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REVIEW

Disseminated Primary Pulmonary Choriocarcinoma Successfully Treated by Chemotherapy: A Case Report and Literature Review

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ABSTRACT

Primary pulmonary choriocarcinoma (PPC) is frequently fatal due to difficulties in diagnosis. Few cases of PPC are bilateral and involve exceptionally large nodules. Here, we report an unusual case of PPC involving disseminated bilateral nodules, which was misdiagnosed as tuberculosis, but successfully treated using chemotherapy. A review of 65 cases revealed six cases of bilateral disease, including the present one. Patients treated with surgery, chemotherapy, or a combination of both showed similar treatment outcomes; however, chemotherapy may be the preferred option. Despite its rarity, PPC should be included in the differential diagnosis for all lung nodules to enable early detection.

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Primary pulmonary choriocarcinoma; human chorionic gonadotropin; chemotherapy

Introduction

Choriocarcinoma is a malignant tumor with early hematogenous dissemination; it develops from an abnormal trophoblastic tissue, which is commonly gestational in origin. Although the lungs are the most common site of metastasis, primary pulmonary choriocarcinoma (PPC) is very rare. Due to its rarity, the specific clinical manifestations and typical lung lesions of PPC have not been well-studied, making differential diagnosis challenging. This leads to delayed treatment initiation, resulting in death before appropriate treatment can be provided (1,2).

A review of the English literature found a total 64 PPC cases (1–56), and the majority of which were localized in the unilateral lung. Only five cases were of bilateral lung disease, which presented with a large solitary nodule. Herein, we describe an unusual case of PPC with hematolymphangitic dissemination in the bilateral lungs, which was successfully treated with chemotherapy alone. Additionally, we provide a review of the existing the literature.

Patients and methods

Medical literature published in English was searched in Medline to identify reports on PPC. The identified reports provided information on the patients' survival status (alive or dead) and whether the patients had persistent disease after management; none of the studies reported on survival duration or recurrence. As the survival status of patients represents the rates of treatment success and failure, we stratified the patients based on their survival status and compared their clinical characteristics to assess the factors associated with their prognosis.

Continuous variables, presented as medians, were compared using the Mann-Whitney *U* test. Dichotomous variables, presented as numbers and proportions, were compared using either the chi-squared or Fisher's exact test, as appropriate. Categorical variables were analyzed using the Kruskal–Wallis test. All *p*-values reported were two-sided, and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Science (SPSS, version 15.0, Chicago, IL, USA).

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Ethical approval was obtained from the institutional review board of Chung-Ang University Hospital (IRB No, 1990-002-16281), and informed consent was obtained from the patient to publish these data.

Case presentation

A 44-year old woman with gravida 3 para 2 presented with chest wall pain and a febrile sensation. No sputum production, cough, or rhinorrhoea was present. She took antibiotics targeting pneumonia for 1 week at a local hospital but did not improve. Her menses was regular, and her last menstrual period was 2 months prior to presentation. Crackles in both lower fields and tenderness of both chest wall were detected. The results of the routine blood tests and tests for tumor markers, including alpha-fetoprotein, carcinoembryonic antigen, carbohydrate19-9, CA125, and CA15-3, were unremarkable. Chest radiography showed multiple nodular opacities in the bilateral lungs (Figure 1(a,b)). Chest computed tomography (CT) showed multiple nodular lesions of various sizes with a suspicious halo sign and right pleural effusion with passive atelectasis, suggesting tuberculosis or metastatic cancer (Figure 1(c,d)). Tuberculosis polymerase chain reaction and acid-fast bacilli staining using sputum showed negative results. CT-guided percutaneous needle biopsy was performed, and a pathological examination revealed syncytial knots of atypical cells with hemorrhagic necrosis (Figure 1(e)). Immunohistochemical analysis was positive for beta-hCG (Figure 1(f)), CK-7, PAX-8, and WT-1 (focal) and negative for estrogen receptor and TTF-1, thereby supporting choriocarcinoma diagnosis. She denied coitus for 1 year, and transvaginal sonography showed mild adenomyosis and functional cysts in both ovaries. The serum beta-hCG level was found to be elevated to 665,751 mIU/ml (normal range <5.0 mIU/ml).

