

# Pulmonary Pleomorphic Carcinoma Mimicking Primary Sarcoma of the Neck: A Case Report and Literature Review

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**Abstract:** We describe our challenge in diagnosing an unusual and rapidly progressing case of pulmonary pleomorphic carcinoma (PPC)—a rare, poorly differentiated, or undifferentiated non-small-cell carcinoma that can metastasize locally or distantly and has a poor prognosis. Our patient was an elderly man with a one-month history of abdominal pain, anorexia, and weight loss, diagnosed with atrophic gastritis via endoscopy, and treated medically without improvement. A week later, this patient developed pain in the head, neck, and shoulder area, and further examination revealed a thickening of his left neck and shoulder, with no palpable lymph nodes. Computed tomography (CT) of the neck, chest, and abdomen led us to believe that we might be dealing with primary sarcoma of the neck since no lung mass was evident. Further investigation could not be performed because the patient's status deteriorated rapidly. An autopsy revealed that soft tissue in the left neck and the mesentery was invaded by poorly differentiated polymorphic malignant cells, which were also seen in the lung lesion. Immunohistochemically, these malignant cells were all positive for AE1/AE3, CAM5.2, TTF-1, Napsin-A, and Vimentin. The cells were also positive for programmed death-ligand 1 staining with a low level of tumor proportion score (over 1%). The final diagnosis was PPC with metastases to soft tissues in the left neck and the mesentery. A review of previous case reports of PPC revealed that soft tissue is an uncommon site for metastasis, and that our CT findings were rather unusual. We hereby present our case and review of published case reports, with the hope that an awareness of the heterogeneous features of PPC could prompt timely biopsy and histological diagnosis.

**Keywords:** pleomorphic carcinoma of the lung, non-small-cell lung cancer, metastases to soft tissues, mesentery, poor prognosis

## Introduction

Pulmonary pleomorphic carcinoma (PPC) is a poorly differentiated or undifferentiated non-small cell lung carcinoma. Fishback et al in 1994 originally reported it as a new entity among lung cancers.<sup>1</sup> According to the 2015 World Health Organization classification, PPC is a subtype of sarcomatoid carcinoma, containing at least 10% of sarcomatous-like components with spindle and/or giant cells, or consisting only of spindle and giant cells.<sup>2</sup>

PPC is rare, accounting for less than 1% of all lung tumors.<sup>3-5</sup> It usually occurs in men beyond the age of 60 years with a history of heavy smoking.<sup>1,5,6</sup> It has an aggressive clinical course, and the prognosis is poor.<sup>3-8</sup> Many patients are diagnosed at advanced stages because of its aggressiveness.<sup>4</sup> The median overall

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survival time of PPC has been reported as 6–19 months.<sup>1,5–7</sup> PPC can also cause both local and distant metastases occurring in early stages, hence the rapid and tragic clinical course.<sup>5,9–11</sup> Treatment is not yet established. Generally, PPC seems to be resistant to cytotoxic agents, but there is no standard treatment strategy except for resection.<sup>12,13</sup> Some reports show efficacy of immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab.<sup>14,15</sup>

We describe a case of PPC that occurred in a patient in our care and reviewed case reports of PPC with metastases. Cases reviewed were searched via PubMed<sup>®</sup> on October 31, 2020, using the terms “(pleomorphic carcinoma of the lung) OR pulmonary pleomorphic carcinoma” and “case report”, published in English. We limited our focus to cases in which specific sites of metastasis were noted at the time of diagnosis. Through the study, we recognized the fact that PPC could present heterogeneous clinical features, and our case had extremely rare presentations. We must memorize and report this case to diagnose accurately in subsequent patients.

