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Transformation of SCLC into NSCLC-squamous type with invasive fungal co-infection

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Abstract: Small Cell Lung Cancer (SCLC) is a neuroendocrine tumor with and poor prognosis. Transformation commonly occurs from NSCLC to SCLC, that caused by chemotherapy, immunotherapy, and targeted therapy resistance. This case shows a 5% rare case transformation from SCLC to NSCLC. A 69-year-old man had hemoptysis, dyspnea, and chest pain for a month. In 2017, the history of SCLC received 6 series of cisplatin-etoposide chemotherapy. CT-Scan Thorax RECIST was stable disease, and the rest of the treatment was. In April 2022, RECIST showed that the mass increased. KOH sputum obtained hyphae and conidia. Forceps biopsy found Aspergillus. Re-biopsy was squamous cell carcinoma. SCLC transformation is characterized by TP53 and RB1 gene mutations. Interferon-γ (INFγ) production impairment due to IL12RB1 mutation caused macrophages to eliminate intracellular fungi. Fungal interaction (integrin-β1) on alveolar epithelial cells increases EGFR activation, cell damage, and the development of fungal invasion. Patient was given fluconazole and carboplatin-paclitaxel chemotherapy 6 series, then maintenance paclitaxel, currently stable.

Keywords: *Invasive fungal infection, Squamous cell lung cancer, Transformation SCLC.*

1. Introduction

Lung cancer is a cell growth that is uncontrolled and causes excessive and abnormal pathological damage is included in malignant tumors [1]. Lung cancer is the leading cause of cancer death worldwide, with an estimated 2.1 million new cases and 1.8 million deaths in 2018. The incidence of lung cancer in Indonesia at a young age is increasing compared to other countries [2]. In 2018, WHO reported 30,023 new cases of lung cancer in Indonesia and 26,095 deaths, about 2.6% of total deaths in Indonesia [3]. Small cell carcinoma lung cancer (SCLC) has a prevalence of approximately 250,000 new cases and at least 200,000 deaths globally each year [2]. Research by Chozin *et al.* mentioned that the profile of SCLC patients at Saiful Anwar Malang Hospital was lower at around 8.1%, while the type of non-small cell carcinoma lung cancer (NSCLC), such as squamous cell carcinoma, amounted to 16.2% [4]. Lung cancer patients often experience opportunistic infections. Invasive infections of Aspergillus fungi, Pneumocystis Cryptococcus often occur in immunocompromised patients, such as lung cancer, who are given chemotherapy [5]. Some fungal pathogens initiate infection through surface proteins from pathogen-host interactions and cause multiple lesions, especially in tissues [6]. NSCLC patients often transform into SCLC [7]. However, in this case, there was a change in transformation from SCLC to NSCLC, with a very rare incidence of about 5% [8].

2. Method

Patient Mr. P was 69 years old, working as a welder in a factory for 30 years. In April 2022, the patient had a bloody cough with accumulation of 200 ml per day for 1 month. He felt shortness of

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breath for 3 weeks, and right chest pain for the last 1 month. He has decreased appetite, weight loss of 3 kg in 1 month. Patient has a history of smoking 5 cigarettes/day for 30 years (Brinkman's index 150, light smoker), quit since 2017. This patient also diagnosed with COPD since 2017 according to vital lung capacity test FEV1 66% (GOLD 2). Patient with history of SCLC in 2017 with 6 series of Cisplatin-Etoposide chemotherapy, advised to rest chemotherapy with evaluation of Thorax CT scan + RECIST every 3 months. But the patient did not control it again.

On physical examination, vital signs were within normal limits, and oxygen saturation was normal; right lung sounds were found to be decreased, and percussion was faint. Laboratory dated 11/05/2022 found an increase in tumor markers NSE 54.43 ng/mL (N < 16.3) but normal in CEA 2.71 ng/mL (N < 5.0) and AFP 1.38 mmol/L (N ≤ 7.0). Chest X-ray (CXR) from 2017 to 2022 revealed an enlarged right lung mass (Figure 1).

