Case Report

Delays in Diagnosis of Pulmonary Lymphangitic Carcinomatosis due to Benign Presentation

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The diagnosis of lymphangitic carcinomatosis is challenging due to the manifestation of nonspecific symptoms and radiographic abnormalities that bear similarity to those of interstitial lung disease. Herein, we report the case of a 53-year-old woman diagnosed with lymphangitic carcinomatosis from metastatic gastric adenocarcinoma, 3 months after her initial presentation.

1. Case

A 53-year-old female was referred to the pulmonary clinic due to cough and chest pressure for the past 3 months, during which several chest X-rays and a computed tomography (CT) scan of the chest were taken. She was initially expectorating green sputum; however, the sputum production reduced after she received antibiotics from her primary care physician (PCP). Additionally, she received two courses of steroids from visits to the emergency department, which stabilized her cough. The patient also had occasional symptoms of postprandial bloating.

She was a lifelong nonsmoker, who worked in farms and denied any exposure to molds or pets. During examination, she was afebrile with an oxygen saturation of 87% on room air inhalation. Her physical exam revealed coarse breath sounds on auscultation and decreased breath sounds at the level of the left lung base posteriorly. A CT scan of her chest (Figure 1) showed bilateral linear coarse reticulations with no peripheral predilection or ground-glass opacities and a small amount of left pleural effusion; the abdomen did not show any abnormality in the CT scan. Based on her symptoms and chest CT findings, we suspected a diagnosis of interstitial lung disease (ILD).

Laboratory findings were negative for antinuclear antibodies and antineutrophil cytoplasmic antibodies. Video-assisted thoracic surgical biopsy and transbronchial cryobiopsy were discussed, and the risks and benefits of each procedure were explained. She chose to undergo a transbronchial cryobiopsy, which was performed 3 months after her initial presentation to PCP. Three cryobiopsy samples were obtained—two from the lateral basal segment and one from the posterior basal segment of the right lower lobe—for pathologic evaluation. Additionally, four forceps biopsy samples were collected—two each from anterior basal and superior segment of the right lower lobe—for microbiological evaluation. The pathology samples were sent to a tertiary care center to be reviewed by a pulmonary pathologist with expertise in ILD.

Based on the morphology, the patient was diagnosed with a tumor that was characterized as metastatic adenocarcinoma with lymphangitic spread (Figures 2 and 3). Tumor cells were positive for keratin and negative for CD31, thus confirming the diagnosis. A second round of histological staining was negative for keratin and negative for CD31, thus confirming the diagnosis. A second round of histological staining was negative for keratin and negative for CD31, thus confirming the diagnosis. A second round of histological staining was negative for keratin and negative for CD31, thus confirming the diagnosis. A second round of histological staining was negative for keratin and negative for CD31, thus confirming the diagnosis.
primary was suspected. The differential diagnosis in the upper gastrointestinal primary or pancreatobiliary primary at this stage of staining supported the assumption.

Thereafter, the patient underwent a repeat CT scan of the abdomen and pelvis, which did not reveal any mass or abnormality to suggest a primary. Three weeks after the
bronchoscopic biopsy, she underwent an upper endoscopy, which revealed an ulcerated gastric mass occupying the cardia and antrum of the stomach. Biopsies from the mass revealed moderate to poorly differentiated invasive adenocarcinoma with lymphovascular invasion (Figure 4).

Two days after the endoscopic biopsies, the patient was seen by an oncologist in an outpatient setting where several chemotherapy options ranging from aggressive regimens, such as FOLFOX, to the least aggressive 5 FU with leucovorin were discussed. However, the patient declined the treatment. Subsequently, she was hospitalized three times, 2 weeks apart, for worsening dyspnea and was treated with thoracentesis on each occasion. During her last admissions, a chest tube was placed due to iatrogenic pneumothorax after thoracentesis. The patient experienced worsening dyspnea and hypoxemia, and comfort measures were initiated. The patient died 10 days after the last hospitalization, about 2 months after her diagnosis.

2. Discussion

We report the case of occult gastric malignancy with pulmonary lymphangitic carcinomatosis (PLC).

Pulmonary metastasis is rare with gastric cancer, representing less than one percent of distant metastasis. The most commonly seen pattern of pulmonary metastasis is hematogenous which accounts for 52.3%, followed by pleural metastasis (35.2%), and lymphangitic spread is the least common of this rare pattern, accounting for only 26.4% of pulmonary metastasis [1]. Gastric lesions or abnormality in other viscera were absent on the CT scan of the abdomen. Her chest CT revealed interlobular septal thickening. The absence of mediastinal or hilar lymph node enlargement and lung masses or nodules excluded a diagnosis of malignancy. Despite widespread pulmonary parenchymal abnormalities, there was no lymph node involvement. Mediastinal or hilar lymphadenopathy is commonly seen with lymphangitic spread [2], but lymph node involvement is not essential. The mechanism of lymphangitic spread is hematogenous tumor embolism to the lungs and rarely due to contiguous lymphangitic spread [3].

