

Focal positivity of immunohistochemical markers for pulmonary squamous cell carcinoma in primary pulmonary choriocarcinoma: A histopathological study

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Abstract. Cytokeratin 5/6 (CK5/6), p63, and p40 are commonly used as immunohistochemical markers for squamous cell carcinoma (SqCC) of the lung. To elucidate their positivity in primary pulmonary choriocarcinoma (PPC), the present study examined 4 PPCs, including 1 surgically removed PPC and 3 postmortem PPCs. All PPCs consisted of nested cytotrophoblastic tumor cells and occasional syncytiotrophoblastic tumor cells although 1 surgically removed PPC was markedly affected by pre-operative therapy-associated necrosis and 3 postmortem PPCs coexisted with adenocarcinoma. In 1 surgical case, a pre-operative biopsy specimen of PPC contained a few polygonal tumor cells, which mimicked SqCC and exhibited focal p40+ features. Nuclear p63+ and p40+ features of cytotrophoblast-like polygonal tumor cells were focally observed in 3 PPCs (75%) and 2 PPCs (50%), respectively. CK5/6+ trophoblastic tumor cells were focally identified in 1 PPC. Additionally, in 2 other PPCs, CK5/6+ tumor cells were scattered in choriocarcinomatous areas, but possible intermingling of CK5/6+ adenocarcinoma cells could not be ruled out. The results emphasized that PPCs could mimic

SqCC morphologically and immunohistochemically, although PPC was an extremely rare neoplasm. Surgical pathologists should be aware of this diagnostic pitfall when encountering a few squamous marker-positive polygonal tumor cells within hemorrhagic necrotic biopsy specimens from lung tumors.

Introduction

Primary lung cancer is the most frequent cause of cancer-related death worldwide (1,2). Accurate histopathological assessment of lung tumors directly contributes to the establishment of patient management strategies. The 2015 World Health Organization (WHO) classification of lung tumors (3) has recommended that non-small cell carcinoma (NSCC) should be classified into more specific subtypes, even in small specimens, such as squamous cell carcinoma (SqCC) or adenocarcinoma, based on immunohistochemical examination. Accepted immunohistochemical markers for SqCC include cytokeratin 5/6 (CK5/6), p63 and p40, and those for adenocarcinoma include thyroid transcription factor-1 (TTF-1) and Napsin A (1,3). Recently, however, we encountered focal p40 positivity in surgically removed primary pulmonary choriocarcinoma (PPC; unpublished data). PPC is a distinct, primary lung cancer, but is not included in the 2015 WHO classification, possibly due to its extreme rarity. Our review of the English literature yielded only 57 previously reported PPCs (4-39), which exhibited characteristic dimorphic features composed of cytotrophoblastic and syncytiotrophoblastic tumor cells and had considerable amounts of choriocarcinoma components with or without other carcinoma components. In this study, to elucidate the immunoreactivity profiles of PPCs for SqCC markers, we examined this surgical case of PPC and additional 3 autopsy cases of PPC.

Patients and methods

Patients. We consider that PPC should be discriminated from β -chorionic gonadotropin (β -hCG)-producing large or giant cell carcinoma of the lung (20,26). In this study, we defined PPCs as those with characteristic dimorphic morphology composed of mononuclear cytotrophoblastic tumor cells and

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Abbreviations: β -hCG, β -human chorionic gonadotropin; CK5/6, cytokeratin 5/6; CK7, cytokeratin 7; CK18, cytokeratin 18; ¹⁸F-FDG, ¹⁸F-fluorodeoxyglucose; EMA, epithelial membrane antigen; H&E, hematoxylin and eosin; NSCC, non-small cell carcinoma; Δ N, N-terminal transactivation; PAS, periodic acid-Schiff; PPC, primary pulmonary choriocarcinoma; SqCC, squamous cell carcinoma; TBB, transbronchial biopsy; TTF-1, thyroid transcription factor-1; WHO, World Health Organization