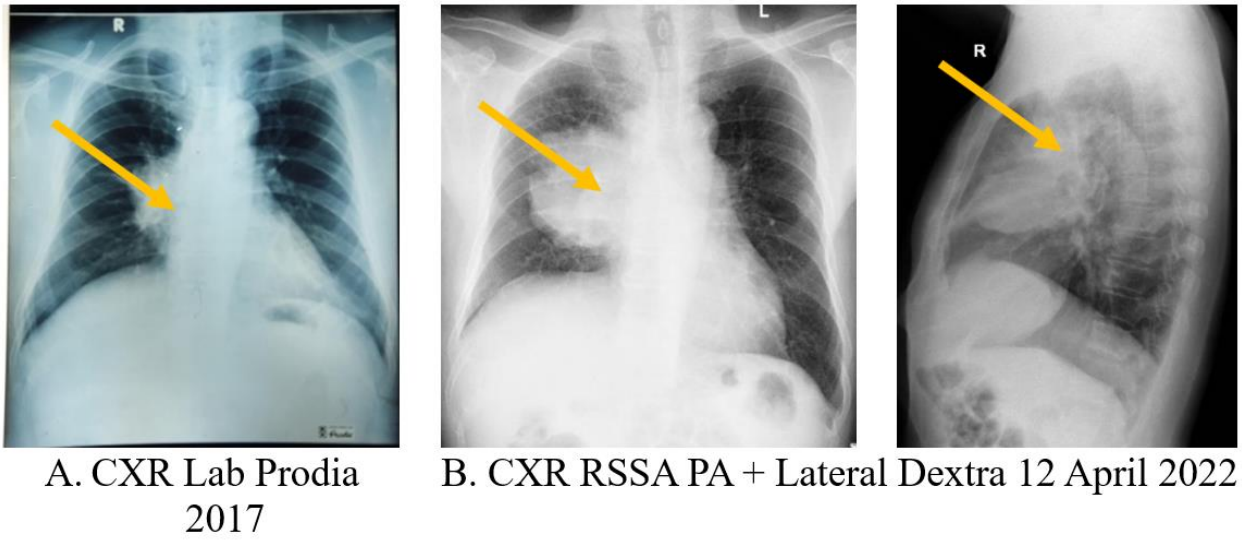

Figure 1.
A. Right Lung Mass; B. Homogeneous opacity, well-circumscribed, irregular edge, perihilar dextral, looking like a right lung mass with left lung emphysematous.

The patient underwent CT-Scan Thorax with repeat contrast in April 2022 and obtained a lung mass of 110 mm (Figure 2).

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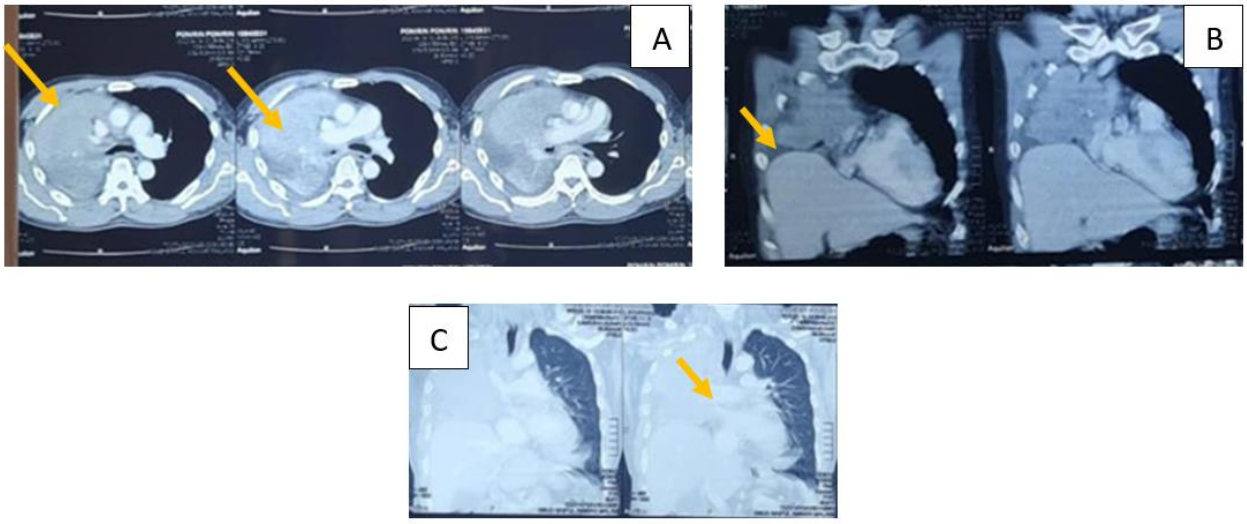

