Primary Pulmonary Leiomyosarcoma: An Extremely Rare, Difficult-to-Manage Case of Lung Cancer

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Abstract

Background: Primary Pulmonary Leiomyosarcoma (PPL) known as <0.5% of total lung cancer. Histopathological examinations are the pillars of PPL diagnosis as clinical manifestations and radiological features are usually not specific. Treatments of PPL include surgical resection, radiotherapy, and chemotherapy.

Case Illustration: A 51-year-old male, smoker, with a productive cough for 2 weeks, accompanied by chest pain, weight loss, and loss of appetite. Imaging studies showed a solid mass in the right lung, which was confirmed through bronchoscopy, cytology, histology, and immunohistochemistry evaluations. Bronchoscopy showed an intraluminal mass in the right main bronchus suggesting malignancy. Immunohistochemistry of Desmin and Smooth Muscle Actin, which were positive, confirmed the diagnosis of PPL of the right lung stage T4N1M1a IVA.

Discussion: Surgical resection is the gold standard treatment for PPL whose clinical conditions and tumor spread still allowed for safe operation. Surgical resection did not undergo because already in stage IVA. Radiotherapy and chemotherapy can be added for patients who are unable to have surgery. There are no guidelines regarding chemotherapeutic regimens that are recommended for PPL. Cisplatin/carboplatin and etoposide are two chemotherapeutic agents that are commonly used in other variants of lung cancer. Cisplatin is successful in 5-23% of patients and etoposide is successful in 8%. Doxorubicin and ifosfamide are usually used for soft tissue sarcoma too. After administration of 4 cycles of carboplatin/etoposide, a chest CT scan with contrast recist shows the progression of PPL.

Conclusion: Carboplatin and etoposide have been long used as therapy for lung cancer. Currently, available literature shows that their effectiveness in PPL is still considered low. Nevertheless, more studies are needed to further explore the possibilities of using carboplatin and etoposide in PPL patients.

Keywords: chemotherapy, lung cancer, primary pulmonary leiomyosarcoma

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Introduction

Primary pulmonary sarcomas (PPS) is a mesenchymal type of tumor that usually originates from lung parenchyma (70%), bronchial wall (20%), or pulmonary artery (10%). Pulmonary sarcoma is an extremely
A rare neoplasm that accounts for <10% of all soft tissue sarcomas. Most of primary pulmonary sarcomas are leiomyosarcomas, followed by fibrosarcomas and hemangiopericytomomas. The prevalence of primary pulmonary leiomyosarcoma (PPL) has been reported to be less than 0.5% of all lung malignancies. *Primary pulmonary leiomyosarcoma* (PPL) may arises from interstitial smooth muscle cells of the lung, bronchi, and vessels. This type of tumor most commonly affects individuals over 50 years of age, with the median age of 51 years. Men have 2-fold higher risk of developing PPL than women. *Primary pulmonary leiomyosarcoma* is a very aggressive tumor that has the capability to grow and to cause symptoms very quickly.\(^1\)\(^-\)\(^5\)

We report a case of pulmonary leiomyosarcoma in a 51-year-old male with the chief complaint of cough in the past 2 weeks before admission. This report will discuss how pulmonary leiomyosarcoma is being treated using Carboplatin/Etoposide chemotherapy based on the existing literatures.

**Case**

A 51-year-old male was admitted to our department with cough and whitish sputum for the past 2 weeks. These symptoms were accompanied with right chest pain which occurred only when the patient coughed. The patient also complaint decreased of appetite and weight loss for the last 3 months. An uncontrollable cough drove the patient to seek for medical treatment in the local hospital. A nodule appearance showed up from the chest radiography examination. The patient then was referred to our hospital. Patient had a history of smoking for 15 years with 10 cigarettes per day (Brinkman index : 150). There was no history of lung cancer in the family. The patient worked as a fish seller.

