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Primary Choriocarcinoma of the Lung

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Abstract. *Primary choriocarcinoma (PCC) of the lung is extremely rare, with about 25 cases previously reported. We describe here a patient with PCC of the lung and review previously described cases to establish the clinical characteristics and most appropriate management of this disease. Survival for patients treated with both surgery and chemotherapy was longer than for patients treated with surgery alone, chemotherapy alone, or optional supportive care. Multivariate analysis of prognostic factors revealed that treatment with both surgery and chemotherapy had independent prognostic significance. Our analysis including previous cases suggests that resection followed by adjuvant chemotherapy is the most effective treatment.*

Primary extragenital choriocarcinoma most often arises in the retroperitoneum, in the mediastinum, or intracranially. Although metastasis to the lung is not infrequent, primary choriocarcinoma (PCC) originating in the lung is extremely rare. The prognosis of extragonadal choriocarcinoma is usually poor, with various symptoms seriously affecting quality of life. Thus, despite the rarity of primary pulmonary cases, optimal management of patients with PCC of the lung is an important goal.

In this report, we describe a patient with PCC of the lung and review 25 previously reported cases (1-22) to elucidate clinical characteristics including survival outcome, as well as to determine the best way to manage this rare disease.

Materials and Methods

The medical literature was searched using Medline to identify reports of PCC of the lung, using the selection criteria of publication in English and histological diagnosis of PCC of the lung.

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Key Words: Choriocarcinoma, chorionic gonadotropin, lung tumor.

Probabilities of survival were estimated using the Kaplan-Meier method and differences between patient groups were evaluated by the log-rank test. Prognostic factors were analyzed using the Cox proportional hazard model. All reported *p* values are two-sided. A *p* value below 0.05 was accepted as indicating statistical significance.

Case Report

A 31-year-old woman complaining of left-sided chest pain and bloody sputum was referred to us on August 11, 2000. The patient had conceived two times; the second pregnancy had been terminated by induced abortion 1 year earlier, with no subsequent abnormal uterine bleeding.

On admission, physical examination was normal. Routine laboratory tests showed no abnormalities except for mild anemia. Elevated serum tumor markers included cytokeratin-19 fragment (4.4 ng/ml) and human chorionic gonadotropin (hCG; 2, 686 mIU/ml); other tumor markers including carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), pro-gastrin-releasing peptide (pro GRP), α-fetoprotein (AFP) and carbohydrate antigen (CA) 19-9 were within normal limits. Chest radiography and computed tomography (CT) demonstrated an 8 x 6 cm pulmonary mass in the left upper lobe, without enlargement of intrapulmonary or mediastinal lymph nodes (Figure 1). Screening for additional masses including CT of the abdomen and brain as well as bone scintigraphy showed no abnormality. The patient then underwent transbronchial lung biopsy, which failed to yield a definitive diagnosis.

Suspected of having lung cancer, the patient then underwent left upper lobectomy on August 29. The tumor was focally adherent to the chest wall. Macroscopically, the tumor was a lobulated, subpleuraly located mass showing extensive necrosis and hemorrhage. Microscopically, the tumor was characteristic of choriocarcinoma, with large multinucleated cells representing syncytiotrophoblast admixed with medium-sized cells, often with clear cytoplasm, similar to cytotrophoblasts or intermediate trophoblasts (Figure 2A). Immunohistochemically, the tumor cells were reactive for hCG (Figure 2B) and cytokeratin AE1/AE3, but not for CEA. The tumor therefore was diagnosed pathologically as choriocarcinoma.