Figure 2.
A. Right lung mass with involvement of a. pulmonic, attached to v. cava superior, Obliterating the right main bronchus, causing obstructive atelectasis of the right lung, B. Right pleural effusion, C. Mediastinal lymphadenopathy.

The results of KOH sputum culture for 3 days in May 2022 showed conidia and hyphae morphology.

Table 1.
The results of KOH sputum culture for 3 days in May 2022 obtained conidia and hyphae morphology.

11/05/22	12/5/22	13/5/22
No budding cell, hyphae, or conidia morphology found (typical fungal morphology)	Found morphology of conidia and hyphae	No budding cell, hyphae, or conidia morphology found (typical fungal morphology)

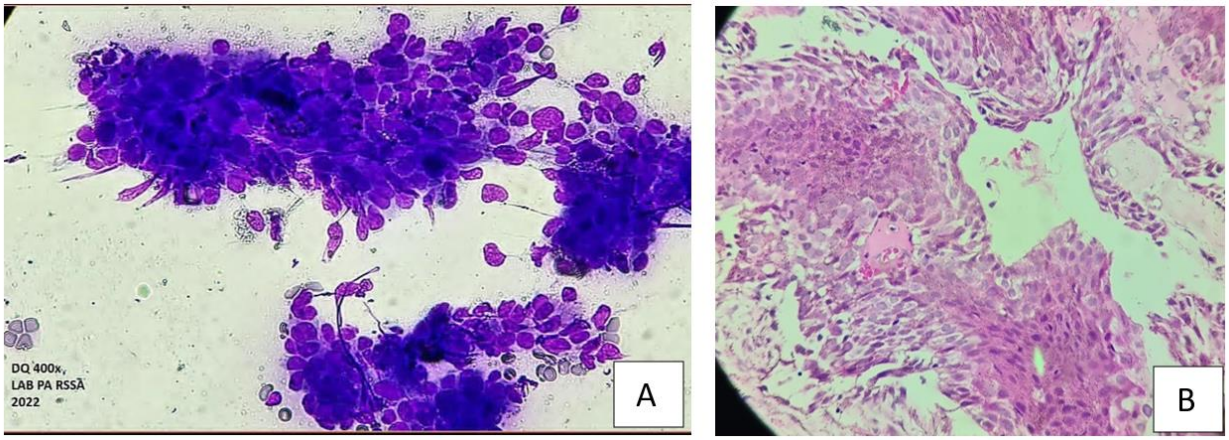

Figure 3.
A. FNAB of the right chest of Saiful Anwar Hospital 12/12/2017 showed small cell carcinoma with hyperchromatic oval-shaped cell nuclei, some without cell nuclei, scant cytoplasm, and molding pattern. B. Result of transbronchial needle aspiration (TTNA) on 19/05/2022 showed atypical cells with well-differentiated keratinization and presence of cytoplasm, which is squamous-type carcinoma cells.