## Case Presentation

### Clinical Findings and Course

An 85-year-old man with a 60-pack-year history of smoking presented with epigastric discomfort, loss of appetite, and weight loss of 2 kilograms over the past month. The patient quit smoking in his 50s and had a pacemaker implanted for complete atrioventricular block 7 years earlier. He had been medicated for hypertension, dyslipidemia, diabetes mellitus, hyperuricemia, chronic heart failure, and benign prostatic hypertrophy for more than 5 years, and these diseases were well controlled. During the first visit, upper gastrointestinal endoscopy revealed chronic atrophic gastritis with a small ectopic pancreas. A proton pump inhibitor, mosapride, and digestive enzymes were administered to him for a week. However, his symptoms were not alleviated, and he complained of additional multiple pains appearing in the head, neck, and left shoulder. Pregabalin was additionally administered, but his symptoms gradually worsened. As a result, the patient was admitted to our hospital for further evaluation and treatment.

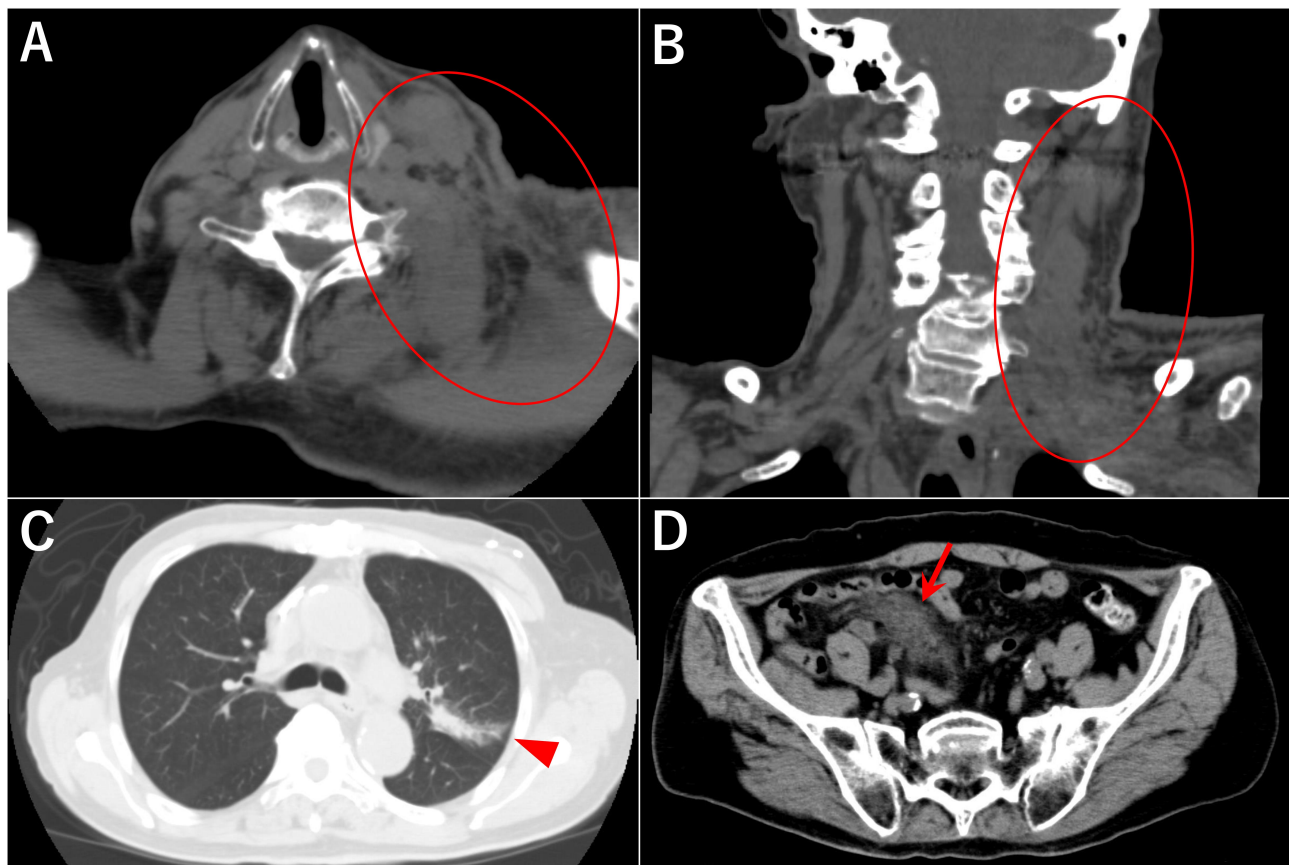
On physical examination, thickness and rigidity of his left neck and shoulder were detected. No lymph nodes were palpable. Wheezes were audible at the end of expiration. Oxyhemoglobin saturation was 98% without oxygen