Key words: choriocarcinoma, lung, squamous cell carcinoma, immunohistochemistry, p63, p40, cytokeratin 5/6, primary pulmonary choriocarcinoma

multinucleated syncytiotrophoblastic tumor cells showing immunoreactivity for β -hCG focally or multifocally. Cases of β -hCG+ primary pulmonary cancer without such dimorphic morphology were not included. To identify additional autopsy cases of PPC, we reviewed hematoxylin and eosin (H&E)-stained slides of 191 primary lung cancers from 179 patients retrieved from autopsy files (1975-2017, June) of the Department of Pathology, Japan Self-Defense Forces Central Hospital (Tokyo, Japan) and identified 3 PPC cases (1.6%), including a previously published case (24). Therefore, we examined a total of 4 cases of PPC. Biopsies had been performed in 1 surgical case and 1 autopsy case. In all 4 cases, PPC components occupied a considerable amount of the primary lung tumor (>10% of the tumor volume) with or without other histological components. We histologically evaluated or assessed PPC and other components of lung cancer referring to the description of previously reported PPCs (4-39), published textbook of surgical pathology (40), and the 2015 WHO classification (3). The present study was a retrospective study, which was approved by the Medical Research Ethics Committee of Japan Self-Defense Forces Central Hospital (June 5, 2017; approval no. 29-004).

Methods. For all surgically removed, postmortem, and biopsy specimens, 10-20% buffered formalin-fixed and paraffin-embedded samples were available. Samples were recut, stained with H&E, and immunostained for β -hCG (C6405; Nichirei Biosciences, Inc., Tokyo, Japan), CK5/6 (D5/16 B4; Nichirei Biosciences, Inc.), p63 (4A4; Nichirei Biosciences Inc.) and p40 (BC28; Nichirei Biosciences Inc.). If needed, selected sections were stained with periodic acid-Schiff (PAS) and immunostained for TTF-1 (SPT24; Novocastra, Newcastle, UK), Napsin A (IP64; Novocastra), and epithelial membrane antigen (EMA; E29; Nichirei Biosciences, Inc.). Clinical information was obtained from patient medical charts and/or autopsy request forms.

Results

Clinical details

Case 1 (surgical case). A 53-year-old man presented with cough and chest pain. Imaging examination revealed a 6-cm left lung tumor. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography revealed FDG uptake in the lung tumor, and the maximum standardized uptake value was 12.02. Serum β -hCG level was not examined. Transbronchial biopsy (TBB) specimens from the lung tumor contained a few SqCC-like polygonal cells focally showing p40 positivity (Fig. 1). They showed no distinct keratinization or intercellular bridges and were diagnosed as NSCC according to the algorithm described in the 2015 WHO classification (3). After chemoradiotherapy (carboplatin and paclitaxel plus 60 Gy), the patient underwent left upper lobectomy, which was diagnosed as a necrotic PPC and associated pulmonary metastasis. Serum β -hCG levels 5 days after the surgery were within the normal range (≤ 0.10 mIU/ml), but were increased (31.23 mIU/ml) 9 months after the surgery with metastases in the brain, right lung, and stomach, despite additional chemotherapy (etoposide, methotrexate, actinomycin and cisplatin). Lung and gastric metastases were histologically confirmed

by biopsies. The patient died of disease 15 months from the initial presentation.

Case 2 (autopsy case). A 70-year-old man was hospitalized for hemoptysis and involuntary movement. Imaging examination demonstrated the presence of a 7-cm right lung tumor and multiple metastatic nodules in the brain, liver, right adrenal gland, and both kidneys. Serum β -hCG levels were not examined. Pathological examination of ultrasound-guided percutaneous lung biopsy specimens provided a possible diagnosis of large cell carcinoma. The patient died of disease 2 months after hospitalization.

Case 3 (autopsy case). A 77-year-old man was admitted to our hospital for evaluation of bloody sputum and loss of appetite (24). Imaging examination revealed a 5-cm left upper lobe nodule, which had been detected 2 months before at another hospital, and multiple metastatic nodules were observed in both lungs as well as the liver, spleen, and pancreatic body. Serum carcinoembryonic antigen levels were slightly increased (6.8 ng/ml). Serum β -hCG levels were not examined. The patient's condition rapidly deteriorated, and the patient died of respiratory failure due to hemorrhagic pulmonary metastases 6 days after admission.

Case 4 (autopsy case). A 77-year-old man was hospitalized for a stroke-related fall. Imaging examination demonstrated right hemisphere brain infarction and a 4-cm right lung tumor. Serum levels of sialyl Lewis^x were slightly increased (50 ng/ml). Serum β -hCG levels were not examined. The patient died of respiratory failure due to lymphangiosis carcinomatosa 4 months after hospitalization.