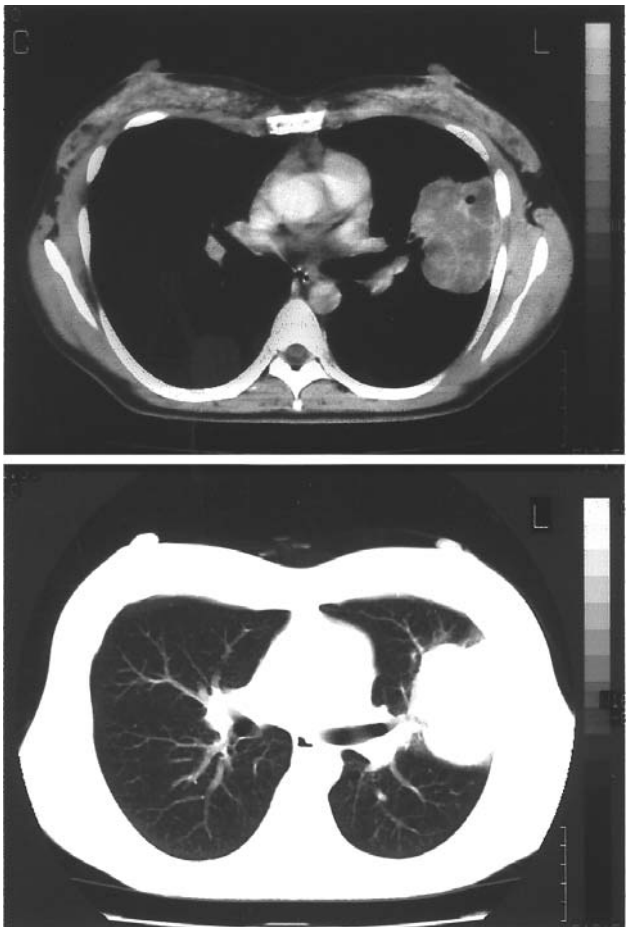

Figure 1. *Computed tomography of the chest in our patient disclosed an 8 x 6 cm lung mass in the left upper lobe without enlargement of intrapulmonary or mediastinal lymph nodes.*

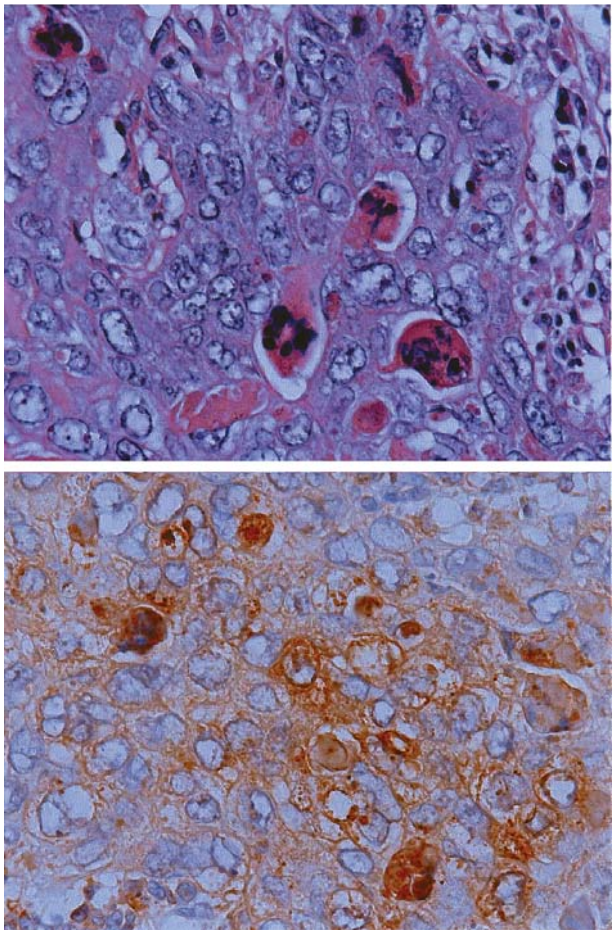

Figure 2. *Histological appearance of our patient's tumor.*
A: Microscopically, the tumor consisted of giant syncytiotrophoblastic cells and mononuclear cytotrophoblastic or intermediate trophoblastic cells. This choriocarcinoma pattern was distinct in all portions of the tumor. Hematoxylin and eosin; original magnification, x 200.
B: Immunostaining for human chorionic gonadotropin (hCG) shows positivity in many tumor cells. Original magnification, x 200.

After the lobectomy, an intensive systemic workup carried out in search of an occult choriocarcinoma was negative for tumor; including hysteorosalpingo-oophorectomy, the digestive organs, the reproductive tract and the surrounding tissues were all intact. Serum hCG concentrations fell to 14.4 mIU/ml during the second postoperative week. In consideration of the various findings, the patient was diagnosed with PCC of the lung. The postoperative course was uneventful and adjuvant chemotherapy including methotrexate, actinomycin-D, etoposide and calcium folinate was administered. At 36 months following surgery the patient is well without evidence of relapse, and continues to undergo follow-up in our outpatient clinic.

