

# Three cases of combined small cell lung carcinoma with review of the literature

## Kombine küçük hücreli akciğer karsinomu: Literatür eşliğinde 3 olgu sunumu

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### ABSTRACT

Combined small cell lung carcinoma is an uncommon entity and constitutes 1-3% of all cases with small cell lung carcinoma (SCLC). We reported three cases of combined small cell lung carcinoma. All the cases were male (ages: 77, 60 and 55 years, respectively) with a history of heavy smoking and presented with lung masses. Additionally, first case had been a history of asbestos exposure for 5-6 years. Histopathological examination of biopsy specimens revealed a rare variant of small cell lung carcinoma ie combined small cell lung carcinoma. In addition to histological evidence of small cell lung carcinoma, the first biopsy specimen also contained areas of squamous cell carcinoma and the other two biopsy specimens revealed adenocarcinomatous cells. Immunohistochemical findings supported the diagnosis. Combined small cell lung carcinoma is very rare, but is nevertheless a well described diagnostic category among lung cancers. In this case report, because of the rarity of these tumors, we discussed combined small cell lung carcinoma in view of the literature.

**Key word:** Combined small cell carcinoma, lung

### ÖZET

Kombine küçük hücreli akciğer karsinomu nadir bir antitedir. Tüm küçük hücreli karsinom olgularının %1-3'ünü oluşturur. Burada kombine küçük hücreli karsinomlu 3 olgu sunulmuştur. Tüm olgular erkek olup yaşları sırasıyla 77, 60 ve 55 idi. Hastaların tümü ağır sigara içicisiydi. Akciğer kitlesi ile kliniğe başvurmışlardı. Ek olarak ilk olgunun 5-6 yıllık asbestoz maruziyeti öyküsü vardı. Histopatolojik incelemede küçük hücreli karsinom alanları yanı sıra ilk olguda skuamöz hücreli karsinom ve diğer ikisinde adenokarsinom alanları izlenmiş, bulgular immünohistokimyasal sonuçlarla da desteklenmiştir. Kombine küçük hücreli karsinom nadir bir varyant olmakla birlikte tanımlanmış ayrı bir kategoridir ve burada sık karşılaşılmayan bu varyanta sahip 3 olgu klinik, radyoloji ve patolojik olarak sunulmuş, literatür eşliğinde tartışılmıştır.

**Anahtar sözcükler:** Kombine küçük hücreli karsinom, akciğer

### INTRODUCTION

Under the headline of small cell lung carcinoma (SCLC), two different categories have been recognized according to the criteria of World Health Organization/International Association for the Study of Lung Cancer (WHO/

IASLC) since 1999. These are; SCLC and combined SCLC (1). SCLC accounts for 10-20% of all lung cancers and among them the incidence of combined SCLC has been reported as 1-3%. Affected patients are usually male and heavy smokers (2,3,4,5). Combined SCLC contains any subtypes of non-small cell lung carcinoma (NSCLC) such as adenocarcinoma (AC), squamous cell carcinoma (SCC), large cell carcinoma and less commonly spindle cell or giant cell carcinoma in addition to small cell carcinoma

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areas (1). In this report, we present three cases of combined SCLC and review the literature.

### CASE REPORTS

**Case 1:** A 77-year-old man was admitted to the hospital because of dispnea and cough. He had a history of asbestos exposure and heavy cigarette smoking. Chest computerized tomographic (CT) scans demonstrated a 9x10 cm lung mass located in the left upper lobe. Pleural involvement and contralateral hilar lymphadenopathy were detected, and so the case was evaluated clinically as Stage III B. Bronchoscopic and pleural biopsies were performed for diagnosis.

Bronchoscopic and pleural biopsy specimens revealed two different tumor cell types. The SCLC component was characterized by small round cells which had finely granular and hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm. A very common artifact, which is defined as “nuclear molding” was seen. The other part of the tumor was composed of medium-sized cells with pleomorphic nuclei containing vesicular chromatin and abundant keratinized eosinophilic cytoplasm. This component was diagnosed as squamous cell carcinoma (Figure 1).

