Pulmonary Lymphangitic Carcinomatosis as the Initial and Only Presentation of Gastric Cancer in a Young Male and Literature Review

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Abstract

Background

Pulmonary lymphangitic carcinomatosis (PLC) is a malignant lung disease characterized by metastatic tumor lesions in the lung lymphatic vessels with a poor prognosis. Early diagnosis is the key to improve the outcome. However, when PLC is the first manifestation of patients without a known malignancy, it often leads to delayed diagnosis and treatment, and even fatal consequences due to non-specific symptoms. Here, we describe a young male presenting PLC as the first and only manifestation followed by diagnosis of gastric adenocarcinoma and systemically summarized previously reported clinical properties of PLC cases in the literature.

Case presentation

A 32 years old male presented nonproductive cough for 20 days and progressive exertional dyspnea in a week. He was diagnosed with pneumonia and received antibiotics for almost 3 weeks without any improvement. Chest computed tomography showed multiple nodules and thickened interlobular septa in bilateral lung. PET/CT revealed a primary gastric tumor with PLC and the biopsy of the cervical lymph node confirmed a poorly metastatic differentiated gastric adenocarcinoma. The patient's general condition deteriorated rapidly and he developed respiratory failure, requiring non-invasive mechanical ventilation on day 9 after admission. Chemotherapy was given to the patient on the tenth day. However, few hours after receiving the first dose, the patient died of respiratory failure. It was only one month from the onset of symptoms to death of our case.

Conclusions

Patients presenting PLC as the first manifestation of an unknown malignancy carry a bleak prognosis. PLC be considered for differential diagnosis in patients who present with dyspnea, dry cough with or without loss of weight. Particular attentions need to be given to patients, especially young ones without histories of malignancy, whose chest imaging exhibits thickened interlobular septa. While the stomach, lung and prostate are the most likely origins of the primary tumors, patients with PLC derived from prostate cancer may have a better prognosis after anti-cancer treatment.

Background

Pulmonary lymphangitic carcinomatosis (PLC) refers to the metastatic malignant tumor infiltration of the lung lymphatic vessels secondary to a primary site [1]. It is believed that PLC occurs in the 6–8% of the intrathoracic metastasis while exact prevalence not known because its delayed diagnostic consideration often lead to autopsy confirmation [2].

PLC as the initial presentation of malignancy is relatively rare. Dyspnea and cough are the common manifestations associated with PLC [3]. The symptoms are non-specific, patients with no history of tumor

are easily misdiagnosed as interstitial lung disease [4], pneumonia [5], tuberculosis [6], heart failure [7], pulmonary embolism [8], even diffuse alveolar hemorrhage [9], which usually leads to the delay of diagnosis and treatment. Patients often appear in poor physical condition at the time of definite diagnosis and cannot tolerate anti-tumor therapy. Therefore, early diagnosis and diagnostic awareness of PLC are of paramount importance to improve the prognosis. However, there are no systemic reviews to summary the clinical characteristics of PLC as the first manifestation of malignancy.

Here, we reported a case of a previously healthy young man with PLC as the first and only manifestation of malignancy, which was initially misdiagnosed as pneumonia. We also systemically summarized previously reported clinical properties of PLC cases in the literature. To best of our knowledge, this is the first complete study to picture the clinical characteristics of patients with PLC as the initial presentation before malignancy diagnosis.

Case Presentation

A 32 years old male attended our hospital with complaint of nonproductive cough for 20 days and progressive exertional dyspnea in a week. He also complained of chest pain on the right side when coughing violently. The patient was an employee of a company and healthy before this attack, with a history of 15 pack years of smoking. He was diagnosed with pneumonia at the local hospital and received antibiotics. The patient became increasingly ill and had difficulties in breath so he was transferred to our hospital.

Physical examination revealed coarse breath sounds on auscultation and respiratory frequency with 22 times/min. Blood tests showed elevated WBC count (19,680 / μ L), CRP level (43.9 mg/L) and reduced hemoglobin (101 g/L). The serum LDH level was 616 U/L and the serum albumin was 30.8 g/L. Chest computed tomography (CT) scan revealed multiple nodules in both lungs, thickened interlobular and bronchovascular interstitium, bilateral pleural effusions and multiple enlarged lymph nodes in mediastinum (**Fig. 1A**). The imaging findings, especially lymphadenopathy, suggested a differential diagnosis of tumor. So tumor biomarkers were analyzed and the elevated tumor biomarkers were as follows: AFP, 47.86 ng/mL (N < 20 ng/mL); CEA, 72.7 ng/mL (N < 5 ng/mL); CA-125, 287.07 U/mL (N < 35 U/mL); CA-199, 56.07 kU/L (N < 35 kU/L). On day 3, the patient's breathing became more difficult. Arterial blood gas analysis with supplemental oxygen delivered via nasal catheter at 3 L/min revealed the following: pH, 7.446; arterial carbon dioxide tension (PCO₂), 51.9 mmHg; arterial oxygen tension (PO₂), 61.9 mmHg; and arterial oxygen saturation (SaO₂), 91.6%. Ultrasound-guided fine needle aspiration biopsy of the cervical lymph node was performed on the fifth day and revealed the presence of metastatic poorly differentiated gastric adenocarcinoma (**Fig. 1B**). 18F-FDG PET/CT imaging confirmed the primary tumor at the lesser curvature of the stomach (**Fig. 1C, D and E**) with diffuse lung lymphatic metastasis as well as skeletal metastases (**Fig. 1C, F and G**). In spite of patient's poor physical condition, by considering the patient's young age, previous health and the desire of his family, we used the chemotherapy scheme of oxaliplatin, docetaxel combined with fluorouracil for the gastric cancer on the