therapy. Laboratory tests revealed hypoproteinemia (total protein 6.5 g/dL), renal dysfunction (serum creatinine 1.44 mg/dL), and mild inflammation (C-reactive protein 0.86 mg/dL). The other common biochemical tests and blood cell counts were within the normal range. Urinalysis revealed no remarkable abnormal findings, and the fecal occult blood test was negative. Computed tomography (CT) revealed an obscure soft tissue in the left supraclavicular fossa, a swollen left levator scapulae muscle, and enlarged lymph nodes in the left neck (Figure 1A and B). CT also detected pulmonary consolidation, with an interlobular pleural shift in the left upper lobe and misty mesentery (Figure 1C and D). Although no tumor mass was detected in the neck, sarcoma or another malignancy was suspected. In addition, coexisting infectious diseases, such as cellulitis of the neck and/or bacterial pneumonia, were also considered.

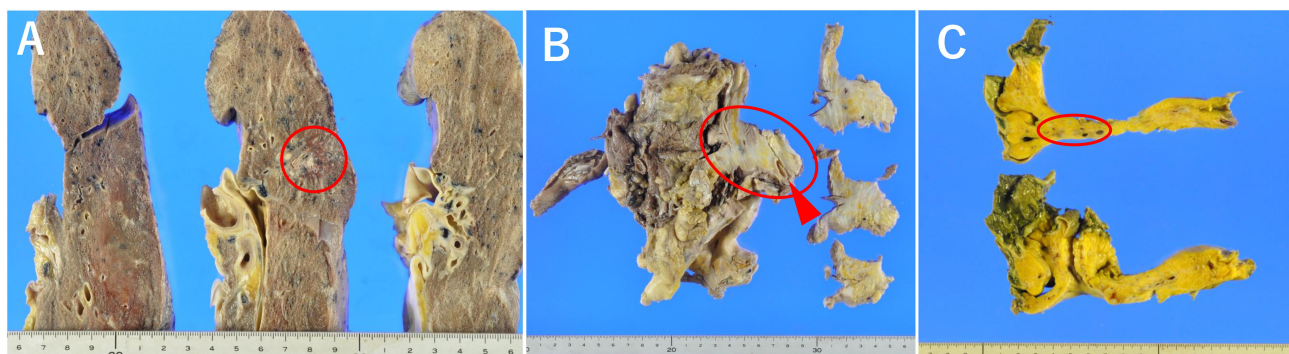
His general status worsened by the day. A biopsy from the affected lesions of the neck was considered but could not be performed owing to his deteriorating state, which featured high fever, unconsciousness, and circulatory insufficiency. The epithelial tumor marker, carcinoembryonic antigen, was elevated (264.3 ng/mL) on the sixth day of hospitalization. Thereafter, he required steroids and antibiotics, as well as opioids, to relieve his symptoms. He died only 16 days after admission to the hospital.