Pathological findings. The main clinicopathological findings are summarized in Table I. PPCs were located on the left upper and right lower lobes in 2 cases each, and their sizes ranged from 3.5 to 10 cm. In case 1, the surgically removed PPC was necrotic (Fig. 2A), and 90% of the tumor volume was histologically affected by necrosis, possibly due to chemoradiotherapy. Viable tumor cells were scattered (10% of the tumor volume) in the peripheral areas (Fig. 2B), with sheet-like growth features of cytotrophoblast-like tumor cells (Fig. 2C) and occasional syncytiotrophoblast-like multinuclear cells (Fig. 2F). A 1.8-cm metastatic nodule in the lingual segment distant from the main PPC and postoperative biopsy specimens from contralateral lung and gastric metastatic lesions exhibited typical choriocarcinomatous features (Fig. 2I and L). No other carcinomatous components were found. In cases 2-4, primary lung tumors had similar choriocarcinoma components (15-35% of the tumor volume; Fig. 3A) coexisting with adenocarcinoma cells (Fig. 3D and F; 5-30% of the tumor volume) and hemorrhagic necrosis (50-60% of the tumor volume). All of these adenocarcinomatous components focally or multifocally showed papillary or papillotubular growth with nestic proliferation and occasionally contained PAS + lumina. In case 3, dedifferentiated carcinomatous features were also observed (5% of the tumor volume) (24). Polygonal tumor cells in the biopsy specimens from PPCs in cases 1 and 2 were retrospectively consistent with trophoblastic tumor cells (Fig. 1B).

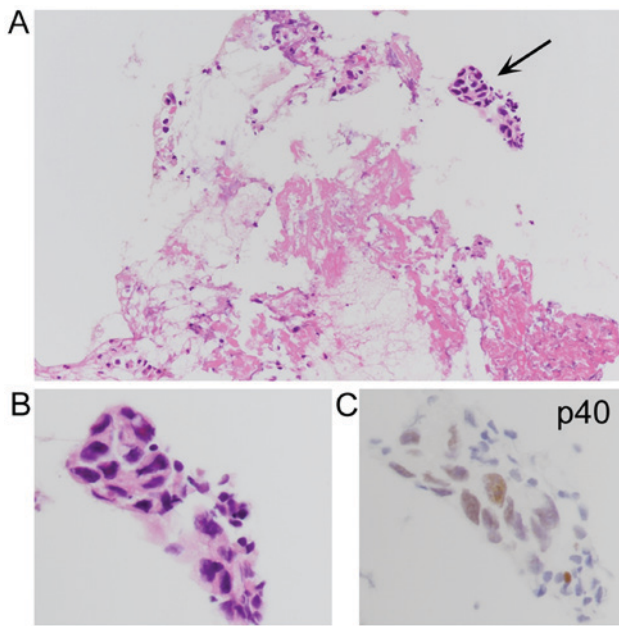


Figure 1. Pre-operative biopsy from a primary pulmonary choriocarcinoma in case 1. (A) Biopsy specimens containing a tiny tumor nest (arrow) and necrotic tissues (magnification, x200). (B and C) High-power views [of area indicated by arrow in (A)] of (B) nested polygonal cells mimicking squamous cell carcinoma and (C) present focal p40+ nuclei (magnification, x400).

Immunohistochemically, all PPCs and biopsy specimens from PPCs and metastatic lesions showed scattered cytoplasmic β -hCG positivity, mostly in syncytiotrophoblastic tumor cells (Figs. 2C, inset, G, J and M, and 3B). The p63+ and p40+ nuclei of cytotrophoblast-like tumor cells were observed (Fig. 2D and E) in 3 and 2 PPCs, respectively, and occupied 5% and 1-5% of choriocarcinomatous components, respectively. Similarly, p63+ and/or p40+ nuclei accounted for 5-10% of tumor cells within biopsy specimens from metastatic lesions in case 1 (Fig. 2K, N and O). Positivity for p63 and p40 was not present in syncytiotrophoblastic tumor cells or concomitant adenocarcinoma cells. In case 1, cytoplasmic CK5/6 positivity was focally found in multinucleated or mononuclear trophoblastic tumor cells (Fig. 2H), accounting for 1% of the tumor cells. Additionally, in cases 2 and 4, CK5/6+ tumor cells were focally found in choriocarcinomatous areas (Fig. 3C). However, in these cases, 30% of concomitant adenocarcinoma cells were positive for CK5/6 (Fig. 3E and G). Therefore, possible intermingling of CK5/6+ adenocarcinoma cells within choriocarcinomatous areas could not be ruled out. CK5/6+ adenocarcinoma cells showed poorly differentiated features, but occasionally had distinctive PAS+ lumina (Fig. 3D, inset and F, inset). These cells were strongly positive for EMA, but negative for TTF-1 (Fig. 3H) and Napsin A. CK5/6+ features were not identified in case 3 or any of the biopsy specimens.

