

Primary Pulmonary Leiomyosarcoma Managed With Pazopanib: A Case Report and Literature Review

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Abstract

Primary pulmonary leiomyosarcoma (PPL) arises from pulmonary smooth muscle tissue, with less than 0.5% incidence among pulmonary malignancies and 30% among primary pulmonary sarcomas. Here, we present a case of PPL managed with pazopanib. Moreover, a brief review of relevant literature was conducted. A 65-year-old female presented with chronic cough, weight loss, and recurrent pneumonia, with a medical history including diabetes mellitus, hypertension, and hyperlipidemia, as well as past surgical colectomy and hysterectomy (due to abnormal uterine bleeding with normal pathology and no evidence of uterine leiomyosarcoma). Upon admission, she exhibited fever, cough, dyspnea, and decreased breath sounds over the upper lung lobe. Diagnostic workups revealed a large pulmonary mass, diagnosed as leiomyosarcoma via core needle biopsy and subsequent immunohistochemical staining. Neoadjuvant treatment with ifosfamide and adriamycin followed by chemoradiotherapy was attempted, but surgery for tumor resection was not feasible. Then, gemcitabine and docetaxel were chosen as the new treatment after ifosfamide and adriamycin were not effective. Imaging revealed tumor not reacting to latest treatment, either. Given the disease's persistence and the patient's diminished capacity for chemotherapy, the patient is presently undergoing pazopanib treatment, with ongoing monitoring of its effects. After 3 months of treatment with pazopanib (administered orally at 200 mg twice daily), the patient experienced a significant reduction in tumor size, with a notable decrease from 135 mm to 80 mm, approximating one-third of the initial size, indicating a positive therapeutic effect. This case report provides preliminary evidence suggesting that pazopanib, an oral multi-tyrosine kinase inhibitor, may be a promising therapeutic option for the management of PPL. However, further in-depth and long-term studies are warranted to evaluate the clinical efficacy and superiority of this treatment.

Keywords: Primary pulmonary leiomyosarcoma, pazopanib, core needle biopsy, case report, review

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Introduction

Primary pulmonary leiomyosarcoma (PPL) is an uncommon malignancy that originates from the smooth muscle tissue of the pulmonary parenchyma, pulmonary arteries, and the bronchial tree. It has been reported that the tumor has an incidence of less than 0.5% among all pulmonary malignancies and 30% among all primary pulmonary sarcomas, that is, the most common pathological type of pulmonary sarcoma.^{1,2}

There are several conditions that may facilitate PPL development such as exposure to chemicals, radiation, and occupational and environmental factors.³ Primary pulmonary leiomyosarcoma can cause symptoms that are not specific to this condition, making it challenging to detect early on. Some of these symptoms are similar to other types of primary pulmonary tumors, such as dyspnea (shortness of breath), cough, fever, chest pain, or it could even be asymptomatic. As a result, it may be

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difficult to differentiate PPL from other lung disorders based solely on the symptoms. Often, it appears as a circular mass with clear boundaries when observed on a chest X-ray.⁴ In contrast to epithelial tumors, PPL does not shed cells that can be collected through methods like bronchoscopy with washings or brushings, which makes these approaches generally unhelpful in confirming PPL. Instead, histological examination, which involves analyzing tissue samples under a microscope, is the most dependable method for confirming the presence of PPL and determining its grade of differentiation.³ Here, we present a case of PPL managed with pazopanib. Moreover, a brief review of relevant literature was conducted.

Methods

In the preparation of this report, we have meticulously adhered to the CARE checklist, which is provided as Supplemental material for reference.

Case Presentation

A 65-year-old lady referred to the Ayatollah Rohani Hospital, Babol, Iran, with chronic cough, weight loss, and recurrent pneumonia. She was a known case of diabetes mellitus, hypertension, and hyperlipidemia. She had past surgical history of colectomy (10 years ago) and hysterectomy (12 years ago and due to abnormal uterine bleeding with normal pathology and no evidence of uterine leiomyosarcoma).

On admission, she had a temperature of 38.6 °C; blood pressure, 130/90 mm Hg; respiratory rate, 27 breaths per min; pulse rate, 113 beats per min; and oxygen saturation, 86% (without any oxygen therapy). On physical examination, she had fever, cough, dyspnea, and decreased breath sounds over the upper lung lobe. Diagnostic workups were initiated with focus on infectious agents, and she was treated with empirical antibiotics. The laboratory data are presented in Table 1.