The patient had stable vital signs with normal findings on the lung examination. Other physical examinations revealed unremarkable results. Initial laboratory tests showed mild hypokalemia (potassium 3.41 mmol/L, reference range 3.5 – 5.0 mmol/L), azotemia (creatinine 1.68 mg/dL, reference range < 1.2 mg/dL), and increased neuron specific enolase (NSE, 57.29 ng/mL, reference range < 16.3 ng/mL). Chest radiography revealed a lung nodule on the anterior segment of the right lobe (Figure 1). Chest computed tomography (CT) with contrast showed right endobronchial mass of the posterior segment in anterior superior lobe that attached to the branch of right pulmonary artery. Chest CT also revealed bilateral lung nodule in accordance with

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T4N1M1a (Figure 2). The patient also underwent bronchoscopy that showed a white intraluminal mass in the right main bronchus suggesting malignancy (Figure 3).

Figure 1. Chest radiograph PA and lateral view showing right lung nodule.

Figure 2. Chest computed tomography (CT) with contrast before treatment showed an endobronchial mass at posterior segment of the right lung, anterior superior lobe, difficult to separate from the right perihilar lymph nodes, attached to the branch of right pulmonary artery, obliterating the 3rd segment bronchial tree with partial atelectasis of 3rd segment, bilateral lung nodules according to T4N1M1a. RECIST 1.1 (baseline) found target lesions: right lung mass measuring 51mm and non-target lesions: right lung segment 3 nodule measuring 6.6mm and left lung nodule segment 9 measuring 7.2mm.

Figure 3. Bronchoscopy suggesting malignancy of the right main bronchus

During bronchoscopy, we performed washing and brushing for the histopathological analysis. The result was class III, with atypic cell focus. Biopsy results showed spindle mesenchymal tumor focus, with the differential diagnosis of leiomyosarcoma, malignant peripheral nerve sheath tumor, and carcinoma with sarcomatous appearance.

Immunohistochemical (IHC) staining demonstrated positivity toward smooth muscle actin (SMA) (Figure 4) and desmin (Figure 5), which showed an immunophenotype indicating a leiomyosarcoma. This confirmed the diagnosis of PPL of the right lung stage T4N1M1a IVA.
Figure 4. Smooth muscle actin IHC staining showed fibrous connective tissue with spindle-shaped atypical cells with oval, pleomorphic, hyperchromatic nuclei (red arrow). Smooth Muscle Actin IHC staining revealed a positive result in the cytoplasm of tumor cells. (1) IHC 40x. (2) IHC 400x.

Figure 5. Desmin IHC staining showed fibrous connective tissue with spindle-shaped atypical cells with oval, pleomorphic, hyperchromatic nuclei (red arrow). Desmin IHC staining revealed a positive result in the cytoplasm of tumor cells. 1) IHC 40x. (2) IHC 400x.

Figure 6. Serial chest radiograph during chemotherapy. (1) Chest radiograph PA/lateral January 10th 2022 showed right hilar thickening with ground glass opacity in superior lobe of the right lung suspected right lung nodule with a component of right lung superior lobe atelectasis. (2) Chest radiograph PA/lateral January 25th 2022 showed thickening of right hilar, suggesting right lung mass, with atelectasis of the superior and medium lobes of right lung. (3) Chest radiograph PA/lateral March 9th 2022 showed a central stenoting right lung mass and bilateral lung nodule because of the metastatic process.

Figure 7. Chest CT with contrast after chemotherapy showed an endobronchial mass in the posterior segment of the right lung, anterior to the superior lobe, which completely obliterated the right main bronchus, causing atelectasis of the superior lobe of the right lung. Bilateral pulmonary nodules suspected the metastatic process. RECIST 1.1 found a target lesion on the right lung mass measuring 78mm.
(Progressive disease) and a non-target lesion on the right lung segment 10 nodule with a size of 5mm and a segment 3 left lung nodule with a size of 9.4mm (stable disease). No new lesions were found. Overall Response: Progressive disease.

Our patient was planned to receive the combination of chemotherapy carboplatin 350 mg and etoposide 180 mg for 6 cycles. The chemotherapy cycle was 21 days. In every chemotherapy cycle, we performed a laboratory examination and dose adjustment based on toxicity degree. The patient also underwent chest radiography (Figure 6) and chest CT with contrast (Figure 7) to evaluate response toward chemotherapy. Due to the results from chest CT with contrast showed a progressive disease according to Recist 1.1, we discontinued the chemotherapy regimen of carboplatin/etoposide after the fourth cycle and replaced with a second line regimen of Docetaxel 120 mg every 21 days. After the administration of first cycle of Docetaxel, the patient decided to receive the best supportive care. The patient still survives until now.