tenth day. However, few hours after receiving the first dose, the patient died of respiratory failure despite receiving noninvasive mechanical ventilation and placed on 100% oxygen.

Discussion And Conclusions

PLC, as the only clinical manifestation of patients without a history of malignant tumors, is relatively rare, so it is easy to be misdiagnosed. However, literature survey showed that there are many case reports rather than system reviews or case series with a large number of patients so far.

To summarize the clinical characteristics of patient with PLC as the first manifestation and enhance the diagnostic awareness, we searched PubMed to screen PLC related literature from inception to 12 October 2020. No language restrictions were applied. We also manually researched the references for eligible articles. The included studies should contain at least the following clinical information: gender, age, chief complaint/pulmonary symptoms, diagnosis methods and definite/probable primary tumor. Published abstracts involving these data were also included. Case series were excluded if the above information had not been documented for each case. We finally identified 78 publications comprising 96 patients with PLC as the initial presentation by reviewing and assessing the searched articles, including 66 full-text studies [4–6, 8–70] and 12 abstracts [71–82]. The search strategy (**Supplementary Table 1, Fig. 1**) and flow diagram of the study (**Supplementary Fig. 2**) were shown in the supplementary information files. We then pooled data of 97 patients including our case to further analyze the clinical features of the patients. To evaluate the efficacy of antitumor therapy, we defined the treatment was effective if the patients survived after receiving 4 cycles of chemotherapy or an improvement was reported in the study.

Primary Site, Gender And Age

The mean age of the 97 patients was 48.3 ± 18.1 years (range 7 to 88 years) and the majority of the patients were males ($n = 61$, 62.9%). The top three common primary malignancy sites were stomach ($n = 34$, 35.1%), lung ($n = 19$, 19.6%) and prostate ($n = 15$, 15.5%) (**Fig. 2, Table 1**). More than half (50/97) of the primary tumors were originated from digestive system, while the live, gallbladder and choledochal cyst were relatively uncommon. The youngest patient was a 7 year-old boy with kidney cancer [71], and the oldest one was a 88 years old female with lung cancer [6]. 19.6% of the patients were found in 51–60 year age group which was most commonly affected, 70.1% were within the age of 60 years ($n = 68$) and 33% of the patients ($n = 32$) were under the age of 40 years. 61 patients were males, especially in cases with lung cancer (15/19, 78.9%), while gastric cancer was more common in females (19/34, 55.9%). In view of the primary sites, sex and age, PLC as an initial manifestation probably occurred in young patients with tumors originated from digestive system.

Symptoms and imaging features

Almost all the patients presented with progressive dyspnea. We further analyzed the chief complaints and imaging features of the cases with full-text. A total of 82 patients including our case were identified. The

most common chief complaints were dyspnea (90.2%), dry cough (56.1%) and loss of weight (51.2%), while the most common chest imaging findings were thickened interlobular septa (95.1%), reticulonodular opacities (37.8%) and pleural effusion (36.6%) (**Table 2**).

The prognosis of PLC

Among all the patients, 47 cases received anti-tumor treatment including chemotherapy, surgery and endocrine therapy while 44 improved (**Table 3**). Of note, all the patients with prostate tumor were relieved after treatment. Moreover, we further summarized the PLC course of the patients with recorded prognosis (**Table 4**). Out of the 78 patients, 23 patients died within 2 months after the onset, 5 patients died within 1 month after PLC diagnosis with an overall survival time (OST) more than 2 months. Out of the 3 patients without a definite survival time, one patient died within 1 month after PLC diagnosis and the left two patients were diagnosed by autopsy.

The mechanism of PLC

Regrettably, there were few basic researches conducted on the pathogenesis of PLC. We only found one preclinical study which showed vascular endothelial growth factor-C (VEGF-C) facilitated the induction of lymphangiogenesis and expansion of already disseminated cancer cells throughout the lung tissue in vivo, moreover, the metastatic breast cancer cells in the lung expressed high levels of VEGF-C in patients with PLC. A clinical meta-analysis showed ALK-rearranged NSCLC was more likely to have PLC, pleural metastasis and pleural effusion compared with ALK/EGFR-negative NSCLC95. These data imply that there may be some regulatory factors in the occurred of the PLC. Taking together, there is a great gap between fundamental researches in particular molecular aspects and clinical practice on the mechanism of PLC.