Discussion

Previous studies of p63 and/or p40 expression in PPC have been limited, with reports describing only 3 PPCs (Table II),

Table I. Clinicopathological results of primary pulmonary choriocarcinoma.

Case	Age (years)/sex	Site of PPC	Size (cm)	Therapy	Specimens	Histology (proportion of components)	Immunohistochemistry of Chor				Follow-up
							p63	p40	CK5/6		
1	52/M	LUL	6	CRT+L+CT	Pre-OP biopsy	A few polygonal tumor cells ^b	+ ^d (5%)	+ ^d (5%)	-	DOD, 15 months	
					Main tumor	Chor 10%, Nec 90%	+ ^e (5%)	+ ^e (5%)	+ (1%)		
					Post-OP biopsy ^a	Chor (metastasis in the right lung)	+ ^e (60%)	+ ^e (60%)	-		
2	70/M	RLL	10	None	Post-OP biopsy ^a	Chor (metastasis in the stomach)	+ ^e (60%)	+ ^e (60%)	-		
					Antem biopsy	Polygonal tumor cells ^b	+ ^d (5%)	+ ^d (5%)	-	DOD, 2 months	
3	77/M	LUL	5.5	None	Main tumor	Chor 35%, Nec 60%, Ad 5%	+ ^e (5%)	+ ^e (1%)	- ^f		
					Post-OP biopsy ^a	Chor 15%, Nec 50%, Ad 30%, Dediff 5% ^c	+ ^e (1%)	-	- ^e	DOD, 2 months ^h	
4	77/M	RLL	3.5	None	Main tumor	Chor 30%, Nec 50%, Ad 20%	-	-	- ^f	DOD, 4 months	

^aPost-operative biopsies from metastases in the right lung and stomach. ^bRetrospective, consistent with histological features of choriocarcinoma. ^cThe detailed histology is shown in a previous article (24). ^dPositivity observed in polygonal tumor cells. ^ePositivity identified in cytotrophoblast-like tumor cells. ^fCK5/6+ tumor cells were focally observed in choriocarcinomatous areas, but possible intermingling of CK5/6+ adenocarcinoma cells could not be ruled out. ^gThere was no CK5/6 positivity in choriocarcinoma components, adenocarcinoma cells, or undifferentiated carcinoma cells. ^hThe patient succumbed ~2 months after when the lung tumor had been detected in another hospital (24). Antem, antemortem; Ad, adenocarcinoma; Chor, choriocarcinoma; CK5/6, cytokeratin 5/6; CRT+L+CT, preoperative chemoradiotherapy + lobectomy + postoperative chemotherapy; Dediff, dedifferentiated carcinoma; DOD, died of disease; LUL, left upper lobe; M, male; Nec, necrosis; Post-OP, postoperative; Pre-OP, preoperative; RLL, right lower lobe.