After being stabilized, spiral computed tomography (CT) scan of lungs and mediastinum with venous contrast showed a very large pulmonary soft tissue mass with a maximum diameter of 135 mm, heterogeneous and lobulated in the upper lobe of the left lung, extending to the hilum of this side (Figure 1). This mass was in contact with the descending aorta in parts, but there was no evidence of invasion and encasement

of the aorta and surrounding bronchus. This mass was also in contact with the left pulmonary artery. The opacity with a diffuse longitudinal mosaic pattern was evident in the lungs. The radiology consultation suggested tissue sampling for her. Given the absence of neurological symptoms in our patient, head CT scan was not indicated.

Core needle biopsy (CNB) was performed and specimens were sent for further laboratory investigations. Sections from so called lung mass revealed a malignant mesenchymal neoplasm composed of hypercellular proliferation of spindle cells with fascicular growth pattern and intersecting bundles. The tumor cells have moderate to occasionally marked nuclear pleomorphism as well as blunt-ended nuclei. Scattered mitotic figures (4-5 per 10HPF) were observed. Necrosis was not seen in the specimen, and lung tissue was not found. Additionally, small foci of myxoid changes and focal chondroid tissue (perhaps due to chondroid metaplasia) were identified. The immunohistochemical staining was performed and the malignant mesenchymal neoplasm with smooth muscle origin was compatible with leiomyosarcoma (Table 2). The pathology consultation suggested systemic and radiological investigations in order to find the origin of the tumor (primary vs secondary). Therefore, spiral chest and abdominopelvic CT scan (with oral and intravenous contrast), upper gastrointestinal (GI) tract endoscopy, and colonoscopy were performed.

Spiral chest and abdominopelvic CT scan with contrast revealed large heterogeneous enhancing mass measuring about 135*75 mm in left upper lobe due to known sarcoma. The mass invaded the left pleural space and anterior aspect of left second rib. No contralateral pulmonary metastasis was observed. There was no evidence of pleural thickening or effusion, and mediastinal lymphadenopathy. There was no mass involving pelvic organs. In summary, it suggested a locally advanced left pulmonary sarcoma with left pleural and chest wall invasion, and without distant metastasis. Upper GI endoscopy and colonoscopy revealed nothing.

Ultimately, the diagnosis of PPL was validated. First, we started 4 courses of neoadjuvant treatment with ifosfamide and adriamycin, and then chemoradiotherapy was also performed for the

Table 1. Laboratory Data on Admission Day.

	Admission day	Normal values
WBC (per μ L)	11,700	4500-11 000
Neutrophil (%)	36.9	40-60
Lymphocyte (%)	56.5	20-40
Hb (g/dL)	10.2	Female: 12.1-15.1
MCV (fL)	81.03	80-100
PLT (per μ L)	347 000	150 000-400 000
Cholesterol (mg/dL)	125	<200
Triglyceride (mg/dL)	212	<200
HDL (mg/dL)	45	>50
LDL (mg/dL)	56	<100
Na (mmol/L)	141.8	135-145
K (mmol/L)	3.8	3.5-5.5
Ca (mg/dL)	9.4	8.6-10.3
Fe (μ g/dL)	31	60-160
BUN (mg/dL)	15	6-20
Creatinine (mg/dL)	0.9	0.8-1.2
PT (sec)	11.6	11-13.5
PTT (sec)	31	25-35
INR	1	0.8-1.1
HbA1c (%) ^a	6.2	<5.7
Abbreviations: WBC, white blood cells; Hb, hemoglobin; PLT, platelets; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; PT, prothrombin time; PTT, partial thromboplastin time; INR, International Normalized Ratio; MCV, mean corpuscular volume.		
^a The most recent HbA1c level.		

patient. Nevertheless, surgical consultation determined that tumor resection was possible, but only to the extent of cytoreduction or debulking surgery. Resection with clear and complete margins was deemed infeasible. After considering this assessment and consulting with the patient's oncologist, it was concluded that debulking surgery would not be beneficial, and it was therefore excluded from the treatment plan. Then, the patient's treatment regimen was changed to include 6 courses of gemcitabine and docetaxel when ifosfamide and adriamycin failed to reduce the size of the tumor. The patient was sent for

imaging; however, the tumor size did not respond well to the revised treatment plan. Due to persistent disease and the patient's reduced tolerance to chemotherapy, following a multidisciplinary tumor board review, pazopanib was proposed as a viable alternative treatment option. After securing informed consent, the patient commenced pazopanib therapy. The patient's response to pazopanib is currently being monitored.