Chemotherapy with etoposide (100 mg/m^2), methotrexate (100 mg/m^2), cyclophosphamide (600 mg/m^2), vincristine (1 mg/m^2), and leucovorin (15 mg) every 2 weeks was promptly started. In total, six cycles of chemotherapy were performed without severe adverse effects, and a complete response was induced. The patient visited the outpatient department for follow-up management, without any signs of recurrence during the 24 months following treatment completion.

Literature review and discussion

After excluding the cases in which the primary origin was not identified due to metastasis to multiple organs, 66 cases of PPC were identified, including the present case (Tables 1 and 2). The age ranged from 4 months to 77 years and women were significantly younger at the time of diagnosis than men. In the majority of the cases, the PPC was localized in the unilateral lung ($n = 34$ in the right lung: $n = 15$ in the lower lobe, $n = 12$ in the upper lobe, $n = 1$ in the middle and $n = 6$ with no description; and $n = 25$ in the left lung: $n = 14$ in the upper lobe, $n = 7$ in the lower lobe, and $n = 4$ with no description). While 14 patients had no chance of treatment, 51 patients received treatment and of them, 17 died. 31 (49.2%) of the 61 patients who had information regarding their status at the end of the study (four patients had no information) were alive.

We stratified the patients by their survival status and compared their clinical characteristics to assess the factors associated with the prognosis (Table 3). Female sex was significantly associated with treatment success. The significantly younger age in women, which only differed based on sex when age, lesion location, and treatment modality were compared (data not shown), could be the possible reason. Patients who received treatment had a significantly better prognosis than those who did not receive treatment. However, treatment success did not differ according to the treatment modalities of surgery, chemotherapy, and a combination of both.

Thirteen of 65 patients were diagnosed with PPC via an autopsy several decades ago when there was limited awareness of PPC. Fifty-two patients were diagnosed by surgery or biopsy before treatment; 28 (53.8%) patients had complete remission; two (3.8%) patients had persistent disease; 17 (32.7%) patients died due to treatment failure; one (1.9%) patient died due to disease deterioration without a chance of treatment; four (7.7%) patients had no information on their