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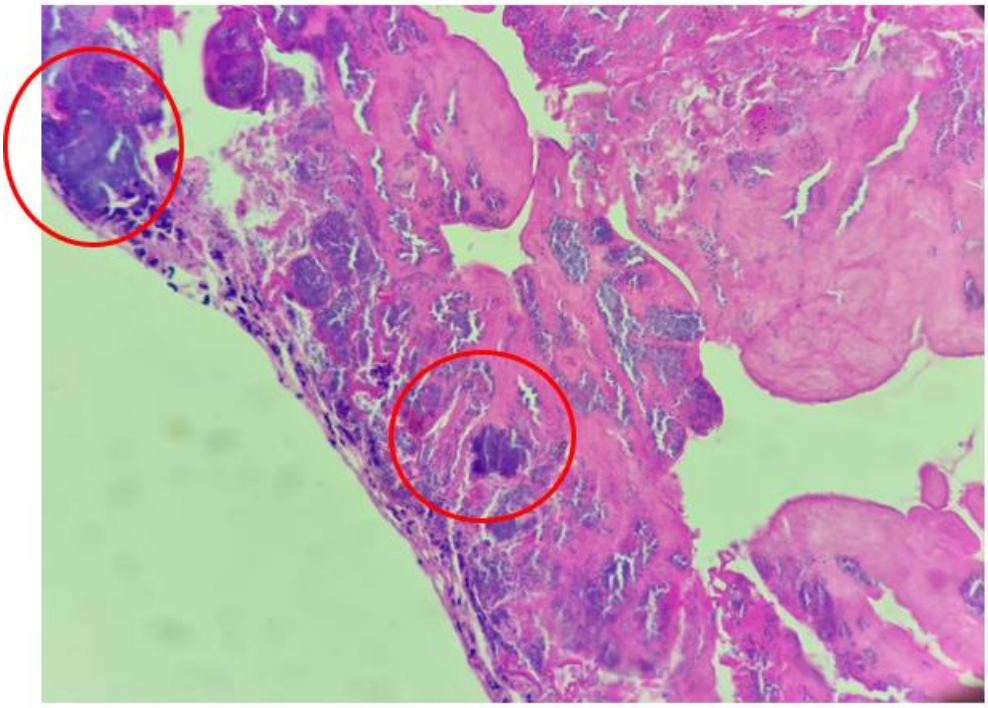

Figure 4.
The results of the forceps biopsy of Saiful Anwar Hospital on 09/05/2022, right lung mass showed fungal infection with hyphal walls stained pink to purple, suggestive of aspergillus.