Following 3 months of treatment with pazopanib (200 mg twice a day), the patient underwent a spiral CT scan of the lungs, mediastinum,

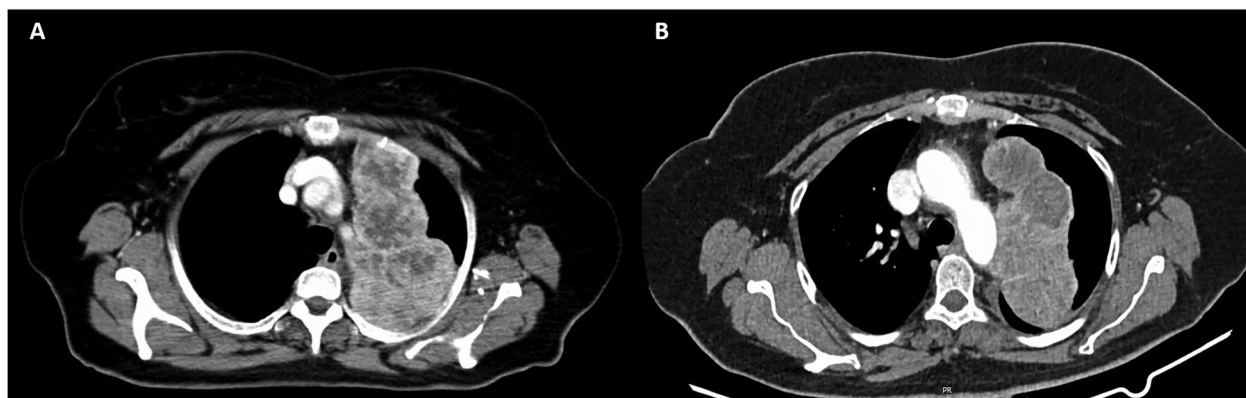


Figure 1. (A and B) Spiral computed tomography (CT) scan of lungs and mediastinum with venous contrast demonstrating a very large pulmonary soft tissue mass with a maximum diameter of 135 mm, heterogeneous and lobulated in the upper lobe of the left lung, extending to the hilum.

abdomen, and pelvis to assess tumor response. The CT report indicated a reduction in tumor diameter to 80 mm (Figure 2). This observation suggests that pazopanib treatment effectively diminished tumor size, with a notable decrease from 135 mm to 80 mm, approximating one-third of the initial size, indicating a positive therapeutic effect.

Although the local invasion of the tumor to the second rib has not been removed, but the tumor volume has decreased, which indicates the effectiveness of pazopanib treatment. It is still too early to comment on the resolution of the tumor's local invasion of the second rib, and we cannot give a definitive opinion, and we are still following up the patient to determine in the next imaging sessions whether there has been a reduction in the invasion or not.

Discussion and Literature Review

Leiomyosarcoma is a rare type of cancer that arises from smooth muscle cells.³ Smooth muscle is located in the hollow organs of the body such as the digestive tract, blood vessels, uterus, and bladder. Leiomyosarcoma can develop in any of these locations, but most commonly occurs in women's uterus, retroperitoneal, or intra-abdominal area.⁵ Leiomyosarcoma can metastasize, or spread to other parts of the body through the bloodstream or lymphatic system. The most common sites of metastasis for leiomyosarcoma are the lungs, liver, and bones. Metastasis to other tissues and soft organs, such as the brain or skin, is less common.⁶

Pulmonary smooth muscle tumors are more commonly seen as metastases from other organs to the lung (it is estimated that up to 40%-50% of people with leiomyosarcoma develop lung metastases), but rarely appear as primary lung tumors.⁷ Primary pulmonary leiomyosarcomas are mesenchymal-type tumors that usually arise from the lung parenchyma (70%), bronchial walls (20%), or pulmonary arteries (10%).⁸⁻¹⁰ This tumor is rare (less than 0.5% lung cancer), is malignant, and has a very aggressive behavior that has the ability to grow and cause symptoms very quickly.¹¹

As of 2006, only 300 cases of PPS had been reported in the literature. It comprises 0.2% to 0.5% of all primary lung malignancies. The prevalence of PPL is less than 0.5% of all types of lung cancer. This type of tumor is mostly reported in people over 50 years old with an average age of 51 years, men are 2 times more likely to develop PPL than women.^{9,11,12}

According to the location of the tumor, PPL can be classified as intraductal (endobronchial), intrapulmonary, or pulmonary vascular. Intrapulmonary is the most common subtype, while endobronchial is less common. To date, there are only 14 patients over the age of 20 who have been diagnosed with primary endobronchial pulmonary leiomyosarcoma. About 25% of PPS patients show lymph node metastasis.^{9,11,12}

The exact cause of leiomyosarcoma is not fully understood, but certain risk factors have been identified that may increase the likelihood of developing this type of cancer.¹³ Inherited

Table 2. Results of the Immunohistochemical Staining of Lung Specimen Collected Through Core Needle Biopsy (CNB).

