A Case of Pulmonary Carcinosarcoma
(Squamous Cell Carcinoma and Osteosarcoma)
Treated with Cisplatin and Doxorubicin

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Abstract. Background: Pulmonary carcinosarcoma is a rare malignancy composed of epithelial and mesenchymal elements. Little information is available on systemic treatment options for this tumor entity. Case report: A 65-year-old man with severe chronic obstructive pulmonary disease (COPD) was diagnosed with primary pulmonary carcinosarcoma after percutaneous fine-needle biopsy of a right-sided calcified mass. The tumor was composed of squamous cell carcinoma and true osteosarcoma. A second, non-calcified mass was present in the left lung. The patient received six cycles of chemotherapy with cisplatin and doxorubicin, resulting in partial remission of both tumor manifestations. However, a few months thereafter, the patient died from spinal and cerebral metastases, the former of which was of adenocarcinomatous differentiation. Conclusion: Cisplatin and doxorubicin may be effective in pulmonary carcinosarcoma. Nevertheless, the aggressiveness of this rare tumor entity, its histological heterogeneity, and its potential coexistence with non-small cell lung cancer (NSCLC) make the management of patients with pulmonary carcinosarcoma a diagnostic and therapeutic challenge.

Pulmonary carcinosarcoma is a rare tumor entity accounting for only 0.2-0.3% of all malignant lung neoplasms (1). It is characterized by an admixture of both epithelial and mesenchymal elements similar to those seen in well-defined carcinomas and sarcomas. It was initially suggested that carcinosarcomas of the lung occur as two distinct clinicopathological types (2): a central endobronchial type, which is slow-growing and shows squamous epithelial differentiation in >90% of cases; a peripheral invasive type, characterized by early metastatic spread, poor clinical outcome and glandular epithelial differentiation in approximately 50% of cases. This classification, however, has been considered less stringent in the last decades. A recent case series has only identified increased tumor size (>6 cm) as a prognostic indicator for reduced survival (3).

In most cases, a definitive diagnosis of pulmonary carcinosarcoma is not made until surgical resection or at autopsy (1, 4). Consequently, there are only few data available in the literature on primary systemic therapy for this rare tumor entity. In this case report, we describe the successful diagnosis of primary pulmonary carcinosarcoma using fine needle biopsy in a patient with severe chronic obstructive lung disease and its initial treatment with combination chemotherapy.

Case Report

A 65-year-old Turkish man was referred to our institution for systemic therapy of primary pulmonary carcinosarcoma. Six weeks earlier, the patient had been admitted to another hospital for diagnostic work-up of two pulmonary masses incidentally revealed by routine chest radiography and computed tomography (CT). One mass, measuring 5.5 cm in diameter and showing focal calcifications, was located in the right lower lobe (lung segment, S8) (Figure 1A), and the other mass, measuring 5.0 cm in diameter, was located in the left upper lobe (S3) (Figure 1B). The patient was a heavy smoker and suffered from arterial hypertension, coronary artery disease with a history of repeated angioplasty and stenting, bilateral cystic kidney disease with chronic compensated renal insufficiency, and severe chronic
obstructive lung disease (GOLD stage, III-IV) with pulmonary emphysema. As repeated transbronchial biopsies were non-diagnostic and surgical thoracotomy with lung segment resection was not feasible due to the patient’s impaired cardiopulmonary function, a CT-guided fine-needle biopsy of the right-sided pulmonary mass was performed. On microscopic examination, the tumor was composed of squamous epithelial cells and mesenchymal sarcomatous cells producing a mineralized extracellular osteoid matrix (Figure 1C). The former tumor component stained strongly positive for pancytokeratin, a marker for tissue of epithelial origin, whereas the latter tumor component stained strongly positive for vimentin, a mesenchymal cytoskeleton protein (Figure 1D and E).

Based on the histological and immunohistochemical findings, a diagnosis of true pulmonary carcinosarcoma with predominant differentiation into squamous cell carcinoma and osteosarcoma was made. Additional abdominal and skeletal tumor manifestations were excluded by ultrasonography and radionuclide bone scanning, respectively.

