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COMMUNICATION

Could Spindle Cell Lung Carcinoma be Considered and Treated as Sarcoma, According to its Clinical Course, Morphology, Immunophenotype and Genetic Finding?

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Abstract The actual nature of spindle cell carcinoma has been debated extensively because of its rarity. It carries a poor prognosis, even when early-stage disease is diagnosed and resected. In view of the rarity and the significance of the histological diagnosis, we report a patient with rapidly progressing spindle cell lung carcinoma with soft tissue metastasis. Diagnosis was confirmed by immunohistochemistry finding. Analysis of the TP53 gene mutations by polymerase chain reaction and DNA sequencing revealed insertion of single thymine resulting in frameshift mutation in the exon 8. Prognosis of spindle cell lung carcinoma might be determined by the sarcoma component of the tumor and, based on that, we wonder if this type of lung carcinoma could be followed-up and treated by strategies for soft tissue sarcomas, because of its rapid, sarcomatous type of growth, beside the properly lung carcinoma oncological treatment.

Keywords Spindle cell lung carcinoma · Immunophenotype · Oncogenetic · p53 · Sarcoma

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Introduction

Spindle cell carcinoma (SCC) is a rare form of lung cancer, representing 0.2 to 0.3 % of all primary pulmonary malignancies [1]. It is more common in male than female patients (4 to 5:1), in smokers, and in patients between 50 and 80 years of age [1]. Lung resection is the treatment of choice for these patients, because in most cases the preoperative diagnosis is incomplete. It was defined in the World Health Organization classification updated in 2004 as a group of poorly differentiated NSCLCs with sarcomatous elements [2–4]. These tumors are characterized by a more aggressive outcome than other histological subtypes of non-small cell lung cancer (NSCLC). Most of them fall into the category of pleomorphic carcinomas because of the presence of a double-cell component—spindle and/or giant cells and of epithelial cells, but their pure forms exclusively composed of spindle cells are extremely uncommon [5].

Understanding clinicopathologic behavior and prognosis for this tumor and verifying the proper selection of treatment strategy is crucial. The actual nature of SCC has been debated extensively because of its rarity, but no large studies have been conducted regarding the prognosis of spindle cell lung carcinoma. In view of the rarity and the significance of the histological diagnosis, we report a patient with rapidly progressing spindle cell lung carcinoma with soft tissue metastasis. The problems concerning our patient's

diagnosis, therapy, and prognosis after resection treatment are discussed, with consideration of the literature.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Case Report

Clinical and Imaging Findings

A 43 year old woman, Caucasian, who had a family history positive for malignant lung tumor, was referred to our hospital because of a month permanent cough, left hemithoracis pain and intermittent hemoptisis. Patient was smoker, 25 years/40 cigarettes per a day. On admission patient was pale and cachectic, with tachycardia (120/min). Chest auscultation was not significant. Blood count report was within regular range, except high erythrocyte sedimentation rate (30 mm/h). The biochemical findings as well as urinalysis were within regular range. Arterial blood gas analysis and pulmonary function tests were normal.

Chest radiography revealed a tumor in the left upper lobe. CT showed in left upper lobe peripheral inhomogeneous mass with low-attenuation area. Adjacent chest wall invasion and peritumoral areas of ground-glass attenuation were present (Figs. 1 and 2).

Pathological Finding

Percutaneous needle biopsy and transbronchial biopsy were performed, but they were insufficient for pathological diagnosis. As distant metastasis was not found, left upper lobectomy was performed.

On gross examination tumor node was measured 85×75×55 mm. It involved parietal pleura and intercostals muscles. Microscopically, tumor cells purely consisted of

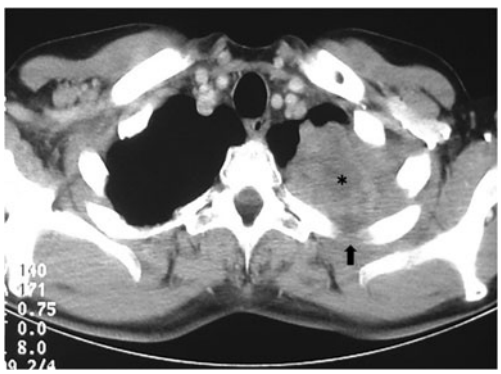

Fig. 1 Transverse contrast-enhanced CT scan shows inhomogeneous enhancing mass lesion with low-attenuation area (∗) in peripheral lung area in left upper lobe. Chest wall invasion (*arrow*) was also noted