Literature Review

Patients. To establish the characteristics of pulmonary PCC, we searched the literature by Medline using criteria described in the Materials and Methods section. A review of the literature in English revealed 25 previously reported cases of primary choriocarcinoma originating in the lung, (1-22) with histological features similar to those of choriocarcinomas arising elsewhere. We analyzed our case together with the other 25. The patients, whose profiles are summarized in Table I, included 12 men and 14 women with a median age of 41 years (range, 3 to 71). In 24 out of 26 patients (92%) the tumors produced symptoms at the time

Table I. *Clinicopathological findings in the reported cases of pulmonary choriocarcinoma.*

Case	Age (years)	Gender	Location	Tumor size (cm)	Metastasis	Initial symptom(s)	Treatment	Survival (months)	Reference
1	29	F	Bilateral	3	lung	Chest pain, cough	CT	72	1
2	54	F	RUL	9	brain, liver, kidney	Chest pain	OP, CT	12	1
3	57	F	RUL	ND	adrenal gland	Dyspnea, cough	CT	8	1
4	29	F	RUL	11	lung	Cough	OP	3	2
5	21	F	LUL	ND	brain	Dyspnea, cough	CT	1	3
6	22	F	LUL	25	lung, brain, spleen	Dyspnea, cough	CT	0.23	4
7	34	F	RUL	4		Cough	OP,CT	6	5
8	27	F	RML	2.8		Vaginal spotting	CT,OP	36	6
9	0.6	F	RUL, RML	5.5	lung	Dyspnea, fever	OP	0	7
10	0.3	M	RLL	6.5		Precocious puberty	OP, CT	5	8
11	60	F	R	11	lung	Hemoptysis	OP	0.23	9
12	69	M	RLL	18	liver, adrenal gland	Hemoptysis	CT	1.5	10
13	71	M	RUL	2	lung, brain, liver, adrenal gland, kidney, spleen	Dyspnea, chest pain		6	11
14	37	M	RUL	19	brain	Cough, chest pain	CT, OP, RT	15	12
15	19	M	RLL	2		Cough	CT	2.5	13
16	69	M	LUL	3		Asymptomatic	OP, CT	6	14
17	61	M	RLL	3		Hemoptysis	OP, CT, RT	0.46	15
18	51	M	LUL	15	lung, brain, liver, spleen	Cough, weight loss		0.23	16
19	45	M	LUL	7	lung, liver, kidney, spleen	Gynecomastia	RT	6	17
20	57	M	RLL	10	brain	Cough		12	17
21	27	M	RLL	4		Pleuritic pain	OP, CT	24	18
22	67	M	LUL	3.5		Hemoptysis	OP	36	19
23	60	M	R	6	lung, brain	Asymptomatic		5	20
24	23	M	Bilateral	3	lung	Hemoptysis, dyspnea	CT	0.75	21
25	37	F	RLL	9		Asymptomatic	OP, CT	12	22
26	31	F	LUL	8		Hemoptysis, chest pain	OP, CT	36	The present case

M, male; F, female; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; R, right lung; LUL, left upper lobe; LLL, left lower lung; L, left lung; OP, operation; CT, chemotherapy; RT, radiotherapy; ND, not described.

of discovery, including persistent cough (38%), chest pain (23%), hemoptysis (23%) and dyspnea (23%); the other 2 tumors were asymtomatic at presentation (Table II).

Correlation between gender and clinicopathological factors. When we analyzed the relationships between gender and other clinicopathological features in patients with primary choriocarcinoma of the lung, the men were older than the women ($p=0.042$), Table III. No statistically significant difference between the genders was noted for location, size, presence of metastasis, smoking habit, history of hemoptysis, or treatment.

Survival. Considering all reported cases together the median survival time (MST) was 5.0 months (Figure 3A). Although some individual reports suggested that long-term survivors were rare, the present overall review disclosed 1-, 2- and 5-year survival rates of 41%, 34% and 34%, respectively.

Univariate analysis of prognostic factors is shown in Table IV. Survival for patients without metastases at presentation was longer than for patients with metastases ($p=0.019$, Figure 3B). Patients treated with both surgery and chemotherapy survived longer than those treated with either alone, or with optimal supportive care ($p=0.038$, Figure 3C). Female patients tended to survive longer than male patients ($p=0.235$), but significantly. Patients with smaller tumors (< 5 cm) tended to survive longer than patients with larger tumors, but this difference fell short of statistical significance ($p=0.052$). Age, tumor location, symptoms and smoking history demonstrated no significant prognostic influence.

As shown in Table V, multivariate analysis of prognostic factors using the Cox proportional hazards model revealed that treatment combining surgery with chemotherapy had independent prognostic significance ($p=0.023$).

