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CASE REPORT:

Mixed Lung Cancer in 46 Years Old, Male Smoker, Untreated Patient

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ABSTRAK

Keganasan pada paru terdiri dari banyak tipe yang secara klinis dibedakan menjadi SCLC dan NSCLC. Small cell lung cancer (SCLC) merupakan 20% dari keganasan paru yang secara morfologi merupakan neoplasma neuroendokrin. Kasus combined SCLC ini merupakan salah satu tipe SCLSC yang dilaporkan karena kejarangannya. Insiden yang dilaporkan adalah sekitar 1-14,6% dari semua tipe SCLC. Secara fenotip gambaran morfologinya merupakan campuran dari SCLC dan NSCLC, sehingga terkadang diagnosis dengan menggunakan pengecatan rutin akan sangat sulit dilakukan. Selain itu c-SCLC adalah tipe SCLC yang sangat agresif. Pada kasus ini dilaporkan seorang laki-laki yang dirujuk karena adanya masa soliter paru disertai metastasis di otak dan limfonodi. Diagnosis histopatologi menunjukkan gambarna campuran dari adenokarsinoma, karsinoma sel skuamosa dan karsinoma *large cells.* Dilakukan panel imunohistokimia meliputi *CK-7, CK-20, TTF-1, P63 dan Chromoganin,* sehingga dapat dipastikan diagnosisnya sebagai c-SCLC.

Kata kunci: *combined* SCLC, nodul soliter.

ABSTRACT

Lung cancer is a large heterogeneous family of malignancies, with tumors containing more than one subtype are very common. Over 50 different histological variants are recognized within the WHO typing system. Small Cell Lung Cancer comprises approximately 20% of all lung cancers and exhibits a neuroendocrine phenotype while Non Small Cell Lung Carsinoma (NSCLC) lacks these features and makes up the remaining 80% of cases. This case was reported in view of the rarity of this combination of morphologic patterns. The incidence of c- SCLC (Combined- Small Cell Lung Carsinoma) has been reported ranging from less than 1% to 14.6% of all SCLC. Mixed lung cancer in untreated patients suggests a common endodermal origin for c-SCLC which contains small-cell and non-small-cell pulmonary tumors. Quoix et al found that presentation as a solitary pulmonary nodule (SPN) is particularly indicative of a c-SCLC. Combined- Small Cell Lung Carsinoma contains a squamous cell and/or adenocarcinoma component. It's becoming more important for pathologists to correctly subclassify NSCLC's as distinct tumor entities, or as components of c-SCLC cause it's more agrresive. A 46-year-old smoker man was referred because of rapid growth of a solitary nodule mass revealed by chest radiography with brain and limfonodes metastases. There was mixed histological feature including adenocarsinoma, squamous cell carsinoma and large cell carsinoma. The patient is dead after a few weeks later. It was revealed a panel immunohistochemistry stain (CK-7, CK-20, TTF-1, P63 and Chromoganin). It was concluded as c- SCLC.

Keywords: *Mixed lung cancer, combined Small Cell Lung Carsinoma (c-SCLC), solitary nodul*

INTRODUCTION

Lung cancer is a large heterogeneous family of malignancies, with tumors containing more than one subtype being very common. Over 50 different histological variants are recognized within the World Health Organization (WHO) typing system. Tobacco smoke is a major etiological factor, especially in Small cell lung carsinoma (SCLC). Small cell lung carsinoma comprises approximately 20% of all lung cancers and exhibits a neuroendocrine phenotype while Non Small Cell Lung Carsinoma (NSCLC) lacks these features and makes up the remaining 80% of cases (Travis *et al.,* 2004). Small cell lung cancer exhibits a more aggressive phenotype. Mixed lung cancer is neoplasm characterized by mixed histology feature. Mixed lung cancer in untreated patients suggests a common endodermal origin for Combined- Small Cell Lung Carsinoma (c-SCLC) which contains small-cell and non-small-cell pulmonary tumors (Roggli, *et al.,* 1985).