In conclusion, PLC can an initial manifestation of the malignancy. The most common symptoms are dyspnea, dry cough and loss of weight, while the common imaging features are thickened interlobular septa, reticulonodular opacities and pleural effusion. PLC should be considered when patients present with the above clinical features and fail to response to the treatment base on the initial diagnosis, especially in the young males. Stomach, lung and prostate should be the focus area for identifying primary tumor. However, the prognosis of PLC is so far poor, but the patients with prostate cancer showed good response to the anti-tumor therapy. For future, detailed studies are required to find the underlying mechanisms and special intervention targets of PLC.

Abbreviations

PLC

Pulmonary lymphangitic carcinomatosis

CT

Computed tomography

OST

overall survival time

DPLC

the diagnosis of PLC

Declarations

Availability of the data and materials

All data generated or analyzed during this study are included in this article and its supplementary information file.

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Contributions

Li DD was responsible for this patient's treatment, conducted a literature search, data analysis and manuscript writing. Yuan ZH and Wang HB were involved in reviewing and accessing the literature. Zhang XD and Zhang XJ wrote the final version of the manuscript. The authors read and approved the final manuscript.

Ethics approval and consent to participate

This is a case report. The Institutional Review Board at the Henan Provincial People's Hospital has confirmed that no ethical approval is required. Consent was obtained from the patient for participation in this study.

Consent for publication

We obtained the patient's consent for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Primary site in relation with sex and age

Primary site	Sex	Age, years									Total
		0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	
Stomach	M			5	3	4		3			15
	F			5	3	2	5	2	2		19
Lung	M		1	1		3	4	3	3		15
	F				1	1		1		1	4
Prostate	M						5	7	2	1	15
Colon & Rectum	M				1	1		2			4
	F			1	2		1		1		5
Pancreas	M						3				3
	F			1							1
Thyroid	M		1								1
	F			1	1						2
Ovary	F			1		2					3
Kidney	M	1				1	1				3
Liver	M					1					1
Breast	F					1					1
Cervix	F				1						1
Gallbladder	M									1	1
Choledochal cyst	M		1								1
Mediastinum	M			1							1
Pleura	M					1					1
Total		1	3	16	12	17	19	18	8	3	97

Table 2. The chief complaints and imaging features in 82 patients

Clinical characteristic	No.	Incidence (%)
Chief complaint		
Dyspnea	74	90.2
Dry cough	46	56.1
Loss of weight	42	51.2
Thoracic pain	16	19.5
Productive cough	15	18.3
Fever	14	17.1
Malaise	14	17.1
Hemoptysis	11	13.4
Night sweats	7	8.5
Pain of back	1	1.2
Imaging characteristics		
Thickened interlobular septa	78	95.1
Reticulonodular opacities	31	37.8
Pleural effusion	30	36.6
Mediastinal lymphadenopathy	19	23.2
Small nodules	16	19.5
Ground glass opacification	12	14.6

Table 3. Primary site in relation with anti-tumor treatment and therapeutic effect

Primary site	Untreatment	Improved/Treatment	Unrecorded	Total
Stomach	18	6/11	5	34
Lung	6	4/9	4	19
Prostate	0	13/13	2	15
Colon & Rectum	1	5/7	1	9
Pancreas	4			4
Thyroid		3/3		3
Ovary		2/2	1	3
Kidney	2		1	3
Liver	1			1
Breast	1			1
Cervix		0/1		1
Gallbladder	1			1
Choledochal cyst			1	1
Mediastinum		1/1		1
Pleura	1			1
Total	35	34/47	15	97

Table 4. Prognosis in relation with primary sites of PLC

Primary site	Untreatment	Improved/Treatment	Unrecorded	Total
Stomach	18	6/11	5	34
Lung	6	4/9	4	19
Prostate	0	13/13	2	15
Colon & Rectum	1	5/7	1	9
Pancreas	4			4
Thyroid		3/3		3
Ovary		2/2	1	3
Kidney	2		1	3
Liver	1			1
Breast	1			1
Cervix		0/1		1
Gallbladder	1			1
Choledochal cyst			1	1
Mediastinum		1/1		1
Pleura	1			1
Total	35	34/47	15	97

Figures

Figure 1

The imaging findings and biopsy. (A) Chest CT showed diffuse increased reticular markings, reticulonodular shadows and bilateral pleural effusion on admission. (B) The H&E staining of the biopsy of cervical lymph node showed poorly differentiated adenocarcinoma. (C) Coronary PET-CT revealed increase uptake of ^{18}F -FDG involving bilateral lungs and bones on the sixth day. (D) Axial abdominal CT and corresponding PET-CT (E) showed thickened lesser curvature of the stomach and increased uptake.

(F) Axial chest CT and corresponding PET-CT (G) showed increased interstitial infiltration and diffuse uptake.

Figure 2

The composition of primary sites in 97 patients with PLC as the initial presentation of malignancy

Supplementary Files

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- [Supplementarydata.docx](#)