## Autopsy

With the consent of his proxy, an autopsy was performed. Grossly, multiple tumors and tumor-like lesions with lymphadenopathies were found in the left upper lobe of the lung, the mesentery of the small bowel, and the left neck (Figure 2). These findings were compatible with the results of the enhanced CT scan (Figure 1). Microscopically, the lung tumors were composed of poorly differentiated polymorphic cells mixed with spindle cells (Figure 3A). Thickened soft tissue in the left neck was invaded by atypical malignant cells similar to those in the lung (Figure 3B). The invasion had spread to the subclavian vessels, the common carotid artery/vein, and the sternocleidomastoid muscles. The mesentery had also been invaded by malignant cells similar to those in the lung and neck (Figure 3C). Although these three malignant tumors were detected, the origin was unclear by the findings of hematoxylin–eosin stain alone. Immunohistochemically, these cells in multiple organs were all positive for AE1/AE3, CAM5.2, TTF-1, Napsin-A, and Vimentin (Figure 4A–D), but negative



**Figure 1** Images of the chest-abdominal CT scan. **(A and B)** Swollen left levator scapulae muscle and enlarged lymph nodes in the left neck (red circle). **(C)** A consolidation with an interlobular pleural shift in the left lung (arrowhead). **(D)** A consolidation in the abdominal soft tissue (arrow).



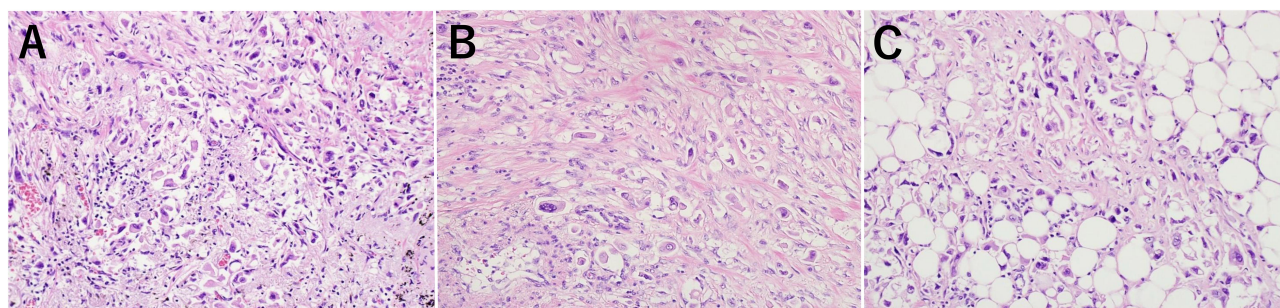
**Figure 2** Gross findings of the autopsy. The tumors are shown inside the red circles. **(A)** Left lung. **(B)** Soft tissue, muscles, and carotid artery (arrowhead) of the left neck. **(C)** Mesentery.

for P40/CK14, PAX8, Thyroglobulin, Desmin, MyoD1, and S100 (data not shown). Based on these findings, the tumors had their primary origin in the lung; therefore, they were diagnosed as PPC with an adenocarcinoma component with metastasis. The expression of programmed death-ligand 1 (PD-L1, clone 22C3) was detected with a low level of tumor proportion score (TPS) in the lung tumor cells (Figure 5). The autopsy