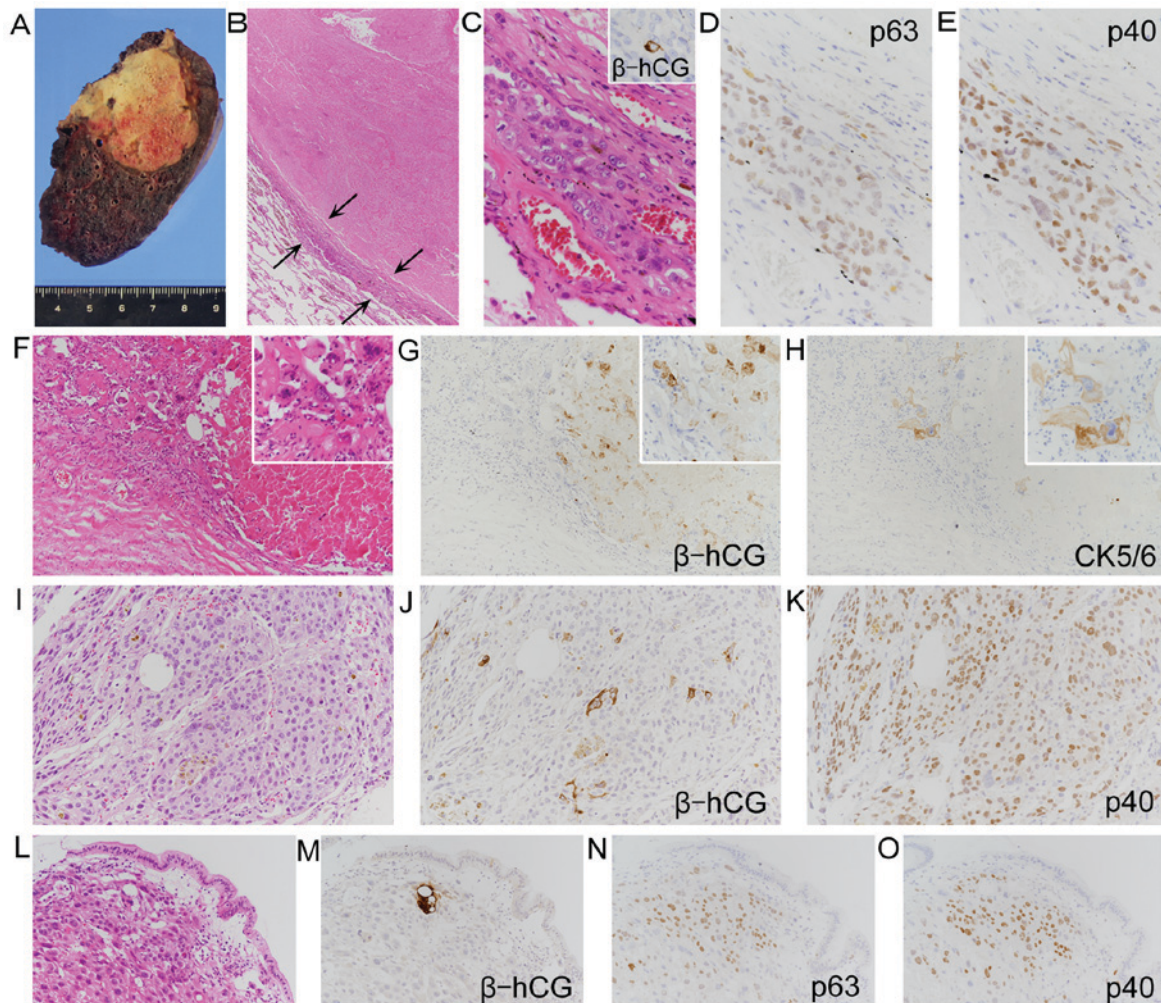


Figure 2. Surgically removed primary PPC and postoperative biopsy of metastases in case 1. (A) Gross necrotic appearances of PPC. (B) PPC composed of marked necrosis and residual tumor cells (arrows; magnification, x40). These residual tumor cells primarily consisted of (C) nested cytotrophoblast-like tumor cells and presented focal β -hCG positivity (inset). Immunostaining of the same areas revealed (D) p63+ nuclei and (E) p40+ nuclei of tumor cells (magnification, x400). (F) PPC containing scattered mononuclear and multinucleated tumor cells and high-power views (inset). The same areas containing (G) β -hCG+ tumor cells and (H) CK5/6+ tumor cells, and insets depicting high-power views of positive cells (magnification, x100, and x400 for all insets). (I-K) Post-operative biopsy specimens of pulmonary metastasis mainly composed of (I) nested cytotrophoblast-like tumor cells, containing (J) scattered β -hCG+ cells and (K) showing diffuse p40+ nuclei (magnification, x200). (L-O) Post-operative biopsy specimens of gastric metastasis consisting of (L) mononuclear and multinucleated tumor cells and (M) exhibiting β -hCG+ tumor cells, (N) p63+ tumor cells and (O) p40+ tumor cells (magnification, x200). PPC, pulmonary choriocarcinoma; β -hCG, β -human chorionic gonadotropin; CK5/6, cytokeratin 5/6.

all of which were concomitant with prominent necrosis and were positive for β -hCG (30,32,37). Two PPCs were positive for p63 (32,37), but their detailed morphology was not determined. The other PPC was negative for p63 (30). One of the 2 p63+ PPCs was negative for p40 (37), but p40 positivity was not examined in the other 2 PPCs. However, in addition to tumors of pulmonary origin, some authors (41,42) have observed focal p63/p40 positivity (<10% of tumor cells) in 38-100% of gestational uterine choriocarcinomas. Shih and Kurman (41) demonstrated the presence of p63+ nuclei in cytotrophoblastic tumor cells. In addition, in the normal placenta, p63+/p40+ features were commonly found in cytotrophoblasts (41-43), but not in syncytiotrophoblasts (41,42). These findings strongly supported our current results demonstrating that focal p63+ and p40+ cytotrophoblastic tumor cells were detectable in 75 and 50% of PPCs, respectively, and that no p63+ or p40+ syncytiotrophoblastic tumor cells were found in any PPCs. These findings of p63

and/or p40 positivity in PPCs indicated trophoblastic differentiation rather than true squamous differentiation. *p63 gene* products include transcriptional activation isoforms and N-terminal transactivation (Δ N) isoforms (41-43). Currently available anti-p63 antibodies react with both isoforms, whereas anti-p40 antibodies react with Δ N isoforms only (41-43), which may explain the higher incidence of p63 positivity than p40 positivity in PPCs.