However, since there are different forms of malignant tumors generally exhibit diverse genetic, biological, and clinical properties, including response to treatment, accurate classification of lung cancer cases are critical to assuring that patients with lung cancer receive optimum management. With the use of "molecularly targeted" agents, it is becoming more important for pathologists to correctly subclassify NSCLC's as distinct tumor entities, or as components

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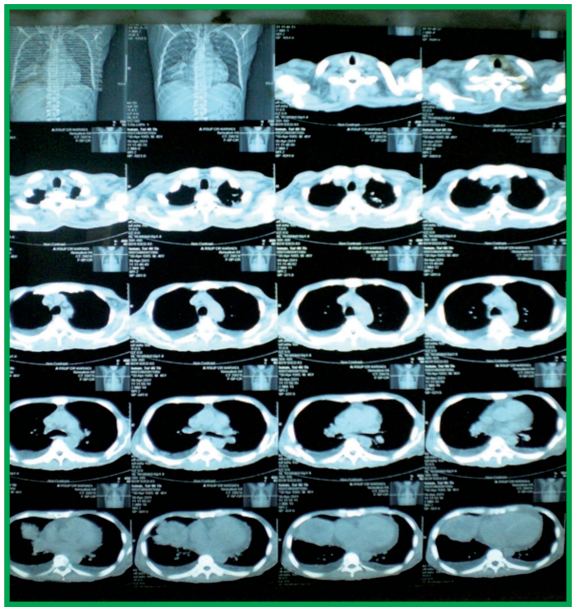

Figure 1. CT scan show a mass in S 4-5 of the right lung and multiple nodul in the liver.

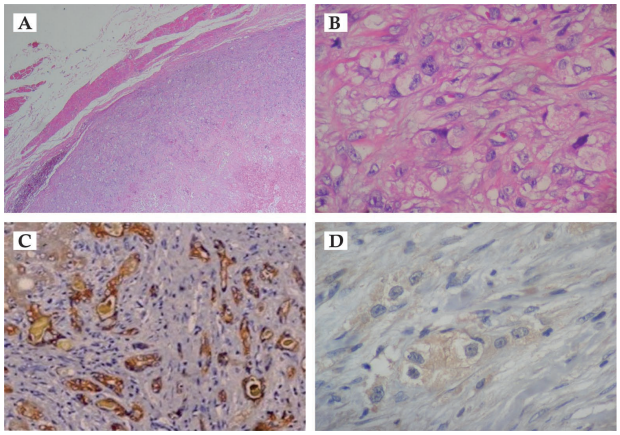

Figure 3. Lymphonodes biopsy. A. HE. Staining 20x. B. HE staining 40x. C. CK7 staining. D. Chromoganin staining.

of c-SCLC's. This case was reported in view of the rarity of this mixed of morphologic patterns, and it was revealed a panel immunohistochemistry stain (CK-7, CK-20, TTF-1, P63 and Chromoganin) to conclude whether it was c- SCLC or other type of lung cancer. There were some difficulties to diagnose this case based on Hematoxilyn eosin stain only. This case was among the most challenged case for pathologist. Mixed histological features could drive to wrong interpretation and finally wrong management. The incidence of c-SCLC has been reported ranging from less than 1% to 14.6% of all SCLC.

CASE REPORT

A 46-year-old smoker man presented at a local clinic complaining cough almost for 1 year, but as chest

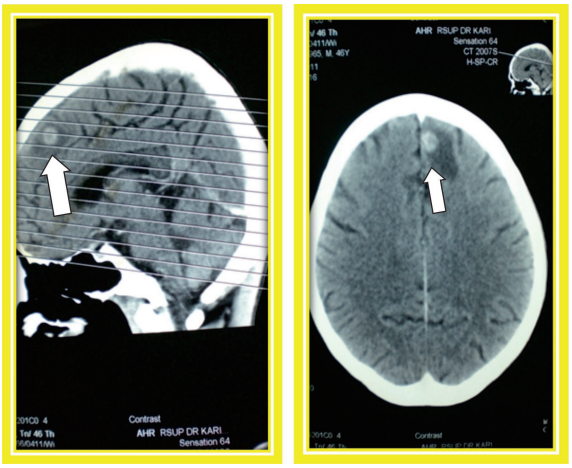

Figure 2. The arrow showed a single nodule in the brain.

radiography revealed there were no abnormalities, he was released and followed up by radiology screening. One month later he coughed out hemosputum and experiencing dispnea, he returned to the same clinic and the patient was therefore referred to our hospital. He was referred because of rapid growth of a solitary nodule mass indicated by chest radiography with brain and limfonodes metastases. Chest radiography revealed a mass lesion in the right mid-lung field and bilateral pleural effusion. Chest computed tomography (CT) was performed on admission revealed a mass in S 4-5 of the right lung, infiltrate to the right Pulmonary artery, and also hilar limfonodes (fig. 1).