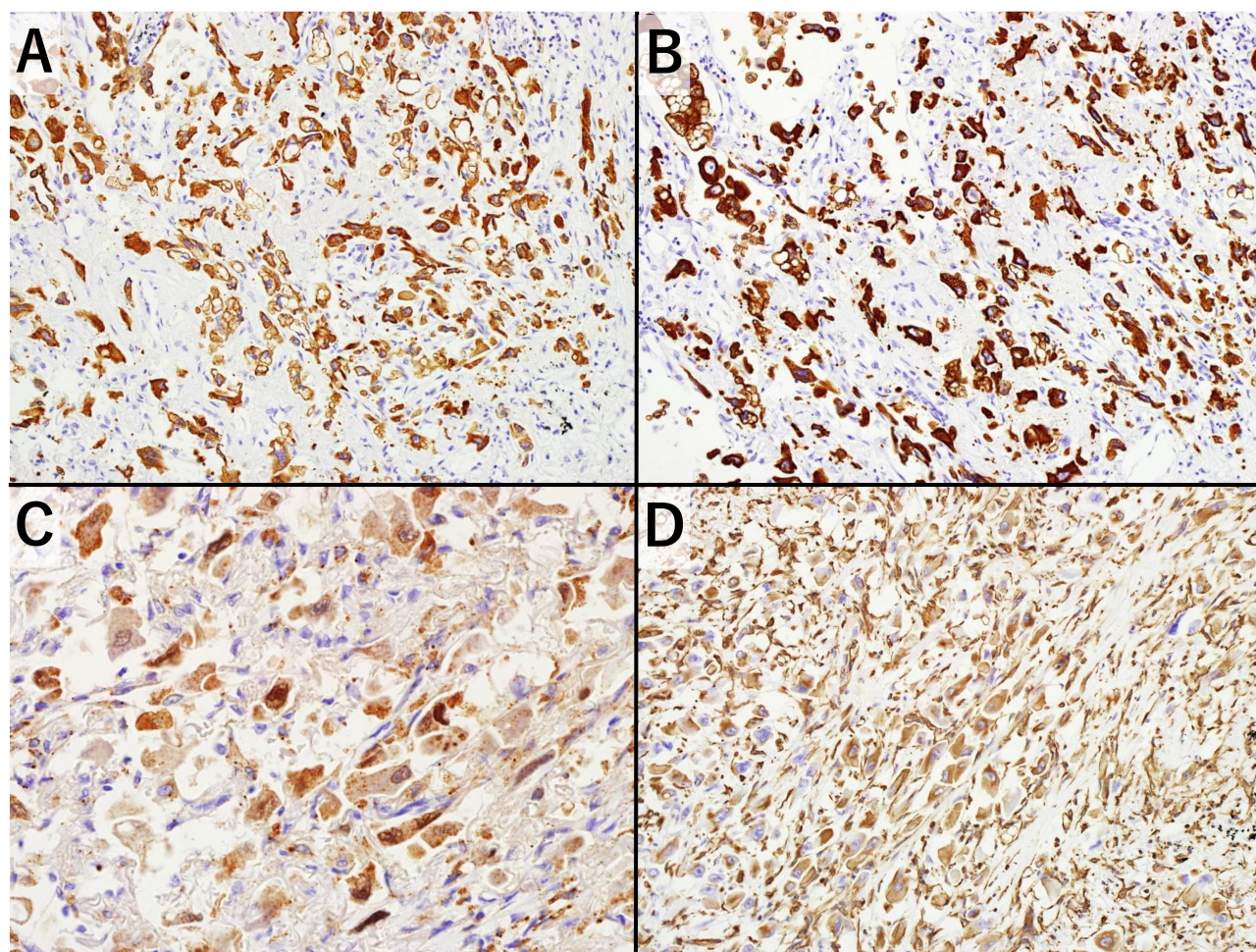
revealed no evidence of infection and concluded that the cause of death was circulatory insufficiency induced by cachexia due to advanced PPC.

## Review of Case Reports

Our review of the literature revealed 33 case reports of PPC having distant metastasis at the time of diagnosis (Table 1).<sup>15-46</sup> The common sites of metastases were the



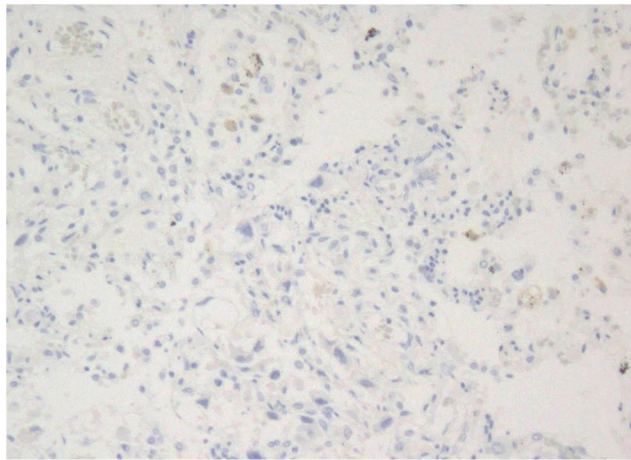
**Figure 3** The microscopic findings of the tumors with hematoxylin–eosin staining. **(A)** The lung tumor was composed of poorly differentiated polymorphic cells mixed with spindle cells. **(B)** Thickened and invaded with atypical malignant cells in the left neck. **(C)** The mesentery had also been invaded by similar malignant cells as the lung and neck.