Discussion

Primary pulmonary leiomyosarcoma (PPL) is a tumor that originates from the interstitial smooth muscle cells of the lungs, bronchi or blood vessels. Primary pulmonary sarcomas (PPS) are mesenchymal-type tumors that usually arise from the lung parenchyma (70%), bronchial walls (20%), or pulmonary arteries (10%). Pulmonary sarcomas are extremely rare, accounting for less than 10% of all soft tissue sarcomas.\textsuperscript{1,2,5} Most of PPS are leiomyosarcomas, followed by fibrosarcomas and hemangiopericytomas.\textsuperscript{4}

Until 2006, there were only 300 cases of PPS that had been reported in the literature. This includes 0.2–0.5% of all primary lung malignancies.\textsuperscript{2,4} The prevalence of PPL was reported to be less than 0.5% of all types of lung cancer.\textsuperscript{1,2} This type of tumor mostly occurs in the age over 50 years, with the median age of 51 years. Men are reported to have 2-fold higher risk to develop PPL than women.\textsuperscript{3,4,6} This is in concordance with our case where the patient was a 51 years old male.

According to its location, PPL can be classified into intraluminal (endobronchial), intrapulmonary, or pulmonary vascular. Intrapulmonary is the most common subtype, while endobronchial is less commonly found. To date, there are only 14 patients aged over 20 years which have been diagnosed with endobronchial primary pulmonary leiomyosarcoma.\textsuperscript{3,4,6} Primary pulmonary leiomyosarcoma (PPL) is a very aggressive tumor that has the capability to grow and to cause symptoms promptly.\textsuperscript{3} Around 25% of
PPS patients show manifestation of lymph node metastasis.\(^5\)

Smoking is a risk factor for lung cancer, where 1 of 9 heavy smokers are reported to develop lung cancer.\(^7\) In contrast, smoking is rarely found as a risk factor in PPL patients. Less than 50% of PPL patients had a history of being a heavy smoker. The risk factors associated with PPL are similar to those of other sarcomas, such as history of radiation, chemical, occupational and environmental exposure.\(^5,8\) The patient in our case had a history of smoking for 15 years with the Brinkman index of 150.

Patients with PPL often represent with mild and non-specific respiratory symptoms, and may even remain asymptomatic for a long time.\(^1,6\) The clinical manifestations may mimic other lung cancer symptoms, such as shortness of breath, cough, chest pain, and hemoptysis. A number of PPL patients may also exhibit cardiac symptom such as palpitation. Moreover, the patients may have systemic manifestations as well, such as weight loss, fatigue, and fever.\(^3,5\) Patients with endobronchial subtype of PPL may show symptoms related to lung obstruction. Patients with large intrapulmonary subtype of PPL may also lead to external bronchial compression. Meanwhile, in patients with primary leiomyosarcoma of the pulmonary artery may exhibit symptoms of progressive right heart failure and may mimic acute pulmonary embolism.\(^6\)

The mechanism of coughing in lung cancer is still not clearly understood. A quarter of patients complain of a cough accompanied by chest pain.\(^9\) The patient in our case also reported a right-sided chest pain that appeared when the patient coughed. Pain in cancer has a fairly high prevalence, which is around 51%.\(^10\) Weight loss and decreased appetite were also experienced by the patient in our case. Weight loss in prediagnosed lung cancer is common and is known to correlate with disease stage. In a study conducted by Morel et al. showed that 61% of patients with stage IV NSCLC, 57% of patients with stage IIIB, 47% of patients with stage IIIA, and 31% of patients with stage 0-IIIB reported prediagnosis weight loss.\(^11\) Sarcopenia (skeletal muscle wasting) is one of the main contributors to cancer cachexia that can lead to decreased physical function, psychological stress, and decreased response to chemotherapy. In addition, tumor progression will lead to chronic hypermetabolic and inflammatory conditions which increase lipolysis and fat oxidation processes, reduce fat deposition, adipogenesis, and browning of white fat cells.
These will cause atrophy of visceral and subcutaneous adipose tissue.\textsuperscript{12}