Cranial magnetic resonance imaging on Figure 2 revealed a mass, while abdominal CT (Figure 1) revealed multiple noduls in the liver, and limfadenopathy of right paratracheal region. Bone scintigraphy revealed metastatic on processus trasversus veterbrae thorac 3,5,7,9,10,11 and lumbal 1. The limfonode biopsy two days later by the surgeon, revealed tumor cell with increased chromatin and round nuclei with a high nuclear/cytoplasmic ratio, and abundant cytoplasm with intercellular bridges, clear cytoplasm, prominent nucleoli, and keratin. Trans thoracal needle biopsy and pleural effusion revealed features of adenocarsinoma, squamous cell carcinoma and large cell carsinoma, namely proliferation of medium- large carcinoma cells with increased chromatin, round nuclei with a high N/C ratio. There were abundant cytoplasm respectively, and small areas of artefactually crushed cells and nuclei, rosset and ink blot appearance. It was conclude as mixed histological feature of small cell carcinoma, squamous cell carsinoma, adenocarsinoma and large cell carsinoma. Microscoping finding with Hematoxilyn eosin staining showed here (Figure 3.).

The tumor was diagnosed as c- SCLC based

on the findings of the rapid enlargement of the tumor and mixed histological feature of limfonode biopsy, transthoracal biopsy and pleural effusion cytology. Therefore, patient was administered paliatif treatment designed for cT4N1M1 c- SCLC. However, the clinical presentation became worsen and the patient was death after a few weeks later.

Immunohistochemical examination performed on each component showed negative staining for TTF-1, and CK-20, positive staining for CK-7 and AE1/3 on the membrane of cytoplasm and the cytoplasm, positive for P63 in the cytoplasm and the nuclear, and partial positive for Chromoganin in the cytoplasm (Figure 3). Based on these results, the patient was diagnosed as combined small cell carcinoma containing three malignant components: large cell carsinoma, squamous cell carcinoma and adenocarsinoma cell carcinoma.

DISCUSSION

There were some difficulties to diagnose this case based on Hematoxilyn eosin stain only. This case is among the most challenging case of pathologist. It is rare and more aggresive. Mixed histological features could lead to wrong interpretation and finaly wrong management. Under WHO-2004, lung carcinomas are divided into 8 major taxonomy namely: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, carcinoid tumor, salivary gland-like carcinoma.

SCLC is generally considered to be the most aggressive form of lung cancer, with the worst long term prognosis and survival rates. Small cell lung cancer comprises approximately 20% of all lung cancers and exhibits a neuroendocrine phenotype while NSCLC lacks these features and makes up the remaining 80% of cases. Small cell lung cancer exhibits a more aggressive phenotype (Roggli VL *et al.,* 1985, Travis *et al.,* 2004) .

Mixed lung cancer in a smoker, old untreated patients suggests a common endodermal origin for c-SCLC which contains small-cell and non-small-cell pulmonary tumors. Quoix *et al* (1990) found that presentation as a solitary pulmonary nodule (SPN) is particularly indicative of a c-SCLC. Combined- Small Cell Lung Carsinoma contains a squamous cell and/or adenocarcinoma component. The incidence of c- SCLC has been reported to range from less than 1% to 14.6% of all SCLC. In a study of 408 consecutive patients with SCLC, Quoix *et al* (1990) found that presentation as a solitary pulmonary nodule (SPN) is particularly indicative of a c-SCLC about 2/3 of their SPN's were pathologically confirmed to be c-SCLC's containing a large cell carcinoma component (Masashi G *et al.,* 2004; Choe B.P *et al.,* 2006; Quoix *et al.,* 1990).