**Figure 4** Immunohistochemical findings of the tumors. The malignant pleomorphic cells are positive for all stains. **(A)** AE1/AE3. **(B)** CAM5.2. **(C)** TTF-1/Napsin-A. **(D)** Vimentin.

adrenal glands (11 cases), bones (9 cases), gastrointestinal tract (7 cases), and brain (5 cases); there was only one case (other than ours) with metastasis to the soft tissue, including the muscle (Case 1, Table 1). Typical CT findings consistently showed one or more distinct lung masses, versus our unusual CT findings (no mass

lesion but focal consolidation). Immunohistochemically, it is interesting to note that some cases had positive results for Vimentin and extremely short survival (Cases 5, 9, 18, 23, and 33, Table 1), and they are similar to our case. However, there are no clear correlations of immunohistochemical markers across all case reports. Various



**Figure 5** PD-L1 staining of the lung tumor. The tumor cells were weakly stained by the anti-PD-L1 antibody clone 22C3 with a low expression level (TPS was slightly over 1%).

treatments were employed, usually in combination, and the range in survival was very broad, from days and weeks to beyond 7 years. No clear correlations between treatment and survival can be drawn in this small collection of cases; however, most patients treated with ICIs were alive at the time of each publication. Most ICIs were adopted as adjuvants to conventional chemotherapy.

## Discussion

Our patient was an elderly man with severe and rapidly progressing PPC who died before the final diagnosis. Death before diagnosis often causes confusion in clinical situations. There were some reasons for the delay in diagnosis. First, his initial symptoms were epigastric discomfort and neck pain, whereas respiratory symptoms were absent. Furthermore, symptoms indicating lung cancer were never seen in his entire clinical course. In contrast, typical symptoms of PPC include chest pain, cough, fever, and hemoptysis.<sup>1,5-7</sup> Second, the abnormal lesion detected by the chest CT could not be recognized as a primary lung cancer because it did not form a nodule or mass; it rather formed a consolidation in the limited area. We initially considered this consolidation as focal pneumonia based on the evidence of mild inflammation in the patient's blood tests. Radiological findings of PPC by CT scan are usually observed as masses or nodules but rarely as consolidations or interstitial pneumonia.<sup>5,47</sup> Meanwhile, his clinical findings were more remarkable in the neck muscles. Therefore, we suspected primary sarcoma of the left neck. Third, a planned biopsy could not be performed because of his deteriorating condition after non-invasive

examinations. We had performed gastrointestinal endoscopy, but biopsy here would not be revealing since the mucous tissue of his intestinal tract was not invaded by PPC. So, the final diagnosis came from the autopsy and gave us a great impression.

Previous observational studies indicated that PPC predominantly occurs in heavily smoking males at an average age of approximately 60 years and present an aggressive clinical course.<sup>1,5,6</sup> The clinical aggressiveness of PPC, such as an early metastasis, might be associated with smoking history. Lung cancer metastasis is promoted by long intergenic noncoding RNA (linc00152) and mediators of inflammation, such as transforming growth factor- $\beta$ 1, Smad2, matrix metalloproteinase 3, and hypoxia inducible factor-1, all of which are induced by cigarette smoking extracts.<sup>48,49</sup> In our patient, therefore, the heavy-smoking habit in his youth, followed by pulmonary inflammation, might have induced these mediators and have been promoting carcinogenesis and metastasis for many years.