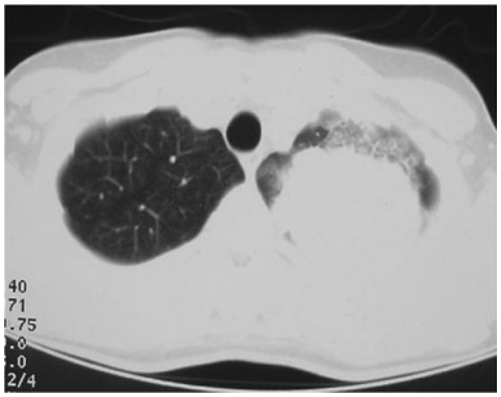

Fig. 2 Transverse CT image in lung window settings shows peritumoral areas of ground-glass attenuation

spindle cells (Fig. 3a). There was no metastasis in regional lymph nodes. Pathological staging was T3N0M0.

Immunostochemically, tumor cell expressed AE1/AE3 (Fig. 3b), Epithelial Membrane Antigen (EMA) (Fig. 3c) and co-expressed vimentin (Fig. 3d). High proliferative index was evidenced, about 70 % of tumor cell population expressed Ki-67 (Fig. 3e). Various mesenchimal tumors were excluded by immunohistochemistry. According to tumor cell immunoprofile, the final diagnosis was spindle cell—variant of sarcomatoid type of lung carcinoma.

Genetic Finding

Genomic DNA was isolated from the paraffin-embedded tissue sample of tumor, using xylene extraction of the paraffin, followed with the standard proteinase K digestion and phenol/chloroform extraction method.

Mutation analysis of TP53 exons 5, 6, 7, 8 and 9 has been performed by polymerase chain reaction and direct DNA sequencing, using the ABI Prism BigDye 3.1 sequencing system, according to manufacturer protocol.

Direct sequencing revealed an insertion of single thymine at exon 8 of the TP53 gene (Fig. 4). This frameshift mutation results in the misincorporation of 30 amino acids starting from amino acid 274, before a premature stop codon is introduced. The resulting truncated protein is predicted to be non-functional.

The patient subsequently received adjuvant chemotherapy (3 cycles of Gemcitabine, Cysplatin). Routine follow-up chest CT performed 6 months after surgery was normal, but just 2 months after that—what was 8 months after the surgery—CT showed very aggressive local recurrence (8×10 cm) and metastasis in soft tissue on the left side of the anterior thoracic wall (2×3 cm) (Fig. 5). This tremendously aggressive malignant behavior was more typical for sarcoma than lung carcinoma, because of its rapid, sarcomatous type of growth.