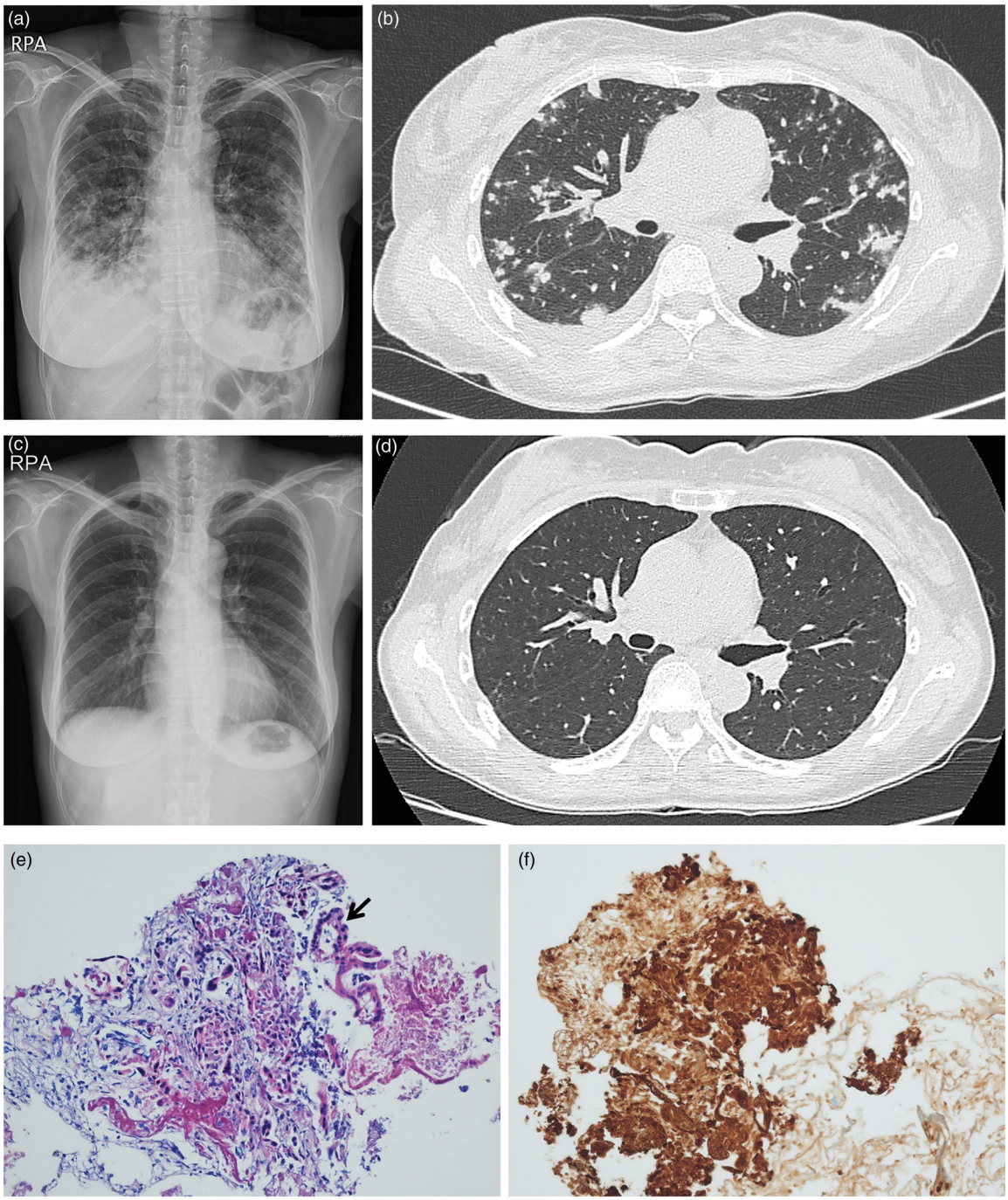

Figure 1. Radiologic and histologic findings: (a) Chest radiography shows multiple nodular opacities in both lungs and consolidation in the right lower lung field with a blunted right costophrenic angle, which may be interpreted as tuberculosis or metastasis. (b) Chest computed tomography shows multiple variable sized pulmonary nodules in both lungs. (c, d) Chest radiography and computed tomography after completing chemotherapy shows complete resolution. (e) Tissues obtained from a needle biopsy show the syncytial knots of atypical cells (arrow) with hemorrhagic necrosis (hematoxylin-eosin stain, ×200). (f) Immunohistochemical analysis shows that the atypical cells have a strong positive reaction for hCG. (Immunostaining, ×200).

prognosis. Of 17 patients with treatment failure, 14 (83.4%) died in 6 months and three (17.6%) died in 15, 15, and 36 months. These findings suggest that the disease was too advanced to treat by the time it was detected or that the diseases were rapidly progressive. These findings highlight the importance of early diagnosis, which can be achieved with an increased awareness of PPC.

Four patients were initially diagnosed with primary lung cancer (14,20,21,56); this was

Table 1. Summary of the primary pulmonary choriocarcinoma cases reported in the literature.

