immunohistochemistry, hCG (hCG monoclonal antibody, Dako Japan Co., Ltd., Kyoto 600, Japan) was clearly detected in the syncytiotrophoblast-like tumor cells (Fig. 2b). These findings indicated that this case was primary choriocarcinoma of the lung and this tumor was distinguished from hCG producing large or giant cell carcinoma of the lung. To further estimate whether tumor cells in this case also express EGF and its receptor which play an important role in the proliferation and differentiation of normal and neoplastic trophoblasts of the uterus [17-18], we performed immunohistochemistry for these proteins (EGF and EGF-receptor polyclonal antibodies, Oncogene Science, Inc., Uniondale, NY). The EGF (Fig. 3a) and its receptor (Fig. 3b) were positively immunostained in both cytotrophoblast-like and syncytiotrophoblast-like cells. EGF was localized mainly in the cytoplasm, while EGF-receptor was expressed more intensively in the cytomembrane than in the cytoplasm. As a positive control, a 10-week placenta was immunostained with EGF and its receptor [17]. Pronounced staining for EGF (Fig. 3c) and its receptor (Fig. 3d) was observed diffusely in the cytoplasm of syncytiotrophoblasts, whereas staining for these proteins in cytotrophoblasts was completely negative [17]. In immunostaining intensity, the expression of EGF seemed to be weaker in the tumor cells than in the normal trophoblasts.

Discussion

Extragonadal choriocarcinoma in a male is very rare. The tumor usually occurs in the testis [3]. The other sites of the tumor are the mediastinum, retroperitonium, alimentary tract, urinary bladder, liver, kidneys, pineal body and pituitary gland [2–9]. Our case showed no evidence of primary neoplastic lesions in these organs in careful autopsy examination. Furthermore, this case showed a marked increase in serum hCG and these tumor cells had hCG-positive immunostaining. The histological findings in this case were very similar to those of choriocarcinoma of the uterus. We therefore consider this case to be a primary choriocarcinoma of the lung and to be distin-

**Fig. 1.** A large tumor with massive necrosis and hemorrhage (*) is localized in the lower lobe of the right lung, and multiple smaller metastatic nodules (arrowheads) are observed in other areas.
guished from hCG-producing large or giant cell carcinoma of the lung. This case is the fifth male we have treated with primary pulmonary choriocarcinoma. Note that all five patients reported had been heavy cigarette smokers.

In pregnancy, normal trophoblasts proliferate and differentiate through the binding of EGF to its receptor in an autocrine-paracrine manner [17]. In choriocarcinoma of the uterus, EGF and its receptor are also expressed in both cytotrophoblastic and syncytiotrophoblastic tumor cells, although the levels of these expressions are lower than those of hydatidiform and invasive mole [18]. For the first time, we herein detected EGF and its receptor in the tumor cells of primary pulmonary choriocarcinoma. Our results suggest that EGF may also act in an autocrine manner in the tumor cells of choriocarcinoma occurring primarily in the lung. Further studies will be necessary to clarify whether EGF and its receptor play potential roles in the proliferation and differentiation or histogenesis of pulmonary choriocarcinoma cells.

The pathogenesis of choriocarcinoma outside gonads is unclear and has been explained by several theories [11, 14]. 1. The tumor arises from retained primordial germ cells which abnormally migrate during embryogenesis. 2. The tumor is metastasized from a primary gonadal choriocarcinoma. 3. The tumor occurs directly in nongonadal tissues through trophoblastic differentiation of some cells, that is, the current concept of cellular and molecular biology interprets the theory as "transdifferentiation". In this case, careful autopsy examinations exclude the possibility of the second theory. Many studies have shown that hCG is detected in some neoplastic or nonneoplastic cells in the extragonadal tissues, i.e., lung, liver, kidney, spleen, esophagus, stomach, small intestine,
large intestine, urinary tract, breast or pituitary gland [19–21]. These studies suggest that the genome responsible for hCG production may not be completely suppressed even in adult extragonadal tissues. It is therefore conceivable that hCG may be produced even in extragonadal cells by hCG-responsible gene expression. We suggest that the pathogenesis of our case may be explained by the
third theory (transdifferentiation), although the possibility that the first theory is correct cannot be completely ruled out.

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References