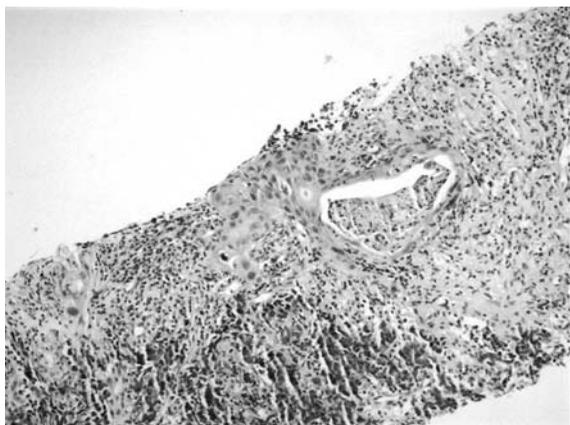


Figure 1. Squamous cell and small cell carcinoma areas (HE x100)

He was treated with 4 cycles of chemotherapy involving cisplatin and etoposide.

**Case 2:** A 62-year-old man with a strong history of cigarette smoking (100 packet/year) was hospitalized because of vena cava superior syndrome. On chest CT scan, a 13x7x5 cm mass was found in the right paratracheal area. On the radiological examination distant metastases were detected in surrenal glands bilaterally. A supraclavicular lymphadenopathy was found on clinical examination and it was excised for microscopic evaluation. By this data, the case was clinically evaluated as Stage IV. He was treated with cisplatin, etoposide and thoracic radiotherapy was performed for vena cava superior involvement.

The histological findings of supraclavicular lymph node were very similar to Case 1 regarding the SCLC component. However in this tumor, the SCLC component was admixed with irregular solid nests and glandular structures of adenocarcinoma which had medium-sized cells with hyperchromatic nuclei and abundant cytoplasm (Figure 2).

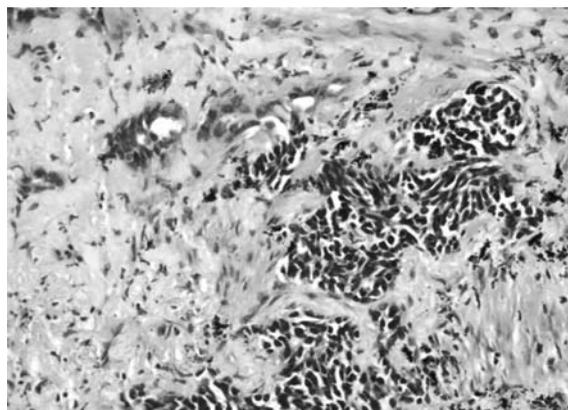


Figure 2. Adenocarcinoma and small cell carcinoma areas (HE x100).

**Case 3:** A 55-year-old man was admitted to the hospital with complaints of cough and chest pain. Radiological studies suggested a mass in 1 cm diameter which originated from the superior segment of the right lower lobe and infiltrated through the upper lobe. Bilateral mediastinal lymphadenopathy was also detected

and wedge resection with mediastinal lymph node excision was performed.

Biopsy materials both from lung and lymph node revealed tumoral involvement. Histopathologically, SCLC component was similar to the other cases whereas other part of the tumor was consisted of moderately differentiated adenocarcinoma that composed of adenoid structures localized within desmoplastic stroma (Figure 3).

Stage of tumor was evaluated as III B according to T1 N3 M0. Both chemotherapy and radiotherapy are being planned for this patient.

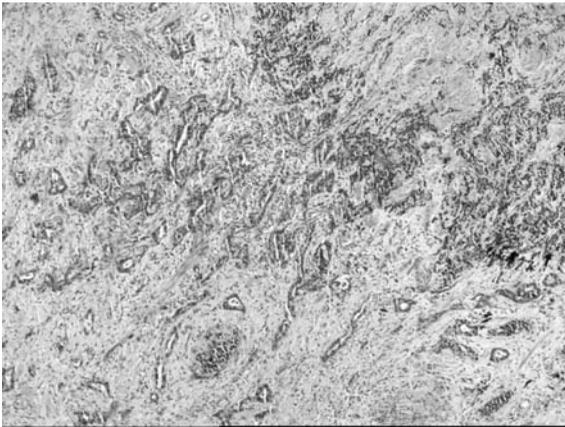


Figure 3. Adenocarcinoma and small cell carcinoma areas (HE x50).