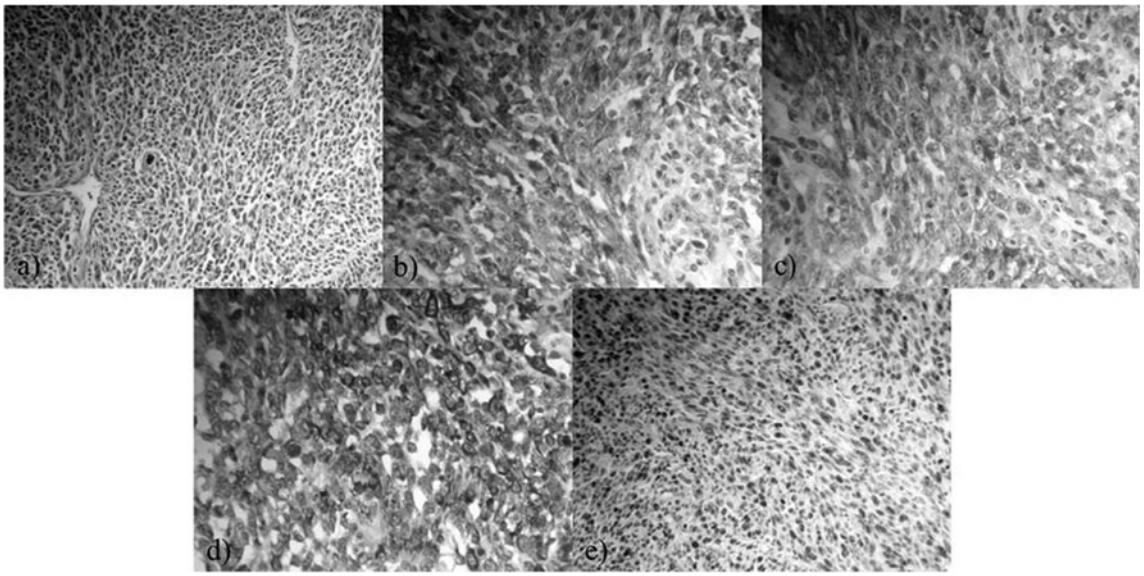

Fig. 3 **a** High cellular spindle cell carcinoma, H&E×40, **b** AE1/AE3 was expressed in tumor cells, ×40; **c** EMA positivity confirmed epithelial origin of tumor, ×40; **d** Vimentin was co-expressed in tumor cells, ×40; **e** High proliferative index in tumor, Ki-67×40

Discussion

The most commonly primary lung spindle cell tumor arise from epithelia and can be distinguished from true sarcoma on the basis of positive AE1/AE3. In the new WHO classification, sarcomatous tumors are of epithelial derivation and assigned as a new category. Sarcomatous carcinomas include the variants of spindle cell carcinoma, pleomorphic carcinoma, carcinosarcoma and giant cell carcinoma. Malignant spindle cell component constitutes from less than 10 % of the tumor, with majority component of squamous carcinoma, adenocarcinoma and large cell carcinoma. True mesenchimal lung tumors may be distinguished from spindle cell carcinomas by their morphologic and immunophenotypic properties. Some types of lung carcinoma and its variants express vimentin in tumor cells [3–6]. Spindle cell tumor of this patient co-expressed epithelial antibodies AE1/AE3 and EMA and mesenchimal antibody vimentin.

Radiologic characteristics of the tumor in our patient are very similar to previous reported data [7]. Sarcomatoid carcinomas can arise centrally or peripherally, but most commonly they present as solitary peripheral masses with a predilection for upper lobes. Chest radiographs show these tumors to be round or oval masses, often lobulated. Chest

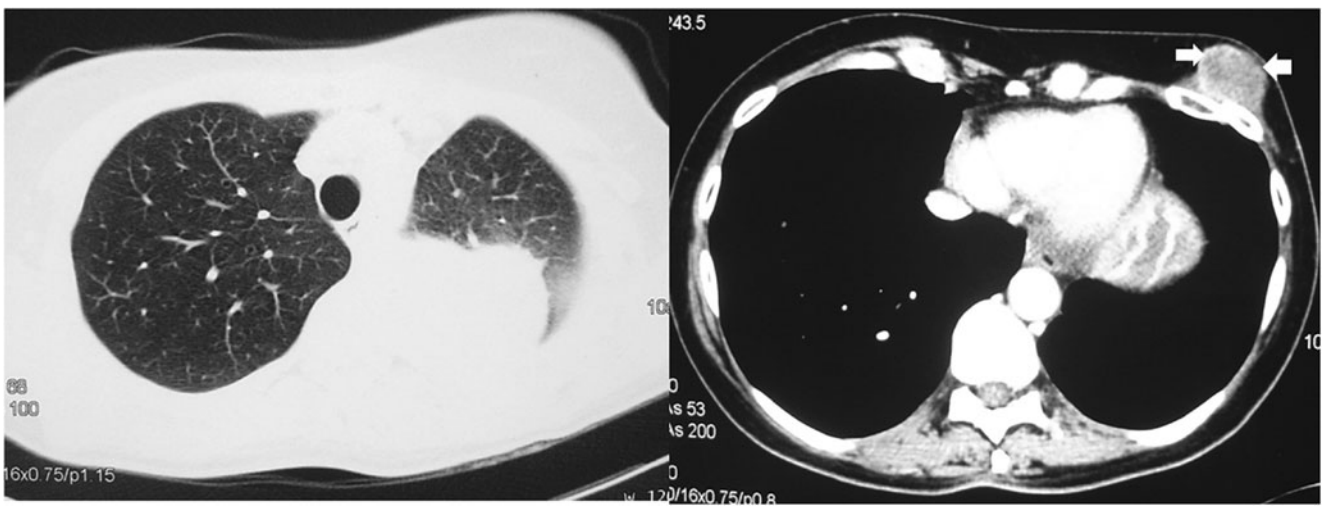

Fig. 4 Follow up axial CT scan 8 months after surgery shows local tumor recurrence (*left*) and tumor mass (*arrows*) in anterior thoracic wall (*right*)