The present study also demonstrated the presence of focal CK5/6+ trophoblastic tumor cells in 1 case. In our review of the literature, we could not find any articles describing CK5/6 positivity in normal or neoplastic trophoblasts, although they were positive for pancytokeratin (AE1/AE3), CK7, and CK18 and negative for CK20 (22,24,30,34,37,44). Moreover, in 2 other PPCs, scattered CK5/6+ cells were identified, although they may have been intermingled CK5/6+ adenocarcinoma cells. These findings implied the possible occurrence of CK5/6 positivity in biopsy specimens of PPCs with or without

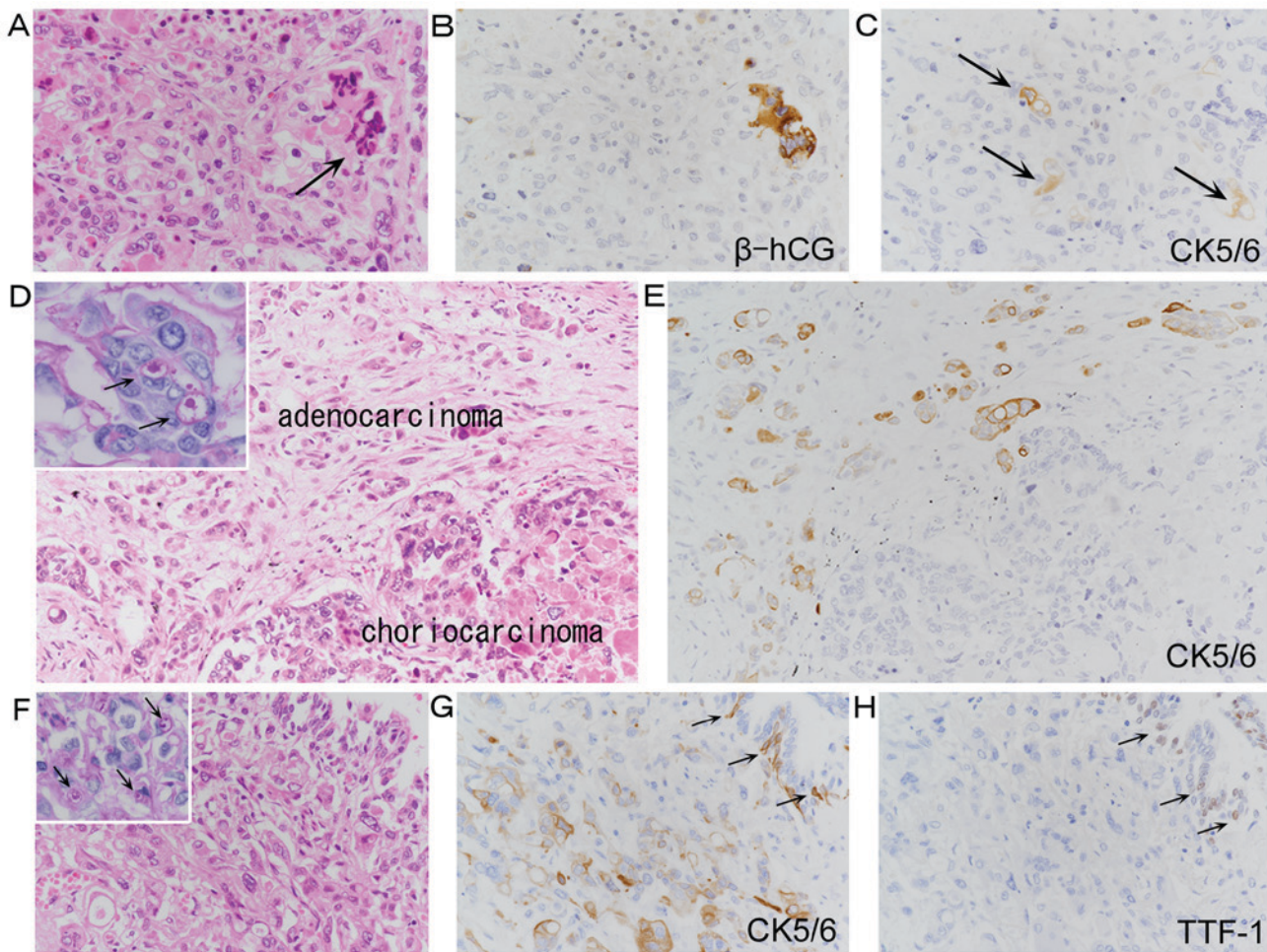


Figure 3. Combined primary PPC and adenocarcinoma in case 4. (A) PPC composed of cytotrophoblastic tumor cells and syncytiotrophoblastic tumor cells (arrow). (B and C) Immunostaining showing (B) β -hCG+ syncytiotrophoblasts and (C) CK5/6+ tumor cells (arrows). However, these CK5/6+ cells could not be discriminated from intermingled CK5/6+ adenocarcinoma cells (magnification, x400). (D and E) Moderate-power views (D) of choriocarcinoma and adenocarcinoma cells exhibiting focal PAS+ lumina (D, inset; arrows). (E) CK5/6 immunostaining revealing positive adenocarcinoma cells (magnification, x200 for D and E, and x600 for D inset). (F-H) Concomitant adenocarcinoma cells in other areas (F) showing poorly differentiated features with occasional PAS+ lumina (F, inset; arrows). (G) CK5/6 immunostaining revealing positivity of adenocarcinoma cells and inner control basal cells of bronchioles (G, arrows). (H) TTF-1 immunostaining presenting negativity of adenocarcinoma cells but positivity of inner control cells of bronchioles (arrows; magnification, x400). PPC, pulmonary choriocarcinoma; β -hCG, β -human chorionic gonadotropin; CK5/6, cytokeratin 5/6; PAS, periodic acid-Schiff; TTF-1, thyroid transcription factor-1.

coexisting adenocarcinoma cells, which may also simulate SqCC.

PPCs are extremely rare; in addition to the novel PPCs described in this study, only 60 PPCs have been described in the English literature (4-39). The incidence of PPC would be less than 0.1% of primary pulmonary cancer. In this study, however, we identified PPCs in 1.6% of the consecutive autopsy cases of lung cancer. This incidence was considered relatively high. Unfortunately, we cannot explain this observation, but we hypothesized that these results may be related to the detailed examination performed using many specimens removed postmortem lung cancers.