Furthermore, our patient showed mild hypokalemia and renal azotemia from the initial laboratory. Disorders of electrolyte and acid-base balance such as hyponatremia and hypokalemia are often found in cancer patients. Several studies reported the prevalence of hypokalemia of 41–48\% in cancer patients. Hypokalemia in cancer patients can be caused by inadequate nutritional intake, anorexia, decreased volume, nausea, and alkalemia which can cause shifting of potassium into cells.\textsuperscript{13} Azotemia is one of the most common cause of acute kidney injury in cancer patients. Prerenal azotemia can be caused by various factors, such as decreased fluid volume due to nausea and vomiting, decreased oral intake, and sepsis. Besides, the use of chemotherapeutic agents can also lead to side effect of acute kidney injury. Cisplatin is known to cause tubular toxicity which will lead to salt wasting, hyponatremia, hypomagnesemia, and acute kidney injury.\textsuperscript{14}

These atypical clinical manifestations often lead to the incidental diagnosis of PPL when the patient performs a routine chest radiography examination.\textsuperscript{5} Diagnosis of PPL is often difficult because the local extension of lung parenchyma results in clinical, macroscopic, and radiographic appearances that mimic non-sarcomatous tumor.\textsuperscript{4} However, PPL is reported to have a more aggressive extension with the appearance of well-circumscribed round, smooth, or lobulated intraparenchymal mass from the chest radiography findings.\textsuperscript{1,4} A chest CT scan can help in visualizing the local extension and excluding primary chest wall tumor that extends into the chest cavity. From chest CT findings, primary pulmonary leiomyosarcoma appears as a solitary, smooth, round, and heterogeneous density lesion with areas of calcification that indicate ischemic necrosis.\textsuperscript{1} Primary pulmonary leiomyosarcoma is more commonly found in the upper lobes of the lungs. Suspicion towards the diagnosis of PPL is increased if a mass is found in the upper lobe of the lung in the non-smoker patient. Before establishing the diagnosis of PPL, the possibility of a secondary source of neoplasms must be ruled out, considering extrapulmonary sarcoma metastases are more common than primary pulmonary sarcomas.\textsuperscript{4}

Our patient underwent a chest radiography examination which revealed a right lung nodule. Follow-up examination with chest CT scan with contrast confirmed an endobronchial mass in the right lung accompanied by right bilateral pulmonary
nodules. From the results of the first contrast CT scan, the patient was diagnosed with stage T4N1M1a lung cancer.

Bronchoscopy is the main procedure in lung cancer diagnosis. This procedure may assist in determining the location of primary lesion, the growth of intraluminal tumor, and obtaining specimens for cytology and histopathological examination, hence that the diagnosis and stage of lung cancer can be determined. Bronchoscopy rarely reveals an endobronchial lesion. However, extrinsic compression of the bronchi can occur if the tumor mass is large enough. We performed a fiber optic bronchoscopy (FOB) in our patient, with the finding of intraluminal mass in the right main bronchus.

Histopathological evaluation is a standard procedure in establishing the diagnosis of PPL. The cells of primary pulmonary leiomyosarcoma cells rarely exfoliate, making the sampling through bronchoscopy or washing/brushing is more difficult. Metastases of leiomyosarcoma mostly occur through blood or lymphatic drainage, so that mediastinoscopy and pleural sampling are not very useful in establishing the diagnosis. Histologically, leiomyosarcoma can be suspected if fascicular proliferation of fusiform cells intersection at the angle of 90 degrees is found. The tumor cells show a spindle-shaped with large cigar-shaped nuclei and scant fibrillar eosinophilic cytoplasm. Mitotic, atypical nuclei, multinucleation, prominent vascularity and zonal necrosis are also frequently found. Further confirmation of the diagnosis is necessary through the immunohistochemical staining. In 60% cases, immunohistochemistry examination reveals positivity towards vimentin, desmin, and actin. Examination with the epithelial marker such as cytokeratin and carcinoembryonic agent will show negative results. Positivity toward vimentin and S100 leads to the diagnosis of melanoma. Furthermore, immunochemistry examination may assist in determining the grading of sarcomas. Low-grade PPL is more likely to show positive results with muscle markers such as SMA, desmin, and h-caldesmone. In contrast, high-grade PPL mostly will show negative results towards those muscle markers.