As the PPC cells were positive for PD-L1, our patient might have been successfully treated using ICIs such as pembrolizumab. However, previous studies indicated that the high efficacy of ICIs was observed only in patients with advanced PPC with a high level of TPS.<sup>14,15</sup> Therefore, even if our patients had a chance to receive ICI therapy, its efficacy could not be fully expected because the TPS of PD-L1 was relatively low. However, an examination of the PD-L1 expression in PPC cells is particularly important because treatment with ICIs such as a PD-L1 or PD-1 inhibitors is expected to be the most effective on PPC for now.<sup>14,50</sup> In addition, PD-L1 expression could be a more specific marker of PPC compared with other subtypes of non-small-cell lung cancer.<sup>51</sup>

In our review of PPC case reports, we confirmed that metastases to soft tissues (particularly to the muscles) is extremely rare and that our patient's CT findings (focal consolidations rather than an obvious tumor) were rather unusual (Table 1). The expression of Vimentin on the PPC cells might be associated with a poor prognosis.

## Conclusion

We presented an elderly patient with PPC presenting unusual clinical findings, which was diagnosed only by autopsy. Awareness of the heterogeneous features and metastatic locations of PPC might have raised clinical suspicion and prompted timely biopsy and histological diagnosis, possibly providing the appropriate interventions and solving the confusion.

**Table 1** Published Case Reports of Pleomorphic Carcinoma with Metastasis

No.	Age	Sex	CT Findings of the Lung Cancer (Maximum Diameter)	Metastases Detected at Diagnosis	Immunohistochemical Findings of PPC	Treatments for PPC	Survival (Months)	Ref.
1	62	M	A solitary mass (5.0 cm)	ADR, OTH (pancreas, erector spinae muscle)	PD-I+, PD-LI+ (clone 28-8, TPS 70%; clone 22C3, TPS 20%), p40-, TTF-I-	CHEM followed by ICI	>14	[15]
2	48	F	A tumor (1.76 cm)	BRA	CK7+, PD-LI+ (TPS 80%), Vimentin+, TTF-I+	ICI followed by CHEM, RT	18	[16]
3	50	M	A mass (3.7 cm)	ADR, OTH (colon)	CK7+, CK20-, SP-A+, TTF-I+	CHEM followed by ICI	NA (died)	[17]
4	73	M	Multiple masses	PUL, ADR	PD-LI+ (TPS 80%)	ICI	>17	[18]
5	59	F	A cavitory mass (6.0 cm)	PUL, PLE, ADR, OSS	AEI/AE3+, CAM5.2+, CK7+, CK20-, Napsin-A-, p40-, Vimentin+, TTF-I-	None	<1 (a few days)	[19]
6	63	M	A lobulated mass (7.3 cm)	OTH (Small bowel)	AEI/AE3+, Napsin-A+, p40-, Vimentin+, TTF-I+	CHEM	>12	[20]
7	81	M	A nodule (1.1 cm)	OSS	NA	CHEM followed by ICI	>36	[21]
8	64	M	A tumor	OSS	CK5/6-, CK7+, TTF-I-	Steroid followed by CHEM	14	[22]
9	65	F	A lesion (3 cm)	PLE, ADR, OSS	Napsin-A+, Vimentin+, TTF-I+	CHEM	<1	[23]
10	50	M	NA	BRA	TTF-I-, p63-, panCK+	RT	5.5	[24]
11	75	M	A solid nodule (1.8 cm)	PLE	PD-LI (TPS >90%)	SURG, CHEM followed by ICI	>24	[25]
12	55	M	A mass (7.0 cm)	ADR	CK7+, PD-LI+ (TPS 90%), TTF-I-	CHEM followed by ICI	>12	[26]
13	51	M	A cavitory nodule	PLE, ADR, HEP	AEI/AE3+, Ki67+, p53+, PD-LI+ (TPS >50%)	ICI	>2	[27]
14	63	M	A mass (7.4 cm)	OSS	CAM5.2+, CK7-, CK20-, p40+, TTF-I-	SURG, RT, CHEM	NA	[28]
15	73	M	A mass (7cm)	BRA	CK7+, Vimentin+	CHEM	>24	[29]
16	67	M	A solitary mass (2.5 cm)	ADR	PD-LI+	CHEM and RT followed by ICI	>43	[30]
17	63	F	A mass (4.0 cm)	OSS	NA	CHEM	11	[31]
18	50	M	Masses	OSS, OTH (retroperitoneal tumor)	panCK+, Vimentin+, TTF-I-	CHEM, RT	4	[32]

