

Case Report

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# Rapidly Progressive Lung Sarcomatoid Carcinoma Managed with Doxorubicin Plus Ifosfamide and Pemetrexed

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## Keywords

Neoplasms · Lung neoplasms · Carcinoma

## Abstract

Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of nonsmall-cell lung cancer (NSCLC). It carries a poor prognosis, even among other subtypes of NSCLC. Currently, most treatment strategies for PSC are derived from regimens aimed at managing soft tissue sarcomas or NSCLC. The use of doxorubicin plus ifosfamide and pemetrexed has been well established in the management of soft tissue carcinoma and other nonsmall-cell lung cancers, respectively. We report the case of a 69-year-old male diagnosed with PSC who was managed with doxorubicin plus ifosfamide and pemetrexed therapy. Our patient initially responded to the therapy but had rapid progression and died 8 months after the initiation of treatment. Upon genetic analysis, it was revealed the patient had overexpression of the MDM2 protein, which has been associated with poor response to therapy. This case highlights the need for a personalized treatment approach, as well as the need for a standardized treatment regimen for managing PSC.

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Published by S. Karger AG, Basel

## Introduction

Lung cancer remains the leading cause of cancer deaths worldwide. It is classified into small-cell lung carcinoma and nonsmall-cell lung carcinoma (NSCLC). NSCLC comprises about 85% of all cases of lung cancer [1]. Pulmonary sarcomatoid carcinomas (PSCs) are a rare subclassification of NSCLC, making up for 0.3%–3% of these types of tumors [2]. Prognosis for PSC is poor, with some authors reporting a 5-year survival of 24.5% [3]. There is no standardized treatment approach for managing PSC, with treatment strategies being derived from those aimed at managing soft tissue sarcomas or NSCLC. Chemotherapy has found some success as adjuvant therapy to surgical management, as very little benefit has been found in using chemotherapy alone [4, 5]. The use of doxorubicin plus ifosfamide has been established in the management of soft tissue carcinoma, while pemetrexed has been used in the management of nonsquamous NSCLC [6, 7]. We hereby report a case of a patient diagnosed with PSC managed with doxorubicin plus ifosfamide and pemetrexed.

## Case Report

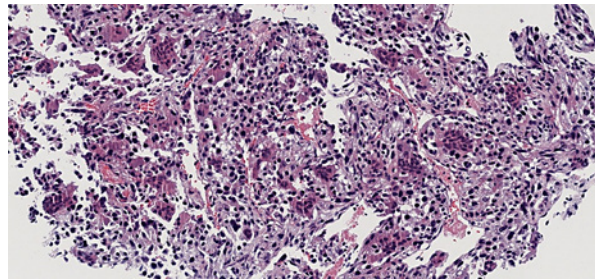
A 69-year-old male presented in 2019 complaining of unintentional weight loss, shortness of breath, and pleuritic chest pain. The patient had no relevant medical, family, or psychosocial history.

Physical examination was significant for dull percussion and decreased breath sounds in the left portion of the thorax. Computed tomography (CT) imaging of the chest was performed, reporting a heterogeneous mass in the left lung. With this finding, a CT-guided biopsy of the lesion was performed. The pathology report was of sarcomatoid carcinoma with abundant giant cells with osteoclastic features (Fig. 1). Genetic analysis was significant for mutation in the MDM2 gene. Mutations in the EGFR, ALK, and PDL genes were negative. A positron emission tomography scan revealed metastatic activity in the diaphragm, adrenal glands, and axial bones.

Treatment with chemotherapy was initiated. Doxorubicin 25 mg/m<sup>2</sup> and ifosfamide 2,500 mg/m<sup>2</sup> were given on days 1, 2, and 3 every 3 weeks for 6 cycles. Mesna was given to counteract ifosfamide toxicity. Follow-up with CT scan was performed. Partial response was achieved in the lung lesion, but new lesions in the liver were found. The patient was then cataloged as having disease progression and had marked clinical deterioration. After deterioration, the patient was given pemetrexed 500 mg/m<sup>2</sup> every 3 weeks for 2 cycles. Treatment cycles were overall well tolerated. The patient died due to disease progression shortly thereafter; the overall survival was of 8 months after the initiation of treatment.