	Age/sex	Location	Treatment[†]	Prognosis	Ref.
1	7 months/F*	Right lobe	Pneumonectomy	Died 4 hours after surgery	(3)
2	24/F*	Left lower lobe	None	Died 9 days after admission	(4)
3	19/M	Left upper lobe	Diagnostic thoracotomy and chemotherapy (chlorambucil, MTX, and actinomycin D)	Died 10 weeks after diagnosis	(5)
4	45/M	Left upper lobe	Diagnostic thoracotomy and radiation therapy	Died 6 months after diagnosis	(6)
5	57/M*	Right lower lobe	None	Died 2 months after diagnosis	(6)
6	27/M	Right lower lobe	Right lobectomy and chemotherapy (vinblastine, bleomycin, and cisplatin)	NED for 2 years	(7)
7	67/M	Left upper lobe	Left upper lobectomy	NED for 3 years	(8)
8	22/F*	Left lobe	None	Died 1 week after admission	(9)
9	34/F	Right upper lobe	Rt. upper lobectomy	NED for 6 months	(10]
10	33/F	Right lower lobe	Chemotherapy (MAC)	Unknown	(11)
11	60/F	Right lobe	Right pneumonectomy	Died 1 week after surgery	(12)
12	71/M*	Right upper lobe	None	Died 2 months after admission	(13)
13	37/M[‡]	Right upper lobe	Chemotherapy (cisplatin, 5-FU, and etoposide), pneumonectomy, and concurrent chemoradiation	Died 15 months after diagnosis	(14)
14	51/M*	Left upper lobe	None	Died 6 days after admission	(15)
15	61/M	Left upper lobe	Pneumonectomy, radiotherapy and chemotherapy (cisplatin, etoposide, vinblastine, and bleomycin)	Died 11 days after the first chemotherapy	(16)
16	4 months/M	Right lower lobe	Surgical tumor removal, chemotherapy (cisplatin, vincristine, and bleomycin), and radiation for multiple metastases and an intracranial lesion	Died 5 months after surgery	(17)
17	27/F	Right lobe	Chemotherapy (methotrexate and actinomycin D), and tight lobectomy	NED for 3 years	(18)
18	69/M*	Bilateral	Chemotherapy (unknown regimen)	Died after the first chemotherapy	(19)
19	69/M[‡]	Left lobe	Lobectomy and chemotherapy (BEP)	NED for 6 months	(20)
20	60/M[*‡]	Right lobe	Chemotherapy for squamous cell lung carcinoma	Died 5 months after diagnosis	(21)
21	61/M	Right lower lobe	Wedge resection, and chemotherapy (2 cycles of EMACO and 2 cycles of BEP)	Persistent disease for 6 months after surgery	(22)
22	41/F	Right lobe	Chemotherapy (8 cycles of bleomycin, vincristine, MTX, platinum, etoposide, and ifosfamide), and right pneumonectomy with lymphadenectomy	NED for 8 months	(23)
23	23/M	Bilateral	Transbronchial lung biopsy and chemotherapy (MAC)	Died after the first chemotherapy	(24)
24	37/F	Right lower lobe	Lobectomy and chemotherapy (BEP)	NED for 1 year	(25)
25	28/F	Right lower lobe	Chemotherapy (8 cycles of EMACOs, 6 cycles of EP-EMA), right lobectomy, right hepatectomy	Died 3 years after diagnosis	(26)
26	31/F	Left upper lobe	Lobectomy and chemotherapy (EMA)	NED for 3 years	(27)
27	36/F*	Left upper lobe	None	Died	(28)
28	29/F*	Left upper lobe	None	Died	(28)
29	43/F*	Left lower lobe	None	Died	(28)
30	25/F	Left lower lobe	Surgical resection	Clinically well at the last follow-up visit (unknown period)	(28)
31	40/F*	Left lower lobe	None	Died	(28)
32	40/F*	Right lower lobe	None	Died	(28)
33	60/M*	Right lower lobe	None	Died	(28)
34	44/F*	Right lower lobe	Chemotherapy (cyclophosphamide)	Died 8 days after admission	(29)
35	77/M*	Left upper lobe	None	Died 6 days after admission	(30)

(*continued*)

Table 1. Continued.