	Marker	Description
1	Desmin	Strongly positive in majority of tumor cells.
2	SMA	Positive in most of tumor cells.
3	CD34	Highlights vascular spaces, negative in tumor cells.
4	CD177	Negative
5	CD99	Positive in some tumor cells.
6	S100	Negative
7	SOX10	Negative
8	BCL2	Negative
9	CD68	Negative
10	TTF1	Negative
11	EMA	Negative
12	Ki67	Positive in about 50% of tumor cells.
13	PanCK	Negative

Abbreviation: SMA, smooth muscle actin; CD, cluster of differentiation; SOX10, Sry-related HMg-Box gene 10; BCL2, B-cell lymphoma 2; TTF1, thyroid transcription factor 1; EMA, epithelial membrane antigen; PanCK, pan-cytokeratin.

genetic conditions such as LiFraumeni syndrome, neurofibromatosis type 1, hereditary retinoblastoma, occupational and environmental exposure to radiation or chemicals, and older age may increase the risk of leiomyosarcoma.¹³ Usually, these tumors can also develop in immunocompromised patients or patients with acquired immunodeficiency syndrome or after lung transplantation in connection with Epstein-Barr virus, however, having one or more of these risk factors does not necessarily mean that it is not that a person will get leiomyosarcoma.¹⁴ Most people with leiomyosarcoma have no known risk factors. Smoking is a risk factor for lung cancer (1 in 9 heavy smokers is reported to develop lung cancer), but smoking is rarely found as a risk factor in PPL patients (less than 50% of PPL patients had a history of smoking).¹⁵

Patients with PPL often present with mild and non-specific respiratory symptoms, which vary depending on the size of the tumor, the stage and the location of the malignancy.¹⁶ Patients with this disease may remain without specific symptoms for

a long time, and even involvement of pleural, mediastinal, and intraparenchymal localization is possible without any symptoms.¹⁷ A number of PPL patients may also show cardiac symptoms such as palpitations.⁹ In addition, patients may have systemic manifestations such as weight loss, nausea and vomiting, fatigue, and fever.^{10,16} In our case, the patient presented with symptoms of chronic cough, shortness of breath, weight loss, fever, and frequent pneumonia. Endobronchial leiomyosarcoma may cause cough, hemoptysis, and dyspnea.¹⁸ Patients with the large intrapulmonary subtype of PPL may also have symptoms of external bronchus compression. Meanwhile, patients with primary leiomyosarcoma of the pulmonary artery may have symptoms of progressive heart failure or mimic symptoms of acute pulmonary embolism.¹² Tumor progression can lead to hypermetabolic and chronic inflammatory conditions that increase the processes of lipolysis and fat oxidation, decrease fat deposition, adipogenesis, and browning of white fat cells. Finally, all these cases develop atrophy of visceral and subcutaneous fat tissues.¹⁹ Pain is usually absent or very mild.¹⁶