The diagnosis of metastatic cancer with pulmonary carcinomatosis is often delayed by months from the onset of symptoms and imaging studies. This delay is mainly due to two attributes that are strongly associated with its presentation and imaging studies. First, patient characteristics play an important role. Most patients present with dry cough and dyspnea due to pulmonary parenchymal involvement, irrespective of the origin of the primary. Hence, the workup for the symptoms is performed and does not involve imaging or diagnostic tests, which can reveal the primary. A patient’s age is usually less than that of a typical lung cancer patient because a wide variety of cancers that occur at a young age may present with lymphangitic spread. Patients are often nonsmokers, thereby lowering the suspicion for lung cancer. Moreover, patients are often empirically treated with

Figure 3: Hematoxylin and eosin-stained slide of cryobiopsy of lung. Arrow pointing to adenocarcinoma.
antibiotics for presumed respiratory tract infection and
inhalers for dyspnea.

Second, a radiologist is often misled by imaging patterns,
whether on chest X-ray or chest CT, and the requesting phy-
sician may be convinced of an ILD diagnosis. The CT pattern
of PLC is very similar to that of many ILDs, including sar-
coidosis, which is an arduous task to differentiate. Subtle dif-
fferences do exist, but these are not easy to spot and include a
great involvement of the interlobular septa and interstitium
in PLC and more distortion of secondary pulmonary lobule
due to fibrosis in sarcoid [4]. Thus, owing to the clinical pre-
sentation and radiographic patterns, our focus was on the
diagnosis of an underlying primary pulmonary parenchymal
disease, specifically an ILD, rather than casting a wider net,
which would have included an examination for malignancy.

We performed a literature search using the PubMed data-
base for studies reporting cases of lymphangitic carcinomato-
sis that were suspected as an ILD by treating physicians. The
extracted publications are listed in Table 1 [5–18]. Informa-
tion on the types of delays that occurred in the case reports
are listed (Table 1), which included time interval from the
first occurrence of a symptom to the first contact with a phy-
sician and the interval from symptoms onset, diagnosis, and
presentation to death.

Delays in the diagnosis of primary lung cancer diagnosis
range from 7 days to 6 months and from onset of symptoms
to contact with a physician [19]. The largest trial that has
investigated 380 consecutive patients with primary lung can-
cer found that the median duration from the onset of symp-
toms to visit with a physician was 7 days, that from the
physician’s visit to diagnosis was 31 days, and that from
symptom onset to diagnosis was 50 days [20]. As depicted,
the wait times are similar to the delays in the diagnosis of pri-
mary lung cancer.

The reason for the delay in the diagnosis of PLC can be
due to the misinterpretation of the presentation and radio-
graphic abnormality by the treating physician, and such
delay reduces patients’ duration of survival after diagnosis.
Compounding this grave situation is that patients spend their
remaining life under intensive care while undergoing inva-
sive procedures to diagnose what was misinterpreted as
ILD. The overall 5-year survival rate for lung cancer for all
stages is 19.4% [21]. In comparison, as depicted in the table,
several diagnoses of PLC occurred in the intensive care unit
on ventilated patients, and most of them died within a day to
few weeks thereafter.

The misinterpretation of PLC as an ILD is more likely to
occur if the imaging study shows
findings of only pulmonary
carcinomatosis, i.e., only interstitial changes, which are very
similar to many ILDs, without lung mass or a nodule.
Although many ILDs present with lymph node enlargement,
the presence of mediastinal or hilar lymph node enlargement
raises the suspicion of malignancy.