### Histochemistry and Immunohistochemistry

Histochemically, mucin stain was applied to all cases. Immunohistochemistry was performed using the following antibodies; Synaptophysin (Neomarker, 1/100, RM-9111), Chromogranin A (Neomarker, 1/100, MS-382), Neuron Specific Enolase (NSE) (Neomarker, 1/100, MS-335), Thyroid Transcription Factor-1 (TTF-1) (Novocastra, 1/100, NCL-L-TTF-1), High Molecular Weight Cytokeratin (HMWC) (Neomarker, 1/50, MS-346) and Carcino Embriogenic Antigen (CEA) (Neomarker, 1/50, MS-613).

SCLC component of all tumors was negative for mucin stain and immunoreactive with Synaptophysin, Chromogranin A, NSE and

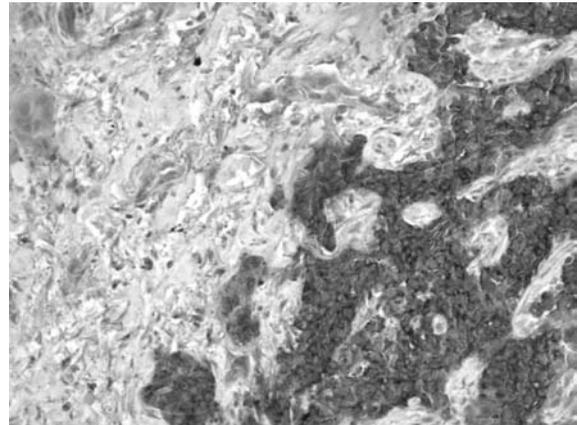


Figure 4a. Immunostaining of Synaptophysin adjacent to adenocarcinoma areas in Case 3 (x100).

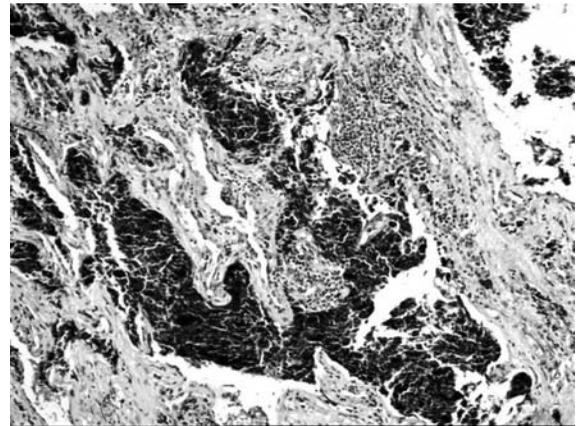


Figure 4b. Immunostaining of Chromogranin A in small cell carcinoma cells of Case 1 (x100).

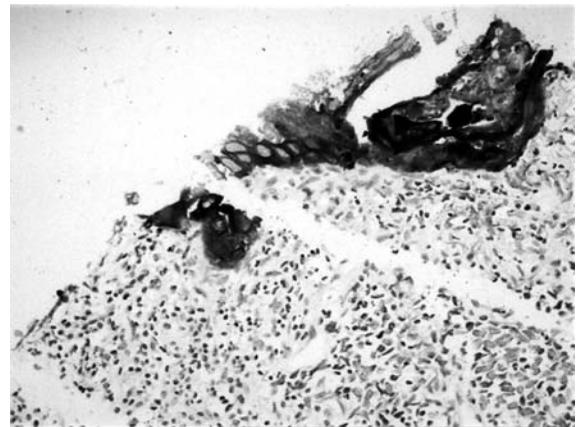


Figure 5. HMWC positivity in squamous cell carcinoma areas of Case 1 (x200).