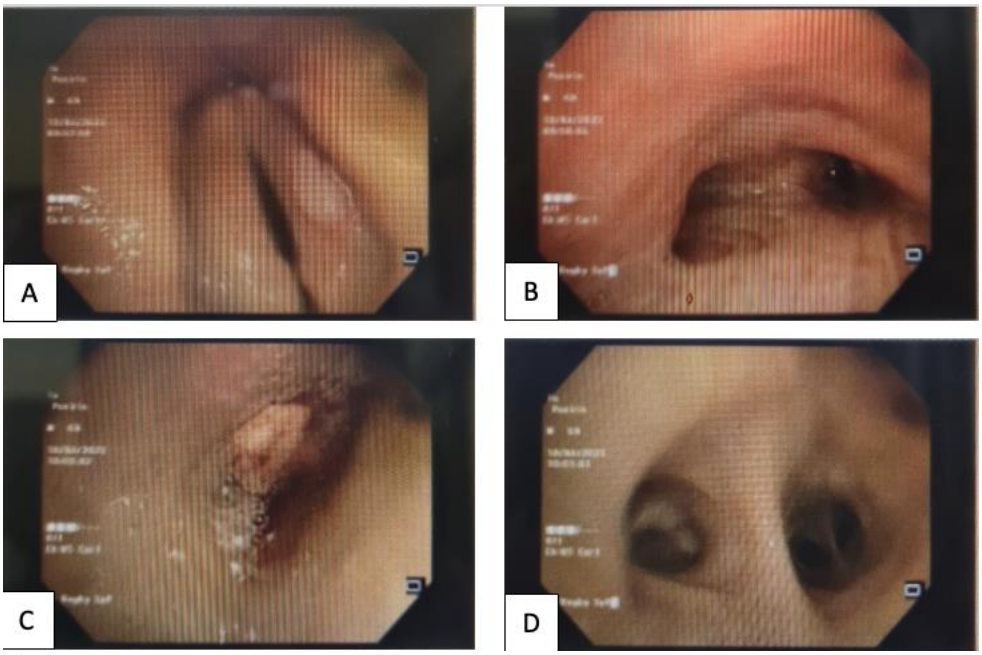

Figure 5.
Bronchoscopy results of Saiful Anwar Hospital on April 18, 2022, showed A. A. Plica vocalis with a nodule on the left, B. Blunt main carina, C. Right main bronchus covered with intralumenal period, D. Left main bronchus within normal limits. The bronchoscopy conclusion is stenotic obstruction in the right main bronchus, suggesting malignancy according to T3N2M1b St IVb.

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Table 3.
Response Evaluation Criteria in Solid Tumors (RECIST) Data CT Scan Thorax Contrast until May 2024.

Target Lesson	**19/4/22 (mm)**	**16/8/22 (mm)**	**20/10/22 (mm)**	**29/12/22 (mm)**	**7/3/22 (mm)**	**23/5/23 (mm)**	**2/8/23 (mm)**	**9/10/23 (mm)**	**12/12/23 (mm)**	**21/2/24 (mm)**	**24/4/24 (mm)**
Lung Mass Right	110	81	82	93	93	99	100	113	110	112	101
Limphadenopathy	30	22	20	20	20	19	19	25	19	19	14
Total	140	103	102	113	113	118	119	132	129	131	115
Non-Target Lesson											
Pleural Effusion Right	(+)	(+)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
Nodular Pleura	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)
RECIST	*Based line*	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable

Target Lesson: Stable disease
Non Target Lession : non progresif disease
New Lession : - (-)
Conclusion : Stable disease

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Based on all examinations, patient diagnosed with right NSCLC (PA: *Squamous Cell Ca*), T4N2M1a St. IV A, PS 0 (*Stable disease*), *proven lung mycosis* type aspergillosis, *cancer pain* vas 2/10, minimal right pleural effusion, grade I hemoptoe, stable COPD group B, and history of *Small Cell Ca* in 2017 *lost to follow up*. Patients received the main therapy of first-line chemotherapy, Carboplatin + Paclitaxel for 6 series, followed by *maintenance* Paclitaxel until May 2024. Patients also received oral Fluconazole 1x150 mg for 14 days, and resolved. Antifungal administration is not based on the main guideline management due to the limited availability of drugs at the treatment site. Based on the results of the latest RECIST Thorax CT-Scan and stable condition, the patient is currently taking a break from chemo and control under clinical control every 3 months.

3. Results and Discussion

SCLC is a distinct subtype of lung cancer with *poorly differentiated neuroendocrine* characteristics characterized by rapid progression and early development of extensive metastases [9, 10]. The main effective chemotherapy regimens in the management of SCLC for advanced SCLC are a combination of *platinum-based* (*cisplatin/carboplatin*) with etoposide or irinotecan for 4-6 cycles, with each cycle lasting 3-4 weeks. SCLC with RECIST *stable disease* evaluation, chemotherapy is stopped, and RECIST Contrast Thorax CT Scan evaluation per 3 months. If *progressive disease* is found more than 6 months after treatment, it can still respond well to the first chemotherapy regimen. If *progressive disease* is obtained sometime after treatment, the chemotherapy regimen should be changed. In advanced SCLC, the main choice of treatment modality is combination chemotherapy. The preferred chemotherapy regimens that can be used at this stage are cisplatin/carboplatin with etoposide or cisplatin/carboplatin with irinotecan. Another option is palliative radiation in primary lesions and metastatic lesions. The regimen of cisplatin combined with etoposide has high efficacy against SCLC [11].