In our patient, histopathological examination was also carried out with samples from washing/brushing, sputum, and biopsy. The results of histopathological evaluation revealed the presence of spindle mesenchymal tumor. Patient's tumor cells also showed positive staining with Vimentin, H-Caldesmon, SMA and desmin, with
negative results were shown in epithelial staining such as cytokeratin and S-100.

Figure 8. Histology specimen of PPL. Hematoxylin & Eosin, 100x): a,b. Lung parenchyma with sarcoma infiltration (arrow). Immunohistochemistry: c. smooth muscle actin (SMA), d. Desmin.

Surgery is the most common treatment approach in PPL, especially in cases with no evidence of metastasis.\(^1\),\(^3\),\(^4\),\(^18\) Surgery is considered as the only curative therapy option, with lobectomy as the gold standard therapy in PPL.\(^5\),\(^6\) Wedge resections may be performed if the tumor is small and peripherally located, although this approach has shown a higher local recurrence rate. Meanwhile, pneumectomy was reported to cause high morbidity. This approach can still be performed if needed to achieve a better local control.\(^5\) Lobectomy and pneumectomy that is performed in early disease was reported to produce a 5-year survival rate of >50%. Complete resection of the entire tumor mass is recommended if the patient can tolerate. Complete surgical excision results in a higher median survival (17-24 months) compared to incomplete surgical excision (6-10 months).\(^3\) Only one-third of PPL patients can undergo surgery because the tumor is often found at an advanced stage.\(^16\) Partial resection of the chest wall, diaphragm, or vascular structures is also necessary in some cases to achieve R0 resection.\(^6\),\(^8\)

Radiotherapy can be performed if the patient has contraindications to surgery or cannot undergo a complete resection. However, radiotherapy is not associated with an increased survival in patients with PPL.\(^4\),\(^8\) Postoperative adjuvant radiotherapy can be performed to improve locoregional tumor control, especially for patients with known regional lymph node metastases.\(^5\) Therefore, radiotherapy is only a palliative treatment approach.\(^6\)

Neoadjuvant chemotherapy is used for patients with unresectable tumors and lymph node metastases to achieve better operability and local control.\(^5\) Doxorubicin and ifosfamide are chemotherapeutic agents that are often used in soft tissue sarcomas. Chemotherapy agent doxorubicin and ifosfamide are more frequently used for advanced stages of PPL and results in reduced tumor size in less than 20% of cases.
Furthermore, doxorubicin was reported to show response in 16–27% cases.\textsuperscript{4} A phase 3 randomized controlled trial compared overall survival in soft tissue sarcoma patients with locally advanced disease or metastasis. Patients were given either doxorubicin or combination of doxorubicin/ifosfamide. Study results revealed that there was no significant difference in the overall survival between doxorubicin and doxorubicin/ifosfamide group. However, this study included all types of sarcomas, with leiomyosarcoma occurred in only a quarter of the study subjects. Another retrospective study on 51 patients (2 patients with thoracic leiomyosarcoma) showed an overall response rate of 12% with a median overall survival 24.6 months in patients that received doxorubicin/ifosfamide combination chemotherapy.\textsuperscript{18} Another randomized controlled trial showed that the use of neoadjuvant epirubicin and ifosfamide can improve survival in patients with high-risk sarcomas, including undifferentiated pleiomorphic sarcoma, myxoid liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumors, and leiomyosarcoma. The advantages of using neoadjuvant chemotherapy are achieving negative histologic margins and increasing the probability of performing a conservative surgical procedure. Tanaka et al. reported that the use of neoadjuvant doxorubicine provides an opportunity for PPL patients who were previously unresectable to become resectable.\textsuperscript{19}