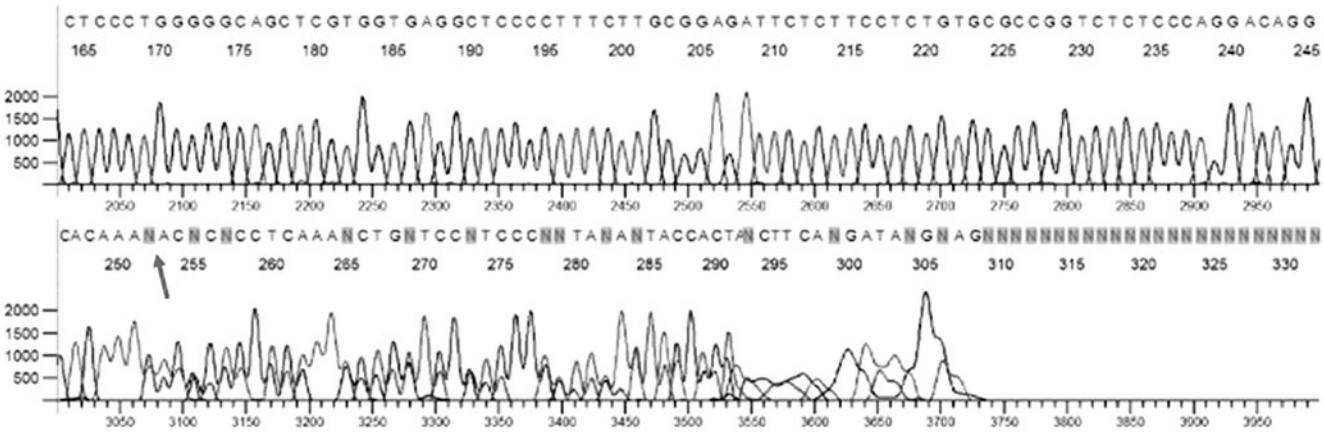

Fig. 5 Part of sequence (analyzed with reverse primers) of TP53 exon 8 that shows insertion of one nucleotide

radiographs, however, do not reveal any characteristic features of sarcomatoid carcinoma that help in the discrimination of them from other primary lung malignancies. CT scans can provide some clues as to the presence of sarcomatoid carcinoma: The tumor is located at the lung periphery and a central low-attenuation area is often depicted within the tumor. The peritumoral areas of ground glass attenuation are usually present. The tumor grows rapidly and more aggressively invades adjacent structures, such as chest wall or pleura, as it was in our case. Areas of central low attenuation within the tumors in the sarcomatoid carcinomas included not only necrosis or hemorrhage but also myxoid degeneration. Local recurrence is typical for this tumor. On chest CT it shows as same characteristics as a primary tumor [8, 9].

Frameshift mutation observed in our patient results in synthesis of truncated p53 that lucks C- terminal tetramerisation domain. This domain is necessary for oligomerisation and subsequently activity of the protein. Additionally, this mutation disrupts part of p53 DNA-binding domain. This genetic finding, that points on the loss of function of TP53 tumor-suppressor gene, is in accordance with highly aggressive malignant features of the tumor.

Multidisciplinary diagnostic approach to some tumors has become very useful for their final diagnosis [6, 10]. Primary lung spindle cell carcinoma, which usually presents as a large peripheral lesion, has a poor prognosis, even when early-stage disease is diagnosed and resected. Survival after relapse is very short. In our case, detected p53 frameshift mutation could explain why this entity had such a tremendously aggressive malignant behavior. Further investigations on a large number of cases should be performed, in order to gain a clearer understanding of the clinical characteristics, behavior and biologic features of primary lung spindle cell carcinoma.

Conclusion

Prognosis of lung spindle cell carcinoma might be determined by genetic finding or the sarcoma component of the tumor. Based on that, we wonder if strategies for treatment of soft tissue sarcomas could be adopted for the follow-up treatment of patients with pulmonary lung spindle cell carcinoma. In addition to standard lung carcinoma oncological treatment maybe this type of lung carcinoma could be treated as sarcoma, because of its rapid, sarcomatous type of growth. Therapeutic response is a top priority issue to be solved, so that suitable treatment strategies could be planned.

Conflict of interest Authors declare no conflicts of interest.

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