Table II. *Primary choriocarcinoma of the lung: Summary of reported cases.*

No. of patients	26
Gender, male/female	12/14
Median age, years	41
Range, years	0.3-71
Initial symptom	
Dyspnea	5
Cough	10
Chest pain	6
Hemoptysis	6
Asymptomatic	2
Location	
Right upper lobe	7
Right middle lobe	2
Right lower lobe	7
Left upper lobe	7
Left lower lobe	0
Bilateral	2
Right lung	2
Tumor size, cm	
≤5	10
>5, ≤10	9
>10	5
Treatment	
OP	14
CT	17
RT	3
No treatment	4
OP + CT	7
OP + CT +RT	2
Status	
Dead of disease	16
Alive	10

OP, operation; CT, chemotherapy; RT, radiotherapy.

Table III. *Differences between female and male patients with choriocarcinoma of the lung.*

Characteristics		Female	Male	*p*-value
Age, years	< 40	9	5	
	≥ 40	3	9	0.042
Location	Right	8	9	
	Left	3	4	0.976
Size, cm	< 5	3	7	
	≥ 5	7	7	0.323
Metastasis	Yes	8	8	
	No	4	6	0.618
Smoking	Yes	2	6	
	No	10	8	0.141
Hemoptysis	Yes	2	4	
	No	10	10	0.469
Treatment				
OP	Yes	8	6	
	No	3	4	0.536
CT	Yes	8	8	
	No	3	2	0.695
OP+CT	Yes	5	5	
	No	6	5	0.835

OP, operation; CT, chemotherapy.

Discussion

Choriocarcinoma most commonly occurs in the female genital tract following gestational events such as hydatidiform moles, normal pregnancy, abortion and ectopic pregnancy. The tumor also occurs in the absence of pregnancy as well, as in men. Primary extragenital choriocarcinoma is rare, usually presenting as a midline lesion in the retroperitoneum, mediastinum, or cranial cavity (especially in the pineal gland). In men, choriocarcinoma occurs most often in the testis. Less frequently, these tumors have also been reported in various organs such as the urinary bladder, liver, stomach and colon. Among such sites, PCC of the lung is extremely rare. Because the lung is a frequent site of metastasis for choriocarcinoma, a careful search for an occult primary tumor is required though preoperative diagnosis of PCC of the lung is difficult.

In the present case, PCC of the lung was diagnosed after operation on the basis of the following observations: hCG fell dramatically after lobectomy: the lesion was limited to the lung, the patient's clinical course after surgery was uneventful, the ovaries, uterus and uterine tubes were found to be free of lesions on surgical removal, and no lesions were found in the digestive system. Indeed, the differential diagnosis of PCC from large cell carcinoma of the lung with choriocarinomatous foci can be difficult, both clinically and pathologically (23). However, histological examination of our patient's tumor showed only the characteristic two populations of tumor cells. Thus, the present case met clinical, cytological, histological and immunohistochemical criteria for diagnosis of PCC of the lung.

Several explanations might be offered for this occurrence of PCC in the lung: origin from retained primordial germ cells that migrated abnormally during embryonic development; metastasis from a primary gonadal tumor that regressed spontaneously; or origin from trophoblastic emboli related to molar pregnancy after a long period of latency. Other reports support a hypothesis of dedifferentiation or metaplasia of nongonadal tissue such as primary lung cancer to trophoblast. The latter explanation also addresses the nosologic problem of whether PCC of the lung is identical to hCG-producing giant cell carcinoma of the lung that arises from histopathological similarity between choriocarcinoma and large cell lung cancer.