	Age/sex	Location	Treatment†	Prognosis	Ref.
36	28/F	Right lower lobe	Lobectomy	NED for 4 months	(31)
37	38/M	Right upper lobe	Pneumonectomy	NED for 3 years	(32)
38	39/M*	Left upper lobe	None	Died 2 weeks after admission	(33)
39	22/F	Left lower lobe	Chemotherapy (EP-EMA), lobectomy, and then chemotherapy (2cycles of EP-EMA)	NED for 2 years	(26)
40	30/F	Left lower lobe	Lobectomy and chemotherapy (MAC and then BEP)	NED	(34)
41	31/F	Right upper lobe	Rt. upper lobectomy and chemotherapy (modified EMACO)	NED for 42 months	(35)
42	19/F	Right lower lobe	Chemotherapy (EMACO)	NED for 1 year	(36)
43	28/F	Right lower lobe	Rt. lower lobectomy with lymphadenectomy	NED for 2 years	(37)
44	32/F	Right upper lobe	Lobectomy with lymphadenectomy and chemotherapy (2 cycles of platinum-based agents)	NED for 1 year	(38)
45	48/M	Bilateral	Chemotherapy (4 cycles of BEP) and thoracoscopic wedge resection	Died 5 days after surgery	(39)
46	34/F	Left lobe	None	Died before treatment	(40)
47	27/F	Left upper lobe	Partial resection	NED for 19 months	(41)
48	26/F	Right upper lobe	Segmentectomy	Unknown	(42)
49	31/F	Right upper lobe	Surgical excision of the tumor	NED for 20 months	(43)
50	37/F	Left lower lobe	Lobectomy and chemotherapy (BEP)	NED for 1 year	(44)
51	29/F	Left upper lobe	Lobectomy and chemotherapy (6 cycles of EP-EMA)	NED for 1 year	(45)
52	26/M	Bilateral	Chemotherapy (4 cycles of BEP)	NED	(46)
53	25/F	Right lobe	Chemotherapy (BEP)	Unknown	(1)
54	35/F	Right lower lobe	Chemotherapy (EMACO) and surgery for lung lesion, and radiation therapy for brain metastases	NED	(2)
55	59/M	Left upper lobe	Left upper lobectomy with lymphadenectomy	Died 1 month after surgery	(47)
56	55/F	Bilateral Brain metastasis	Chemotherapy	Unknown	(48)
57	67/M	Left upper lobe	Lobectomy and chemotherapy	NED for 13 months	(49)
58	70/M	Right upper lobe	Rt. upper lobectomy with lymphadenectomy	NED for 2 years	(50)
59	69/F	Right upper lobe Brain metastasis	Craniectomy, whole brain and lung mass radiation, and then chemotherapy (carboplatin and etoposide)	NED for 1 year	(51)
60	22/F	Right upper lobe	Craniotomy and chemotherapy (EMACO)	NED	(52)
61	32/F	Right lower lobe	Chemotherapy (1 cycle of BEP)	Died after 2 days of chemotherapy	(53)
62	71/M	Right. middle lobe	Rt. med lobectomy with lymphadenectomy	Died 3 months after surgery	(54)
63	28/F	Left lobe	Chemotherapy (3 cycles of an MTX-based regimen)	Symptoms resolved as tumor activity was reduced	(55)
64	53/M‡	Left upper lobe	Chemoradiation (paclitaxel and carboplatin), left lobectomy, and chemotherapy (EP-EMA)	Died 15 months after the initial diagnosis	(56)
65	44/F	Bilateral	Chemotherapy (6 cycles of EMCO)	NED for 2 years	Present case

†Described sequentially; *primary pulmonary choriocarcinoma was diagnosed after autopsy; ‡primary lung cancer was the initial diagnosis.
MTX: methotrexate; NED: no evidence of disease; MAC: methotrexate, actinomycin D, cyclophosphamide; EMCO: etoposide, methotrexate, vincristine, cyclophosphamide; EMACO: etoposide, methotrexate, actinomycin D, vincristine, cyclophosphamide; EP-EMA: etoposide, cisplatin, etoposide, methotrexate, actinomycin; BEP: bleomycin, etoposide, cisplatin.

identified on a histologic examination of tissues obtained from fine needle aspiration or bronchoscopy. However, subsequent examination by pneumonectomy, lobectomy, or autopsy showed the presence of PPCs. This observation could be explained by several reasons, one of which might be insufficient specimen collection. The other might be the similarity in morphology and immunohistochemistry between PPCs and squamous cell carcinoma (56). A third reason could be the rarity of PPCs, which results in PPC not being considered in the differential diagnosis. Three patients who received initial chemotherapy/chemoradiation therapy for the primary lung

cancer with subsequent surgery died. However, one patient who received an initial lobectomy was successfully treated because the surgery enabled the exact diagnosis and selection of proper chemoagents for PPC.

The majority of PPC cases at the time of diagnosis had a unilateral lung lesion. Only six of the 65 cases had bilateral disease. Five cases of PPC with bilateral disease with the exception of the present case, had one or several exceptionally large nodules in their lungs. However, the case presented here had tiny to small nodules disseminated in the bilateral lungs, and none of the nodules were exceptionally large, contributing to an incorrect tuberculosis diagnosis. Two patients, including the present case, had complete remission with initial chemotherapy; one patient died 8 days after admission; one patient died 6 weeks after diagnosis despite having started on chemotherapy (the regimen used is unknown) and was diagnosed during an autopsy; one patient died 5 days after thoracoscopic wedge resection following four cycles of chemotherapy, in which the reason for death was not clear (disease progression or surgical complication); and one patient had no information. These findings indicate that bilateral lung disease associated with PPC should be considered a systemic disease, and chemotherapy might be adequate for treatment. A further accumulation of cases is required to support this conclusion.