On physical examination at admission to our institution, the patient (170 cm, 61 kg) was in no respiratory distress while breathing room air. The blood pressure, heart rate and peripheral oxygen saturation were 150/70 mmHg, 108/min and 91%, respectively. The patient’s thoracic cage showed barrel chest deformity with an increased percussion note over both lungs, decreased expansion during inspiration, and reduced breathing sounds on auscultation, with bilateral wheezes and rhonchi. The physical examination of the heart, the abdomen, and the neurological and musculoskeletal systems was unremarkable. The results of a complete blood count with leukocyte differentiation were within normal ranges. Levels for serum creatinine (normal range, 0.6-1.3 mg/dl) and urea nitrogen (8-26 mg/dl) were slightly elevated to 1.5 mg/dl and 29 mg/dl, respectively. The plasma fibrinogen was 5.6 g/l (1.8-3.5 g/l), and the C-reactive protein was 42 mg/l (<5 mg/l). Electrolytes, liver function tests, and global coagulation tests were within normal ranges. The creatinine clearance was 47 ml/min (100-155 ml/min) as determined by 24-h urine collection. An electrocardiogram and a transthoracic echocardiography were unremarkable except for minor inferolateral ventricular depolarisation and wall motility changes, respectively. Testing of the auditory system by bilateral audiometry revealed a symmetric decline in hearing function at frequencies of greater than 3 kHz, consistent with age-related hearing loss. On lung function testing, the forced expiratory volume in the first second (Tiffeneau’s test) was reduced to 26% of normal with only minimal improvement after the application of bronchodilator agents. The patient’s ambulatory medication consisted of aspirin, an ACE inhibitor (captopril), a diuretic (hydrochlorothiazide + triamterene), acetyldigoxin, a corticosteroid (prednisolone), a lipid-lowering agent (atorvastatin), and a proton pump inhibitor (pantoprazole), as well as inhalative β2-receptor-stimulating (formoterol) and anticholinergic (tiotropium bromide) agents.

Following written informed consent, the patient received systemic chemotherapy with cisplatin and doxorubicin, each administered at a single dose of 50 mg/m² of body surface every three weeks for a total of six cycles. From cycle four on, dosages for both cytotoxic drugs were reduced to 75% due to oral mucositis and prolonged neutropenia (both WHO grade, II). Supportive care consisted of intravenous fluids, serotonin receptor blockade, and dexamethasone.
A chest radiograph obtained after three cycles of chemotherapy showed a significant reduction in the size of the right-sided pulmonary mass (Figure 2). The left-sided pulmonary mass was more difficult to assess due to its close anatomical relationship to the mediastinum. However, a thoracic CT scan obtained after completion of all six cycles of chemotherapy (not shown) demonstrated shrinking of the right-sided and left-sided pulmonary masses to 3.0 cm and 2.5 cm in diameter, respectively, corresponding to partial remission according to RECIST criteria.

Ten weeks after completion of chemotherapy, the patient was readmitted to our institution with severe pain over the middle part of the thoracic spine, which had started about one month earlier and had gradually increased in intensity. There were no focal sensory or motor deficits, but the patient had lost 4 kg in weight and suffered from general malaise and asthenia. A spinal magnetic resonance imaging (MRI) study revealed a mass of 3.5x3 cm in the dorsal part of the sixth thoracic vertebra, with severe narrowing of the spinal canal and the left intervertebral foramen (Figure 3A and B). A thoracic CT scan showed no change in size of the two pulmonary masses. The patient was immediately taken to the operating room where he underwent dorsal stabilization from vertebra Th4 to Th8 with laminectomy of

Figure 2. Response of pulmonary carcinosarcoma to chemotherapy with cisplatin and doxorubicin as assessed by conventional radiography. Compared to a pre-treatment chest X-ray (A), a radiological evaluation after three cycles of chemotherapy demonstrated a significant reduction in size of the right-sided pulmonary carcinosarcoma (B).

Figure 3. Radiological and histological findings of spinal adenocarcinoma metastasis. Axial (A) and sagittal (B) sections of a spinal MRI study demonstrating a mass in the dorsal part of the sixth thoracic vertebra with narrowing of the spinal canal and infiltration of the adjacent skeletal structures. Microscopic examination of the surgically-removed mass revealing mucus-producing tumor cells arranged in a solid and glandular pattern different from the morphology of the epithelial component in the lung biopsy specimen (C) (PAS reaction, original magnification x10).
vertebra Th6 and microsurgical tumor resection. On microscopic examination, the tumor consisted of both solid and glandular structures with intra- and extracellular mucous formation as evidenced by a positive periodic acid-Schiff (PAS) reaction (Figure 3C). The tumor cells were weakly positive for pancytokeratin, but showed strong staining for cytokeratin 7 (CK7), carcinoembryonic antigen (CEA), and thyroid transcription factor-1 (TTF-1) (not shown), consistent with a skeletal metastasis of primary lung adenocarcinoma.

Three weeks after surgery, a cranial MRI study was performed at another hospital for diagnostic work-up of progressive cognitive impairment and disorientation of the patient, demonstrating a right-sided occipital mass of 2.5 cm in diameter with significant perifocal oedema highly suspicious of cerebral metastasis. The patient received high doses of dexamethasone and fractionated external radiotherapy of the neurocranium and the affected thoracic spine with cumulative dosages of 30 Gy each. The treatment was well tolerated, but the patient succumbed to his malignancy a month after completion of radiotherapy, a total of nine months after the first diagnosis of primary pulmonary carcinosarcoma. An autopsy was not performed.