The patient in this case report did not have mediastinal or
hilar lymphadenopathy, unlike most patients with pulmo-
nary carcinomatosis who have lymphadenopathy. If mediast-
tinal or hilar lymphadenopathy were present, then a much
more conservative approach, such as biopsy of the lymph
node with endobronchial ultrasound with or without trans-
bronchial forceps biopsy, would have been considered.
Instead, due to the presentation, a much more invasive
approach than needed for the diagnosis of malignancy, such
as transbronchial cryobiopsy, was undertaken. Transbron-
chial cryobiopsy is a new technique that enables pulmonolo-
gists to obtain a larger specimen than the traditional
transbronchial forceps biopsy [22], but whether it can serve
as an alternative to surgical biopsy for the diagnosis of ILDs
is a subject of investigation. Nevertheless, the risks of
| S. NO | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|
| **Age/gender** | 15 | 8 | F | 31 | 45 | 53 | F | 63 | F | 62 | M | 24 | M | 30 |
| **Symptoms** | Cough, wheezing, syncope, anorexia | Cough, dyspnea | Dry cough, dryness | Progressive dyspnea, weight loss, and rash | Progressive dyspnea, weight loss, and rash | Worsening dyspnea | Dry cough, dryness | Dry cough, night sweats, dyspnea, hemoptysis | Dry cough, night sweats, dyspnea on exertion, weight loss | Cough, wheezing, syncope, anorexia | Cough, dyspnea on exertion | Dry cough, dry cough fever for six weeks |
| **chest CT** | Thinning interlobular septae, B/L interstitial infiltrates | Medial hilar lymphadenopathy, Thinning interlobular septae, ground glass opacities | Intertubular thickening, crazy paving, mild interstitial lymphadenopathy | Enlarged mediastinal LN, diffuse reticulonodular pattern, bilateral mediastinal lymphadenopathy | Ground glass opacities, thickened interlobular septae, bilateral hilar lymphadenopathy | Thickening of paratracheal, tracheal, and interlobular septae, ground glass opacities | Ground glass opacities, thickened interlobular septae, bilateral hilar lymphadenopathy | Ground glass opacities, thickened interlobular septae, bilateral hilar lymphadenopathy | Ground glass opacities, thickened interlobular septae, bilateral hilar lymphadenopathy | Bilateral hilar lymphadenopathy with reticulonodular interstitial pattern | Bilateral hilar lymphadenopathy | Bilateral hilar lymphadenopathy |
| **Diagnosis** | Open lung biopsy | Open lung biopsy | Transbronchial biopsy | Open lung biopsy | Bronchoalveolar lavage | Transbronchial biopsy | Bronchoalveolar lavage negative, cervicodorsal skin biopsy positive | Bronchoalveolar lavage and transbronchial biopsy | VATS surgical biopsy | Bronchoalveolar lavage, central bronchoscopic biopsies. Gastric origin by EGD | Bronchoalveolar lavage, central bronchoscopic biopsies. Gastric origin by EGD | Bronchoalveolar lavage, central bronchoscopic biopsies. Gastric origin by EGD |
| **Diagnosis** | Adenocarcinoma unknown primary | Adenocarcinoma of colon | Adenocarcinoma of colon | Malignant mesothelioma | Signet ring gastric adenocarcinoma | Signet ring gastric adenocarcinoma | Pulmonary adenocarcinoma | Gastric adenocarcinoma | Gastric adenocarcinoma with focal signet cell | Lung adenocarcinoma on RG biopsy | Pulmonary adenocarcinoma | Pulmonary adenocarcinoma |
| **Therapy prior to diagnosis** | Prednisone, clarithromycin, sulfamethoxazole, ceftriaxone, antitubercular, anti-neurotropic therapy | Steroids for secondaries. Review after diagnosis | Ciprofloxacin and amoxicillin for bronchitis, right heart failure, renal failure, and antibiotics for Pnumonia FTCN | Vancomycin and piperacillin-tazobactam | Antibiotics and steroids | Immunosuppressive therapy | NA | Steroids | Broad-spectrum antibiotics for 14 days, high dose steroids | Piperacillin-tazobactam, amphotericin B, and dexameth | NA | Antibiotics | Not applicable. Survivor |
| **Setting of diagnosis** | ICU vent | Non-ICU setting | ICU on ventilator support | ICU on ventilator support | ICU on ventilator support | ICU on ventilator support | NA | NA | NA | NA | NA | NA | ICU |
| **Metastasis** | No available (NA) | Thoracic and lumbar spine | Abdominal wall, rib, femur, right hemi-circular, lumbar spine | NA | NA | Skin | Contralateral pulmonary and spinal metastasis. | NA | Lung, pleura, right rib, right clavicle | NA | NA | NA | NA |
| **Author** | Gilchrist et al., Eur Respir Rev [5] | Vandersman et al., Arch Pediatr [6] | Thomas and Lenox, CMAJ [7] | Khodabaksh et al., J Am Oncotrop Assoc [8] | Bonna et al., Am J Resp and Crit Care Medicine [9] | Dikha et al., Clinics in Surgery [10] | Wang et al., Prount, chest meeting [11] | Geirr et al., [12] Journal of critical care and diagnostic research [13] | Gelen et al., Jof Thoracic and Cardiovascular Research [14] | Mohit et al., BMC thoracic surgery [15] | Melani et al., Thoracic Medicine [16] | Marul et al., Lung Cancer [17] | Cohen et al. [18] | Respiration |
pneumothorax and bleeding are higher than those of forceps biopsy [23], but the overall morbidity is lower than that of surgical lung biopsy [23]. Therefore, patients with PLC undergo more invasive biopsies than needed to obtain a diagnosis, such as surgical lung biopsies, due to the resemblance to ILD in CT scans. However, the limited therapeutic options available for ILDs prevent many patients from undergoing a diagnostic biopsy as the diagnostic procedures are considered to be too risky by their pulmonologist [24]. Therefore, this practice can place patients at the risk of not getting diagnosed for a lethal condition while getting empirically treated for ILD.

ILD is more prevalent than PLC. Therefore, due to the similarity in presentation, clinicians will first seek and investigate the diagnosis of ILD [25] [26], hence being misled. Interestingly, the misdiagnosis of PLC occurs with an even less common disease entity, i.e., Erdheim–Chester disease, which is presented as PLC [27]. Erdheim–Chester disease is a rare disease listed under National Organization for Rare Disorders. Thus, there is precedence for the misdiagnosis of PLC, not only with ILD but also other conditions, warranting robust investigations to enable definite conclusions to be made.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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