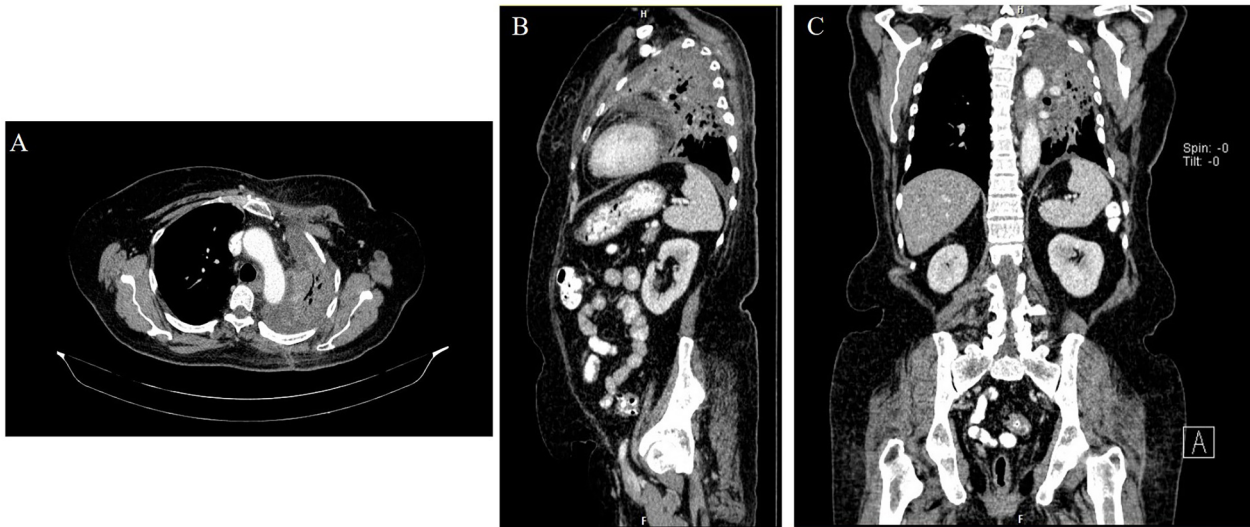


Figure 2. (A, B, and C) Spiral computed tomography (CT) scan of lungs, mediastinum, abdomen, and pelvis with venous contrast to assess tumor response. Advanced imaging showed normal trachea and bronchi, no pulmonary abnormalities, and no adenopathy or lesions in abdominal organs. Pericardial effusion was seen on the left side of the heart. Shift of the heart and mediastinum to the left side was seen. A decrease in the volume of the left lung was evident. Pleural thickening / effusion could be seen at the base of the left lung. A hypodense structure with a density close to a slightly heterogeneous liquid with a maximum diameter of 80 mm has completely occupied the upper lobe of the left lung.

The diagnosis of PPL is often difficult because localized expansion of the lung parenchyma results in clinical, macroscopic, and radiographic appearances that resemble a nonsarcomatous tumor.¹¹ Early diagnosis of the tumor can be done using simple imaging methods such as ultrasound, CT scan, or MRI.²⁰ After histological examination, a definitive diagnosis can be made. Diagnosis requires biopsy, immunochemical staining, and exclusion of secondary neoplasms, as extrapulmonary sarcoma metastases are more common than primary tumors.¹¹ However, PPL has been reported to have a more aggressive spread on radiographs with the appearance of a rounded, smooth, or lobulated intraparenchymal mass.⁸ From chest CT findings, PPL appears as a single, smooth, round, heterogeneous lesion of heterogeneous density with areas of calcification suggestive of ischemic necrosis. If a mass is observed in the upper lobe of the lung in a non-smoking patient, the doubt about the diagnosis of PPL increases.¹¹ Chest radiography and routine CT scan are recommended to detect asymptomatic pulmonary metastases.²¹ In our case, after stabilization, a spiral CT scan of the lung and mediastinum with venous contrast showed a very large, heterogeneous, and lobulated pulmonary soft tissue mass with a maximum

diameter of 135 mm in the upper lobe of the left lung, which reached the hilum. Next, a CNB was performed and showed a malignant mesenchymal neoplasm consisting of proliferation of spindle cells with a fascicular growth pattern and crossed bundles. Tumor cells had moderate to sometimes marked nuclear pleomorphism and also terminal nuclei. Immunohistochemical staining was performed, and malignant mesenchymal neoplasm of smooth muscle origin was consistent with leiomyosarcoma. Positron emission tomography (PET)/CT is useful for evaluating distant metastases or for differentiation, if primary or metastatic. It has even been suggested that PET/CT can be useful even in tumor grading, as metabolic activity correlates well with necrosis and mitotic activity.¹ Accurate diagnosis via bronchoscopy is often challenging due to the presence of extensive necrotic tissue within the tumor and the difficulty in obtaining sufficient cellular samples. Consequently, surgical intervention is frequently necessary for definitive diagnosis. Transbronchial cryobiopsy has emerged as a valuable method that involves rapid freezing of the target tissue. This process generates larger specimens with preserved structural integrity and minimal tissue damage, thereby enhancing diagnostic accuracy.^{15,22}