## Discussion

There is no current consensus in the management of PSC. PSCs are usually managed with the same treatment regimens as soft tissue carcinomas or NSCLC. Karim et al. [4] found in their study that the greatest overall survival benefit was achieved with surgical resection and adjuvant chemotherapy, as chemotherapy alone did not provide any survival benefit in patients with PSC. However, previous reports suggest poor outcomes in patients managed with surgical intervention in advanced stages of the disease [3]. Given the available data, surgical resection was not attempted in our patient due to the presence of metastatic lesions. Doxorubicin plus ifosfamide chemotherapy was given in accordance with its use in soft tissue sarcomas. Furthermore, mesna was added to counteract the toxicity of ifosfamide [6]. After



**Fig. 1.** Sarcomatoid carcinoma of the lung with giant cells with osteoclastic features, HE stain; magnification,  $\times 200$ .

disease progression and due to clinical deterioration, second-line chemotherapy was initiated. Pemetrexed monotherapy was chosen as second-line therapy due to availability, its manageable toxicity profile, and in accordance with its use in NSCLC [7].

The use of doxorubicin plus ifosfamide in soft tissue sarcoma is well established. In a study performed by Blum et al. [6], the overall response rate (ORR) for doxorubicin/ifosfamide in patients with soft tissue sarcoma was 34%, compared to the ORR of doxorubicin alone (20%). The median survival for in this study was 11.5 months [2]. The sarcomatoid component of PSC has been assumed to be susceptible to this regimen. Lee et al. [8] analyzed the use of doxorubicin, ifosfamide, and dacarbazine in patients with pulmonary pleomorphic carcinoma. The overall response rate in this group was 35%, and the overall survival was 8.7 months. The second-line regimen for soft tissue carcinomas includes the use of pazopanib, eribulin, or trabectedin [9]. Due to drug availability and the toxicity profile of said medications (i.e., grade 3 neutropenia in up to 57% of patients in the case of eribulin), second-line management with pemetrexed was opted to be continued [10]. Pemetrexed can be used as first- or second-line therapy in patients with advanced nonsquamous NSCLC. Pemetrexed monotherapy has been approved for second-line treatment in these patients. Hanna et al. [11] found an ORR of 9.1% and an overall survival of 8.3 months for patients with advanced NSCLC where pemetrexed was used as second-line therapy.

Our patient condition rapidly progressed, and the patient died 8 months after the initiation of treatment. Even among NSCLC tumors, pulmonary sarcomatoid carcinoma remains one of the most aggressive subtypes of lung cancer. Martin et al. [3] found a median survival for stage III PSC of 10.3 months, compared to a median survival of 25.3 months for stage III NSCLC. Furthermore, our patient was found to have overexpression of the MDM2 protein. This protein suppresses the expression of p53, contributing to tumor development [10]. The MDM2 protein has also been associated with poor response to chemotherapy and other forms of medication, which was ultimately the case in our patient [12, 13].

Targeted therapy (e.g., immune checkpoint inhibitors) is a promising candidate for treating PSC, as these tumors usually harbor additional mutations in genes such as EGFR, KRAS, MET, and BRAF [5, 14–18]. In the case of MDM2 mutations, MDM2 inhibitors are under development. Idasanutlin was a promising candidate and had advanced to a phase III clinical trial, but this trial was terminated due to futility based on efficacy results [19]. Other possible future strategies for dealing with MDM2 might include the targeting of mutant p53, as well as targeting MDM2/p53 and MDMX/p53 interactions [20].

As evidenced in this case report, pulmonary sarcomatoid carcinomas carry a poor prognosis. Treatment strategies such as the use of chemotherapy have been well established in the management of soft tissue sarcomas and NSCLC. Nevertheless, the aggressive nature of PSCs warrants more research into whether the same benefit can be derived from treatment regimens used in soft tissue sarcomas and other subtypes of NSCLC.

## Acknowledgment

We thank Dr. César Lara Torres for analyzing and providing the image of the biopsy.

## Statement of Ethics

Study approval statement: An exemption from requiring ethics approval was granted by the hospital ethics committee, as no identifying information was given in this case report.

Consent to publish statement: Written informed consent was obtained from the next of kin of the patient for publication of the details of their medical case and any accompanying images.

## Conflict of Interest Statement

Jan Alberto Paredes Mogica, Eduardo Reyes Sanchez, Daniela Arantza Zaragoza Morales, Nathalie Pierre-Louis Guillen, and Manuel Ernesto Magallanes Maciel had no competing financial interests to disclose.

## Funding Sources

None; this study did not receive any funding.

## Author Contributions

Jan Alberto Paredes Mogica conceived and designed the analysis, collected data, contributed data or analysis tools, performed the analysis, and wrote the paper; Eduardo Reyes Sanchez conceived and designed the analysis, contributed data or analysis tools, and performed the analysis; Daniela Arantza Zaragoza Morales contributed data or analysis tools, and wrote the paper; Nathalie Pierre-Louis Guillen contributed data or analysis tools, and wrote the paper; Manuel Ernesto Magallanes Maciel performed the analysis, and contributed data or analysis tools.

## Data Availability Statement

Data were available on request due to privacy/ethical restrictions.

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