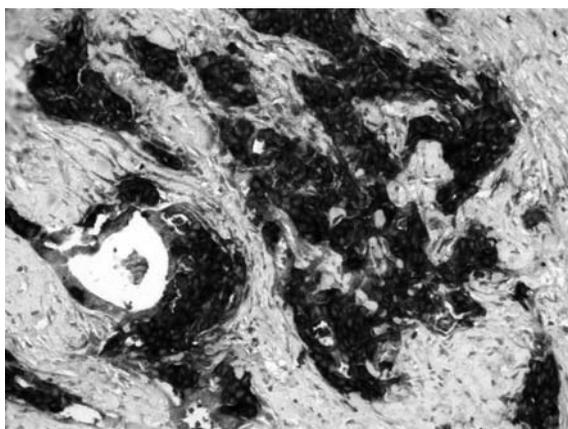


Figure 6. CEA positivity in adenocarcinoma areas of Case 2 (x200).

TTF-1 (Figure 4a and 4b). Intracytoplasmic mucin was shown in AC areas. SCC and AC components of tumors showed positive immunoreactivity with HMWC and CEA respectively, with the characteristic dot-like accentuation in their cytoplasm (Figure 5 and 6) (Table 1). AC cells were positive with TTF-1, whereas SCC cells were negative.

Table 1. Immunohistochemical results.

Case		NSE	Chromogranin A	Synaptophysin	HMWC	CEA	TTF-1
1	SCLC	+	+	+	-	-	+
	SCC	-	-	-	+	-	-
2	SCLC	+	+	+	-	-	+
	AC	-	-	-	-	+	+
3	SCLC	+	+	+	-	-	+
	AC	-	-	-	-	+	+

## DISCUSSION

Many histopathologic classifications of SCLC have been proposed during the last 30 years. However, combined type SCLC as a separate category was proposed for the first time by WHO in 1981. SCLC was then subdivided into oat cell, intermediate, and combined type categories. After a while, WHO criteria were modified by IASLC; the distinction between oat cell and intermediate types was discarded and both

categories were referred to as small cell carcinoma. In addition, a new category -the mixed small cell/large cell carcinoma- was introduced as a subtype of SCLC (2,4). In 1999, WHO adopted the IASLC pathology panel to comprise the core membership of WHO committee and to develop a new revised classification of lung and pleural tumors. This classification is called the WHO/IASLC Histological Classification of Lung and Pleural Tumors. In this classification mixed small cell/large cell carcinoma subtype was discarded and finally a consensus was reached to classify SCLC subtypes as pure SCLC and combined SCLC (1,6).

Combined SCLC is defined as a tumor with predominant features of small cell carcinoma with a minor (5% or less) component of any histological types of NSCLC. Among these components squamous cell carcinoma, adenocarcinoma and large cell carcinoma are commonly seen but spindle cell and giant cell carcinoma variants have been also noted (1,7-9).

In SCLC, tumor cells are small, usually 7-10 µm in size and fusiform shaped. They have a higher nuclear- cytoplasmic ratio with lack of nucleoli and they frequently demonstrate nuclear molding, smearing or crush artifact which are termed as Azzopardi effect (7). Other types of lung carcinomas, e.g. SCC or AC can be differentiated from small cell carcinoma by their abundant cytoplasm, different nuclear features, histologic pattern and immunohistochemical findings.

There is no difference in treatment modality and prognosis between combined and pure SCLC according to the literature (4,10). Adverse clinical prognostic factors for both types of SCLC include advanced stage of the disease, poor performance status, elevated serum LDH or alkaline phosphatase, low plasma albumin and low plasma sodium levels (1). At molecular level, c-kit positivity in tumor cells reported as an independent prognostic factor (11). As to the treatment, chemotherapy and radiotherapy are performed for these patients.

In this report, three cases of combined SCLC of an uncommon type were presented. The first one showed a combination of small cell carcinoma with squamous cell component. Both second and third cases were composed of small cell carcinoma and adenocarcinoma. All of the cases were at an advanced stage so chemotherapy and radiotherapy were performed for the first and the second cases, and same protocols are planning for the last patient.

Combined SCLC is an uncommon type of the lung carcinomas and during clinical and histopathological examination, the diagnosis of combined SCLC especially from bronchoscopic biopsy specimens may be difficult. Differentiation between and combined SCLC is important because of their different therapy modalities than those performed for NSCLC.

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