Although there is no standardized treatment for PPC, surgical resection or chemotherapy should be considered depending on the case. Patients who received surgery with/without chemotherapy were diagnosed postoperatively. Nine patients were successfully treated with surgery only because they had relatively smaller (5–55 mm) single nodules in their unilateral lungs; thus, the lesion might have been resected before dissemination. If PPC in these patients was detected preoperatively, chemotherapy might have been chosen as the treatment modality because choriocarcinoma is a chemo-sensitive tumor. This has been proven by experience from treating gestational choriocarcinoma and the lack of a difference between gestational and nongestational disease. Accordingly, 16 patients diagnosed with biopsy before operation received chemotherapy as the primary method of treatment

Table 2. Characteristics of the 65 cases of primary pulmonary choriocarcinoma.

Characteristics	Number (%)
Age, years, mean ± SD	39.9 ± 17.6
Female	32.8 ± 11.6*
Male	50.1 ± 19.8
Sex	
Female	39 (60.0)
Male	26 (40.0)
Lesion location	
Unilateral	59 (90.8)
Bilateral	6 (9.2)
Treatment	
None	14 (21.5)
Surgery	14 (21.5)
Chemotherapy	13 (20.0)
Surgery and Chemotherapy (±Radiation)	23 (35.4)
Radiation	1 (1.6)
Survival status	
Alive	30 (46.2)
Dead	31 (47.7)
Unknown	4 (6.1)

*Significant difference between female and male patients ($p < 0.001$, Mann–Whitney U test).
SD: standard deviation.

Table 3. Comparison of clinical characteristics according to survival among patients with primary pulmonary choriocarcinoma.

	Alive ($n = 30$)	Dead ($n = 31$)	Unknown ($n = 4$)	p-Value
Age, years, mean ± SD	37.6 ± 15.9	43.0 ± 19.5	34.7 ± 13.9	NS†
Sex				
Female	22	13	4	0.019‡
Male	8	18	0	
Lesion location				
Unilateral	28	28	3	NS§
Bilateral	2	3	1	
Treatment				
None	0	14	0	<0.001*
Surgery	9	4	1	NS**
Chemotherapy	4	6	3	
Surgery and chemotherapy (±Radiation)	17	6	0	
Radiation	0	1	0	

†Mann–Whitney U test; ‡Chi-square test; §Fisher exact test; *comparison among the five groups (Kruskal–Wallis test); **comparison among surgery, chemotherapy, and surgery and chemotherapy (Kruskal–Wallis test).
NS: no significance.

(1,2,5,11,18,23,24,26,36,39,46,48,53,55). Another reason that chemotherapy might be considered the first choice in treating of PPC is the aggressive nature of the disease. A delay in initiation of chemotherapy due to surgery might allow time for dissemination. If the diagnosis is made after surgery, immediate postoperative chemotherapy is imperative. A combination of three to five chemoagents with cisplatin, etoposide, methotrexate, actinomycin D, vincristine, bleomycin, and cyclophosphamide is effective for PPC.

This study had some limitations such as its retrospective nature and the small sample size for the stratified analyses, resulting in a relatively inadequate statistical power. Because the information was obtained from case reports, all the necessary clinical information was not collected. Furthermore, because the data were collected long before this study was conducted and because autopsy data were included, the mortality rate might be higher than we currently expect. Although the accumulation of more cases is needed to clarify this disease, current reports will provide precise information regarding this rare disease.

In the present case, the patient exhibited an unusually disseminated PPC, initially misdiagnosed as tuberculosis—a common disease in Korea; however, upon correct diagnosis, it was successfully treated with prompt chemotherapy. The serum beta-hCG test and CT-guided needle biopsy were critical in the diagnosis of PPC. Based on the evidence from the review of 66 cases, PPC should be ruled out if any lung nodules are identified in the patients. This is because PPC is not characterized by typical lung lesions and tests for serum beta-hCG, a reliable biomarker of PPC, are very simple to perform. Additionally, if PPC is diagnosed, chemotherapy should be considered as the leading treatment option for patients.

Disclosure statement

The authors declare that they have no conflicts of interest.

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