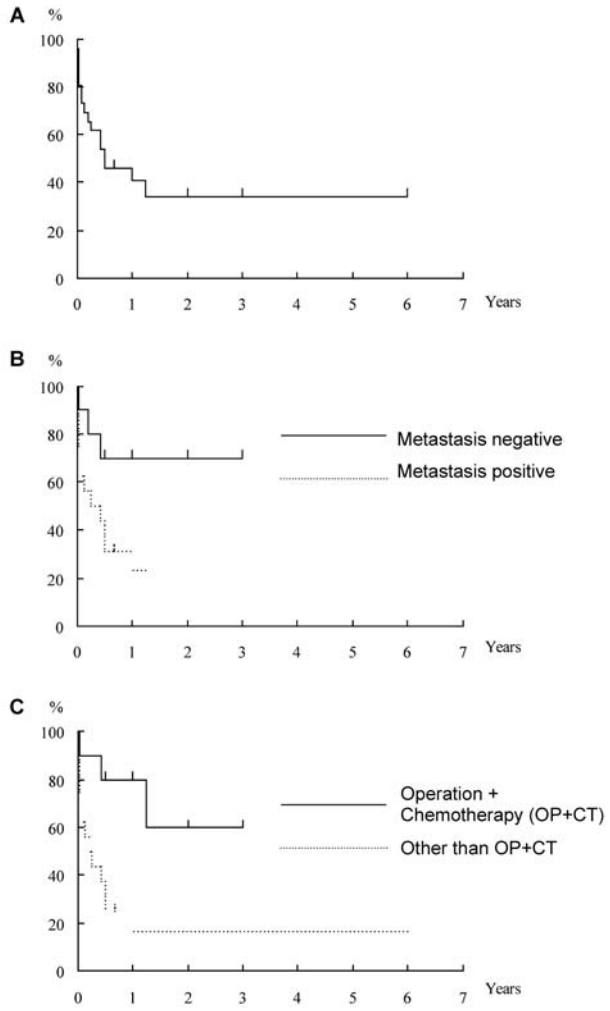

Figure 3. *Kaplan-Meier survival curves. A: Median survival time (MST) considering all reported cases was 5.0 months. B: Survival for patients without metastases (solid line) was longer than for patients with metastases (broken line, p=0.019). C: Survival for patients treated with both resection and chemotherapy (solid line) was longer than for patients treated otherwise, with resection alone, chemotherapy alone, or optimal supportive care (broken line, p=0.038).*

Table IV. *Possible prognostic indicators.*

		n	MST (months)	2-yr survival (%)	*p*-value
Characteristic					
Gender	Female	14	-	58.3	
	Male	12	5.0	17.9	0.235
Age, years	< 40	14	5.0	40.0	
	≥ 40	12	5.0	27.8	0.640
Location	Right	17	6.0	26.1	
	Left	7	6.0	42.9	0.952
Size, cm	< 5	9	-	66.7	
	≥ 5	14	3.0	14.3	0.052
Smoking	Yes	8	1.5	-	
	No	18	6.0	43.8	0.219
Metastasis	Yes	16	3.0	11.7	
	No	10	-	70.0	0.019
Treatment					
OP	Yes	14	-	51.4	
	No	7	1.5	28.6	0.245
CT	Yes	16	15	50.0	
	No	5	0.23	20	0.120
OP+CT	Yes	10	-	60.0	
	No	11	1.5	27.3	0.038

OP, operation; CT, chemotherapy; n, number of patients; MST, median survival time.

In contrast to gestational choriocarcinoma, the natural course of PCC of the lung is rapidly fatal in the great majority of cases. In our analysis of the literature, MST considering all reported cases was 5.0 months. Why nongestational choriocarcinoma behaves so differently from gestational cancers is unknown. Treatment modalities such as chemotherapy, radiotherapy, or surgical resection in patients with widespread, far-advanced malignant tumors usually have proven ineffective in prolonging survival. However, our analysis of PCC of the lung included with reported patients (34.6%) survival exceeding 1 year. Interestingly, six of these long-term survivors underwent both resection and chemotherapy. To discover any relationships between treatment and survival, we carried out univariate and multivariate analyses of prognostic factors. Univariate analysis demonstrated significant prognostic influence for the presence of metastases at diagnosis and combined treatment with surgery and chemotherapy. Furthermore, multivariate analysis of prognostic factors using the Cox proportional hazards model revealed that this combined treatment including surgery and chemotherapy had independent prognostic significance. We know of no reports of extended survival in patients who underwent complete resection without chemotherapy.

In summary, PCC of the lung is a rarity with variable clinical characteristics. Analysis of the literature indicated that treatment with surgery plus chemotherapy independently improved prognosis according to multivariate analysis of potential prognostic factors using the Cox proportional hazards model. Resection followed by adjuvant chemotherapy thus appears to represent the best treatment for PCC of the lung.

Table V. *Multivariate analysis of prognostic factors: Cox proportional hazards model.*

	HR	95% CI	*p*-value
OP+CT			
Yes	1		
No	15.5	1.46 - 165	0.023
Location			
Right lung	1		
Left lung	0.052	0.001 - 1.88	0.107
Bilateral	0.748	0.018 - 31.2	0.879
Gender			
Male	1		
Female	0.296	0.39 - 1.94	0.242
Tumor size, cm			
≥ 5	1		
< 5	0.24	0.04 - 2.28	0.327
Metastasis			
Yes	1		
No	0.60	0.072 – 39.1	0.749
Age, years			
< 40	1		
≥ 40	0.83	0.076 – 9.07	0.879
Smoking			
Yes	1		
No	0.80	0.042-15.3	0.882

HR, hazard ratio; OP, operation; CT, chemotherapy.

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