In the view of the evident hilar adenopathy, rapid enlargement of the tumor, and long distance metastases, this man suggested to develop a small cell carsinoma. Based on clinical finding, radiological examination and histopathological approach, it was concluded as c-SCLC. In most cases, lung cancers probably result from the malignant transformation of a single multipotent cell. Approximately 98% of lung cancers are carcinoma, a term which implies that the tumor derives from transformed epithelial cells, or consists of cells that have acquired epithelial characteristics as a result of cell differentiation (Patrick L *et al.,* 2009). In most cases of c-SCLC, genomic and immunohistochemical studies suggest that the morphological divergence of the separate components in a c-SCLC occurs when a SCLC-like cell is transformed into a cell with the potential to develop NSCLC variant characteristics, and not vice versa. Daughter cells of this transdifferentiated SCLC-like cell then repeatedly divide and, under both intrinsic genomic and extrinsic environmental influences, acquire additional mutations, a process known as tumor progression. The end result is that the tumor acquires specific cytologic and architectural features suggesting a mixture of SCLC and NSCLC (Tatematsu A *et al.,* 2008). Other molecular studies, however, suggest that - in at least a minority of cases, independent development of the components in c-SCLC occurs via mutation and transformation in two different cells in close spatial proximity to each other, due to field cancerization. In these cases, repeated division and mutational progression in both cancer stem cells generate a biclonal collision tumor (Zhang H *et al.,* 2005; Zamecnik J *et al.,* 2002)

Regardless of which of these mechanisms give rise to the tumor, recent studies suggest that, in the later stages of c-SCLC oncogenesis, continued mutational progression within each tumor component results in the cells of the combined tumor developing molecular profiles that more closely resemble each other than they do cells of the "pure" forms of the individual morphological variants (Aoyagi Y *et al.,* 2001). This molecular oncogenetic convergence likely has important implications for treatment of these lesions, given the differences between standard therapeutic regimens for SCLC and NSCLC. Combined- Small Cell Lung Carsinoma also occurs quite commonly after treatment of "pure" SCLC with chemotherapy and/or radiation, probably as a result of a combination of tumor genome-specific "progressional" mutations, stochastic genomic

phenomena, and additional mutations induced by the cytotoxic therapy (Radice PA, *et al.,* 1982). There was no evidence of theraupetic transformation induced on this patient because he never get radiation or chemotherapy treatment before he was referred. The most common forms of NSCLC identified as components within c-SCLC are large cell carcinoma, adenocarcinoma, and squamous cell carcinoma. Rarer variants of NSCLC are seen less commonly, such as combinations with carcinoids, spindle cell carcinoma, and giant cell carcinoma (Masashi G *et al.,* 2004). Giant cell carcinoma components are seen much more commonly in patients who have undergone radiation (Radice PA, *et al.,* 1982; Masashi G *et al.,* 2004). In this patient, there are three component: large cell carcinoma, adenocarcinoma and squamous cell carcinoma.

The classification of lung cancer has always been primarily based on the morphologic assessment of routinely stained histological sections, but this approach may be difficult or even unfeasible in cytological preparations or small biopsies. A more accurate characterization of NSCLC, however, may be hard in carcinomas lacking clear-cut signs of differentiation. But the incorporation into the diagnostic algorithm of poorly differentiated carcinomas of an immunohistochemical panel including markers of squamous (high-molecular-weight cytokeratins, p63), glandular (TTF-1, cytokeratin 7) cell and neuroendocrine differentiation (synaptophysin, CD56, and chromogranin, Bcl-2) seems to be the most promising (Kargi A *et al.,* 2007).

The limfonode biopsy specimen of this patient was stained by AE1/3, P63, CK7, TTF-1 and chromoganin. The evaluation of lung cancer for gene mutations, gene amplification, tumor-related angiogenesis, expression levels of DNA repair genes and genomic or proteomic profiles represents an exciting challenge for the pathologist in the near future. With the approval and use of newer "molecularly targeted" agents revealing differential efficacies in specific subtypes and variants of NSCLC, it is becoming more important for pathologists to correctly subclassify NSCLC's as distinct tumor entities, or as components of c-SCLC.

CONCLUSION

The histopathologic distinction between small cell and non small cell lung cancer is the basis for most clinical decisions in the management of pulmonary neoplasm. The existence of neoplasm with mixed small cell and non small cell differentiation on a smoker- old, untreated patient is particularly indicative of c-SCLC. It is remain unclear wether these tumors represent as separate histologic variant of lung cancer, a subtype of small cell cancer, or even a treatment- induced morphologic chance.

Diagnosing c-SCLC case based on the morphologic assessment of routinely stained histological sections may be difficult or even unfeasible in cytological preparations or small biopsies. The incorporation into the diagnostic algorithm of poorly differentiated carcinomas of an immunohistochemical panel including markers of squamous (high-molecular-weight cytokeratins, p63), glandular (TTF-1, cytokeratin 7) cell and neuroendokrin differentiation (synaptophysin, CD56, chromogranin, and Bcl-2) seems to be the most promising approach.

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