From a pathogenetic point of view, PPCs may be somewhat different from conventional choriocarcinoma arising in the uterus of women during gestation, although some PPCs may develop from gestation-related pulmonary trophoblastic embolism (11,31,38). This is supported by the following observations: 26 PPCs (43% of 60 PPCs) were observed in men (7-9,14-16,18-21,23,24,29,36,37,39); 15 PPCs (25%)

were observed in patients who were at least 60 years old (9,13,14,17-20,23,24,26,37,39); 2 PPCs (3%) were observed in infants (4,16); and 8 PPCs (13%) coexisted with otherwise specified primary pulmonary cancer, such as adenocarcinoma (6 PPCs including the present additional 2 PPCs) (14,20,24,36), papillary embryonal carcinoma (1 PPC) (8), or small cell carcinoma (1 PPC) (9), although this 'papillary embryonal carcinoma' may have been poorly differentiated adenocarcinoma on the basis of histological features shown in the microphotograph of the article (8,24). These findings suggest that PPCs may infrequently represent trophoblastic differentiation of the pulmonary epithelium, pulmonary otherwise specified neoplasm, or abnormally migrated primordial germ cells in lungs (8,20,24,26,32-34). Moreover, in the present study, 2 PPCs coexisted with poorly differentiated adenocarcinoma, which were positive for CK5/6 and EMA, but negative for TTF-1 and Napsin A. We believed that these CK5/6+ tumor cells were adenocarcinoma cells because of occasional presence of PAS+ lumina. Notably, these

Table II. Clinicopathological results of primary pulmonary choriocarcinoma previously examined immunohistochemical markers for squamous cell carcinoma.

Author, year	Reported cases	Age (years)/sex	Site of PPC	Size (cm)	Therapy	Histology of main tumor	Immunohistochemistry of Chor			Follow-up (Refs.)
							p63	p40	Others	
Berthod <i>et al</i> , 2010	1	32/F	RUL	1.5	L+CT	Chor+Nec	-	NE	β-hCG+, CK7+, CK20-, TTF-1-	ANED, 1 year (30)
Ibi <i>et al</i> , 2012	2	27/F	LUL	1.8	PR+CT	Chor+Nec	+	NE	β-hCG+, CK+, inhibin α+, TTF-1-	ANED, 19 months (32)
Zhu <i>et al</i> , 2016	3	67/M	LUL	9	L+CT	Chor+Nec	+	NE	β-hCG+, CK7+, CK20-, TTF-1 ^a	ANED, >13 months (37)