The prognosis of leiomyosarcoma is very poor.²³ The 5-year survival rate for people with leiomyosarcoma ranges from 50% to 70%, depending on the stage of the cancer and other factors (median overall survival of 33 months in operable cases and 4 months in unresectable cases has been reported).^{15,24} Because these tumors are resistant to chemotherapy, the best treatment option is surgical resection with wide safety margins (with a 5-year survival rate of about 22%).¹⁵ A comprehensive meta-analysis of 51 studies involving 1664 patients with advanced uterine leiomyosarcoma by Ijaz et al has provided valuable insights into treatment strategies. They showed that combinations of anthracycline and alkylating agents and gemcitabine and docetaxel demonstrated the highest efficacy as first-line and second-line chemotherapies, respectively. Subgroup analysis indicated that dual-regimen therapies with anthracycline and alkylating agents or gemcitabine and docetaxel are effective options for International Federation of Gynecology and Obstetrics stages III to IVb with distant metastases confirmed by CT scan ($P = .001$). Notably, local radiotherapy and neoadjuvant chemotherapy were associated with improved outcomes in patients with earlier stages of distant relapsed uterine leiomyosarcoma ($P < .001$).²⁵ A recent meta-analysis involving 1380 patients has revealed a significant association between radiotherapy and a reduced risk of metastasis. Specifically, the use of radiotherapy was associated with an odds ratio of 10.84 (95% confidence interval: 4.41-26.61), indicating a substantial reduction in the likelihood of metastatic spread ($P < .01$).²⁶ Pazopanib, an oral multi-tyrosine kinase inhibitor, was initially developed as a potential treatment for a wide range of malignancies. However, its current therapeutic applications are limited to renal cell carcinoma and soft tissue sarcoma (STS). Soft tissues encompass an array of tissues derived from the mesoderm, including blood vessels, fibrous tissue, adipose tissue, smooth muscle, and skeletal muscle. Additionally, soft tissues include peripheral nerve tissue, which originates from the neuroectoderm.²⁷ Despite the diverse histological subtypes of STS, many cases exhibit overexpression of platelet-derived growth factor and vascular endothelial growth factor. Notably, a correlation between the grade of tumor and patient survival has been well-established.²⁸⁻³¹ Studies have demonstrated the efficacy of RAF inhibitors as pan-RAF inhibitors, exerting anticancer effects by suppressing MAPK pathway signaling in tumor cells, independent of any significant antiangiogenic effects.³²

In patients with metastatic soft tissue leiomyosarcoma, pazopanib significantly improved median progression-free survival compared to placebo group.³³ Furthermore, a case report by Inoue et al highlighted the efficacy of pazopanib in treating a metastatic brain tumor in a patient with advanced uterine leiomyosarcoma and several lung metastases.³⁴ These findings suggest that pazopanib may be effective in controlling not only local recurrence but also distant metastases, even in the absence of stereotactic radiosurgery.^{34,35}

One limitation of our study is the limited availability of PET/CT in our country. However, considering that leiomyosarcoma commonly originates in the uterus and frequently metastasizes to the lungs, further evaluation for distant metastases typically relies on clinical suspicion based on signs and symptoms.³⁶ Therefore, we endeavored to optimize our resource utilization by performing lung and abdominal CT scans to identify the most critical potential metastatic sites.

Conclusion

Leiomyosarcoma, an uncommon malignancy arising from smooth muscle cells, typically occurs in hollow organs of the body. Although commonly found in the uterus, retroperitoneum, or intra-abdominal area, it can also manifest as PPL, a rare and aggressive form of lung cancer. In this report, a spiral CT scan of the lungs and mediastinum, employing venous contrast, revealed a sizable, heterogeneous, and lobulated pulmonary soft tissue mass measuring 135 mm in maximum diameter, situated in the upper lobe of the left lung and extending to its hilum. Following 3 months of treatment with pazopanib (200 mg twice a day), the treatment could effectively diminish tumor size, with a notable decrease from 135 mm to 80 mm. This case report offers preliminary evidence indicating the potential of pazopanib, an oral multi-tyrosine kinase inhibitor, as a therapeutic option for PPL management. Nevertheless, more comprehensive and long-term studies are necessary to assess the clinical efficacy and superiority of this treatment approach.

Authors' Note

Consent for Publication: For publication of this article, we obtained written informed consent from the patient to release any potentially identifiable data. **Data Availability Statement:** The Data supporting the findings of this study are available upon request from the corresponding author and with permission from Babol University of

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Author Contribution(s)

Sahar Khosravi: Conceptualization; Investigation; Supervision; Validation; Writing – review & editing.

Sana Keshtegar: Investigation; Writing – original draft; Writing – review & editing.

Ali Tavakoli Pirzaman: Investigation; Supervision; Writing – original draft; Writing – review & editing.

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Supplemental Material

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