(Continued)

Table I (Continued).

No.	Age	Sex	CT Findings of the Lung Cancer (Maximum Diameter)	Metastases Detected at Diagnosis	Immunohistochemical Findings of PPC	Treatments for PPC	Survival (Months)	Ref.
19	71	M	A mass (7.0cm)	BRA	MIB-1+	CHEM followed by SURG	>84	[33]
20	62	M	An irregularly shaped mass (7.6cm)	OTH (kidney)	NA	CHEM	NA (died)	[34]
21	82	F	NA	OSS	AE1/AE3+, CAM5.2+, CK7-, Napsin-A+, TTF-1+	RT	1	[35]
22	46	M	A large mass	OTH (stomach, pancreas)	panCK+	Palliative care	<1 (3 weeks)	[10]
23	78	M	An irregularly shaped tumor (4 cm)	OTH (jejunum and colon)	CK7+, CK20-, Vimentin+	SURG	3	[36]
24	76	M	NA	OTH (pancreas)	NA	CHEM	NA	[37]
25	57	M	A spiculated mass (1.9cm)	OTH (colon)	AE1/AE3+, CK7+, CK20-, TTF-1+, Vimentin+	SURG	3	[38]
26	60	F	A mass (2 cm)	PLE	Keratin+, Vimentin+, anti-EGFR+	SURG, CHEM	21	[39]
27	51	F	A mass	ADR	CK+	CHEM	11	[40]
28	61	M	A mass	ADR	CK5/6+	SURG	21	[41]
29	61	M	A mass	BRA (neoplastic aneurysm)	CAM5.2+	SURG	1	[42]
30	58	M	NA	ADR	NA	CHEM	5	[43]
31	62	M	A tumor (3.3 cm)	OTH (stomach)	AE1/AE3+, CD34-, CK7+, TTF-1-	SURG	>48	[44]
32	57	F	A mass	OSS	NA	CHEM	2	[45]
33	40	F	A lobulated mass (5.0 cm)	OTH (small bowel)	AE+, CD34-, CK7-, CK20-, Vimentin+	SURG	<1	[46]
34	85	M	Consolidation	OTH (soft tissues of neck, mesentry)	AE1/AE3+, CAM5.2+, Napsin-A+, Vimentin+, PD-L1 weak+ (TPS >1%), TTF-1+	Palliative care	<1 (16 days)	Our case

**Notes:** In the column of "immunohistochemical findings of PPC," surface markers specific to epithelial tumors are the focus. In the survival column, ">" indicates that the number recorded is the number of months of follow-up rather than the month in which the patient died.

**Abbreviations:** ADR, adrenal gland; BRA, brain; CHEM, Chemotherapy; CK, cytokeratin; CT, computed tomography; F, female; M, male; HEP, liver; ICI, immune checkpoint inhibitor; NA, not available; OSS, bone; OTH, others; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein-ligand 1; PLE, pleura; PUL, lung; Ref, reference; RT, Radiotherapy; SP-A, pulmonary surfactant protein-A; SURG, Surgery; TPS, tumor proportion score; TTF-1, thyroid transcription factor-1.

## Ethics Statement

Ethical approval for publication was obtained from The Institutional Review Board of Nanto Municipal Hospital (reference number 183-2).

## Consent for Publication

Written informed consent was obtained from the next of kin of the patient for the publication of this report and any accompanying images.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest.

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