To date, there is still no guideline regarding the type of chemotherapy regimen that should be used in PPL treatment. A number of chemotherapeutic agents that are known to be effective for sarcoma in general (e.g. doxorubicin, ifosfamide) are currently being used in the treatment of PPL.\textsuperscript{20} Among these cytostatic drugs, doxorubicin and epirubicin are the most effective drugs with a remission rate of 15-33% for metastatic sarcomas. Meanwhile, etoposide was reported to be successful in only 8% of patients and cisplatin was successful in 5–23%. Furthermore, ifosfamide as a single-agent therapy showed successful remission in 38% of cases.\textsuperscript{20} Currently, the gold standard regimen for the management of soft tissue sarcoma is doxorubicin and/or ifosphosamide based regimen. Combination of these chemotherapeutic agents showed an objective response in 23–48% of cases.\textsuperscript{21} The combination of etoposide, ifosfamide, and cisplatin have shown promising results as a second-line therapy in soft tissue sarcomas.\textsuperscript{20,21} Papai et al. reported the use of etoposide, ifosfamide, and cisplatin...
combination in 104 soft tissue sarcoma patients (4 patients of leiomyosarcoma). This study showed that 37 patients had partial remission and 10 patients had complete remission, with an overall response rate of 46%. A total of 6 patients became resectable after using the combination of these chemotherapeutic agents. The combination of gemcitabine and docetaxel was first reported as a therapy for soft tissue sarcoma (locally advanced or metastatic) in 2002. A phase 2 study showed that 53% of leiomyosarcoma patients showed improvement after treatment with gemcitabine/docetaxel. The responsiveness of leiomyosarcomas toward gemcitabine/docetaxel regimen has led many clinicians to use this regimen as first-line therapy in leiomyosarcomas that are locally advanced or have metastasized.

Our patient was treated with the first-line chemotherapy regimen of carboplatin/etoposide. However, we found a progression of disease after four cycle of carboplatin/etoposide. This is in concordance with the literature regarding the low efficacy of these two agents in leiomyosarcoma. We replaced the therapy in our patient with a second line chemotherapy regimen using doxetaxel 120 mg due to the results of progressive disease on CT Thorax Recist 1.1. Docetaxel is also the recommended chemotherapeutic agent in leiomyosarcoma, although docetaxel is more effective in combination with gemcitabine.

In general, the prognosis of PPL is still poor. In a cohort study with 60.4% of patients undergoing treatment and 14.1% undergoing radiotherapy, the median overall survival was reported to be 14 months, with 1-, 3-, and 5-year overall survival are 52.7%, 29.0%, and 22.2% respectively. Surgery has shown to increase the overall survival by 29 months and reduce risk of death by 57%. Factors that may reduce overall survival in PPL patients include age, tumor size (>5 cm), presence of lymph node metastases, tumor TNM stage, and higher histological grade. In addition, the prognosis was reported to be worse in endobronchial tumors or tumors that show a high mitotic rate. Compared with soft tissue sarcomas of the extremities, PPL has a poorer prognosis with a higher proportion of lymph node metastases.

**Conclusion**

A 51-year-old man came with chief complaint of productive cough for the last 2 weeks. The symptom was also accompanied by chest pain, weight loss and decreased appetite. Radiological examination revealed a tumor mass in the right lung. Histopathological and immunohistochemical
examination confirmed the presence of a tumor mass consistent with the diagnosis of PPL T4N1M1a Stage IVA. The patient is currently receiving supportive management. This case is interesting because primary pulmonary leiomyosarcoma is a type of lung cancer that is very rarely found and reported. Management of primary pulmonary leiomyosarcoma is challenging because the prevalence of this cancer is rare and there are no guidelines in the management approach. Surgery, radiotherapy and chemotherapy are the treatment approach that have been used in patients with primary pulmonary leiomyosarcoma in some literatures. However, there are still no recommendation regarding the type of chemotherapeutic agent that should be used in primary pulmonary leiomyosarcoma.

Consent
Written informed consent was obtained from the patient for publication of this case report.

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