Discussion

In this patient, the diagnosis of pulmonary carcinosarcoma was established using percutaneous transthoracic fine-needle biopsy. Few cases have been described in the literature in which this diagnostic procedure had proven successful. Typically, pulmonary carcinosarcoma is not accurately diagnosed by means of sputum cytology, bronchoscopy (as in our patient), or fine-needle biopsy, and a final diagnosis of this tumor entity is therefore rarely made until surgical resection or at autopsy (1, 4, 5).

The presented case shares features characteristic of pulmonary carcinosarcoma in that the tumor occurred in a male patient 50-80 years of age who was a heavy smoker. However, some clinical and histopathological findings are noteworthy and deserve further attention.

The epithelial component of the fine-needle biopsy specimen from the right-sided calcified mass was predominantly composed of non-keratinizing squamous cell carcinoma (Figure 1C). This finding is in agreement with previous anecdotal reports and larger case series (3) in which squamous cell carcinoma appeared to be the most common epithelial tumor component as compared to adenocarcinoma, adenosquamous carcinoma, or undifferentiated carcinoma. In contrast, differentiation of the sarcomatous component into osteosarcoma with significant extracellular osteoid matrix formation, as in the case under discussion, is rarer, as is its differentiation into mature chondrosarcoma (6-9). Additional histological sub-entities of the sarcomatous tumor component comprise fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, spindle cell sarcoma and undifferentiated sarcoma, all of which may occur separately or in combination with each other (3).

Whereas the left-sided apical mass had not been examined histologically, the resected spinal mass consisted exclusively of adenocarcinoma with both solid and glandular structures as well as intra- and extracellular mucous formation. These features are consistent with a skeletal metastasis of NSCLC. The left-sided pulmonary mass did not show calcifications on CT scanning, which may argue against the presence of osteosarcoma. However, it responded to chemotherapy in a fashion similar to the right-sided pulmonary mass, suggesting a related histological composition. Both lesions remained in remission on repeated follow-up examinations. In contrast, the spinal mass was characterized by a distinct biological behaviour with rapid growth shortly after cessation of chemotherapy. Based on its chronological manifestation, it is very likely that the cerebral metastasis, too, was composed of adenocarcinoma. In pulmonary carcinosarcoma, metastases may be sarcomatous, epithelial, or a combination of both.

The presented histopathological findings underscore the remaining uncertainty regarding the histogenesis of pulmonary carcinosarcoma in light of the concomitant presence of two or more distinct tissue types and the clonal nature of malignancy. However, two recent studies have provided molecular evidence that the divergent epithelial and mesenchymal cell lineages indeed share the same histological origin (10, 11), favouring the classification of pulmonary carcinosarcoma as a biphasic monoclonal malignancy. By using immunohistochemical and ultrastructural studies in a case of pulmonary carcinosarcoma, Haraguchi et al. (12) suggested that the malignant mesenchymal component was derived from the epithelial component, supporting earlier concepts according to which the carcinoma is the principle tumor element, whereas the sarcomatous changes are secondary (e.g., through mesenchymal metaplasia) (13).

Several scenarios are conceivable in this patient, two of which appear most plausible. Firstly, adenocarcinoma, which may occur concomitantly with squamous cell carcinoma in pulmonary carcinosarcoma, was a histological component of the primary tumor and was missed by fine needle biopsy. Secondly, the patient initially presented with two distinct malignancies: pulmonary carcinosarcoma in the right lung and NSCLC in the left lung. In both scenarios, chemotherapy may have caused selective growth and spread of the more resistant and aggressive adenocarcinoma.

Surgical resection is the treatment of choice and potentially curative in localized stages of pulmonary carcinosarcoma (1, 4). Once the tumor is disseminated, the prognosis is poor and most patients die within weeks to
months from rapidly progressive disease (5). Due to severe chronic obstructive lung disease, surgery was not a therapeutic option in our patient despite the fact that both pulmonary masses were relatively small, well confined and located in the lung periphery.

Information on the cytotoxic treatment of pulmonary carcinosarcoma is sparse (1). A combination regimen was empirically chosen in our patient to target both the malignant epithelial (cisplatin) and mesenchymal tumor component (doxorubicin). Overall, this regimen was well tolerated by an elderly patient with significant cardiorespiratory comorbidity as well as renal function impairment, inducing partial remission of both pulmonary masses. The survival was 9 months from diagnosis. Depending on the case series studied, reported median survival times and 5-year survival rates for patients with pulmonary carcinosarcoma are 3-5 months and 0-21%, respectively (1, 4, 5).

In summary, this case highlights the potential difficulties associated with the diagnosis of pulmonary carcinosarcoma. Due to its rare occurrence and histological heterogeneity, the management of pulmonary carcinosarcoma is a therapeutic challenge and remains highly individualized.

References


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