^aOther immunohistochemical expression including positivity for CAM5.2, GATA3, human placental lactogen, and human leucocyte antigen, and negativity for anaplastic lymphoma kinase, Napsin A, and cluster of differentiation 146. ANED, alive with evidence of disease; Chor, choriocarcinoma; CK, cytokeratin; CK5/6, cytokeratin 5/6; CK7, cytokeratin 7; CK20, cytokeratin 20; F, female; M, male; L+CT, lobectomy + postoperative chemotherapy; LUL, left upper lobe; NE, not examined; Nec, necrosis; PR, partial resection of the lung; RUL, right upper lobe; TTF-1, thyroid transcription factor-1.

CK5/6+ and TTF-1-/Napsin A-features were exceptional in primary pulmonary adenocarcinoma (1,3), although CK5/6 positivity of primary pulmonary adenocarcinoma only rarely occurs (45). These features may be associated with unusual trophoblastic differentiation of pulmonary adenocarcinoma cells. Furthermore, in such cases, PPC may be found only in late-stage of lung cancer, and *in situ* or early phase of PPC would not be identified. Unfortunately, however, we did not investigate this hypothesis in the present study, and additional studies are needed.

PPCs are clinically aggressive tumors; 18 (30%) of 60 patients with PPC died within 3 months from disease onset or hospital admission (4-10,13,15,17,21,24-26,29, 36,37). Therefore, accurate diagnosis during the early stage of the disease is important for therapeutic management of patients. However, 16 PPCs (27%) were diagnosed by auto psy (4,5,8-10,13-15,17,19,23-25). TBB or percutaneous biopsies have been performed in 25 cases, and the specific diagnosis of PPC was rendered in only 7 (28%) of these cases (11,12,21,29-31,35). Importantly, the histopathological diagnosis of PPCs seems to be challenging in small biopsy specimens. This may be because PPCs are frequently associated with massive hemorrhagic necrosis (13,15,17,22-27,31,32 ,37), and it is difficult to obtain sufficient amounts of tumor cells for definitive pathological diagnosis. Furthermore, our results in the present study demonstrated that PPCs could mimic SqCC morphologically and immunohistochemically. Morphological mimicry of SqCC has also been noted in percutaneous biopsy specimens (18) and fine needle aspiration cytology specimens (19,27) of PPCs. Recently, Vallonhthaiel *et al* (46) reported a unique case of pulmonary metastatic choriocarcinoma, which was diagnosed as NSCC favoring SqCC, because of the presence of p40+ polygonal tumor cells in the biopsy specimen. These features closely resembled those of the present case 1. In the biopsy specimens from contralateral lung and gastric metastases in case 1, p40+/p63+ tumor cells were not focal and were diffusely distributed. Based on these findings, we suggest that surgical pathologists should be aware of the possible morphological and immunohistochemical mimics of SqCC in biopsy specimens of PPCs or metastatic choriocarcinomas. Particularly when a few SqCC marker+ polygonal cells are encountered in hemorrhagic necrotic biopsy tissues, this diagnostic pitfall should be considered.

Thus, the present study revealed the presence of p63+ and p40+ cytotrophoblastic tumor cells and the possible occurrence of CK5/6+ tumor cells in PPCs. The current results highlighted the diagnostic pitfall that PPCs can mimic SqCC morphologically and immunohistochemically although PPC is extremely rare.

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Availability of data and materials

All data generated or analyzed during the current study are included in this published article.

Authors' contributions

SM assessed the autopsy files and H&E-stained sections, and identified the additional postmortem primary pulmonary choriocarcinoma (PPC). SM drafted the manuscript. SM, YU, KM and HT participated in the histopathological assessment of PPC, including immunohistochemical features, and the editing of photographs. YU, KO, YO and KS participated in the review of the literature and clinical assessment of the PPC cases. SM, KO, YU, KM, HT, YO and SK conceived and designed the study, participated in the study coordination, and edited the manuscript.

Ethical approval and consent to participate

The present study was performed according to the Declaration of Helsinki. The present study was a retrospective study, which was approved by the Medical Research Ethics Committee of Japan Self-Defense Forces Central Hospital (June 5, 2017; approval no. 29-004).

Patient consent for publication

At the time of autopsy or surgery, written informed consent for the use of postmortem and surgical materials in histopathological studies was obtained from the patients' families or the patients.

Competing interest

The authors declare that they have no conflicts of interest.

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