The patient works as a welder and factory worker with a smoking habit. Chronic exposure to welding pollution can cause oxidative stress and increased chromosome disruption and DNA damage in lymphocytes. DNA damage in peripheral blood lymphocytes may be an index of genotoxicity in welding. Chronic exposure may lead to tissue remodeling and fibrosis. Welding workers were found to have a 3.9 times higher risk of COPD [12]. Cigarette smoke exposure causes chronic inflammation, resulting in respiratory epithelial damage [13]. Exposure to welding pollution and cigarette smoke was concluded to be the cause of COPD and lung cancer in patients. Cigarettes consist of 60 carcinogenic ingredients, which can damage the p53 gene, mutate, and cause lung cancer [14].

SCLC cases are 15% and NSCLC is 85% in the form of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Frequent transformation of NSCLC to SCLC, especially the adenocarcinoma type, due to EGFR-TKI (*epidermal growth factor-tyrosine kinase inhibitor*) mutation, was 3-14% [15]. The transformation of SCLC into NSCLC is characterized by genetic and molecular changes. SCLC transformation is characterized by the mutation of the TP53 and RB1 genes. Inactivation of RB1 and TP53 is the process of combined tumorigenesis of SCLC/NSCLC [16]. During transformation, further changes in mutations or inactivation of these genes may trigger histologic changes from SCLC to NSCLC. Mutations in the EGFR, ALK, and ROS1 genes associated with NSCLC can also be found in some cases of this transformation [17]. SCLC transformation is also characterized by the presence of SMAD4 mutations that contribute to small cell transitions, mainly by affecting the neuroendocrine phenotype by inactivating TP53 [18]. Activation of oncogenes such as KRAS, EGFR, and ALK may play a role in the development and transformation from SCLC to NSCLC. For example, treatment with EGFR inhibitors in patients who initially have SCLC may trigger clonal selection, leading to the emergence of a subpopulation of cancer cells that exhibit characteristics of NSCLC [19, 20].

Patients with lung cancer undergoing immunosuppressive therapies such as chemotherapy, targeted therapy, or immunotherapy are more susceptible to fungal infections. Fungal infections, such as those caused by *Aspergillus*, *Candida*, or *Pneumocystis jirovecii*, can worsen the patient's condition and lead to increased complications [21]. Immunosuppression in cancer patients can affect their immune response,

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which can lead to opportunistic fungal infections and worsen the histological transformation of the cancer, potentially accelerating the change from SCLC to NSCLC or adding clinical complexity to the treatment of such cancers. Loss of function due to IL12RB1 mutation results in impaired IFN-γ production, so that macrophages cannot eliminate intracellular fungi. Fungal interaction with integrin-β1 on alveolar epithelial cells further increases EGFR activation, cell damage, and the development of invasive fungi [5]. Mycosis occurring in lung cancer patients may increase levels of pro-inflammatory cytokines and growth factors that may influence cellular signaling pathways involved in cancer cell transition, such as the change from SCLC to NSCLC [5, 10, 16]. However, the exact relationship between mycosis and histologic transformation in lung cancer still needs to be further investigated.

Patients with invasive aspergillosis should first be given oral or intravenous voriconazole with a *loading dose of* 6mg/kg/12h on the first day, then 4mg/kg/12h [22]. In lung cancer patients, fluconazole is generally not fully effective for treating *Aspergillus* infections due to its limited effectiveness. Fluconazole is an inhibitor of ergosterol synthesis, which is essential for fungal cell membranes. *Aspergillus* can develop resistance to fluconazole due to variations in its target protein (lanosterol 14α-demethylase). However, some studies have shown that platinum-based chemotherapy is effective in increasing life expectancy and fluconazole in treating pulmonary mycosis in cancer patients [23].

In advanced NSCLC, management may include chemotherapy, immunotherapy, targeted therapy, radiotherapy, and palliative care, depending on the patient's response and clinical condition. Platinum-based regimen combination of cisplatin or carboplatin with other chemotherapeutic agents such as paclitaxel, gemcitabine, or docetaxel is the first-line treatment in many patients with stage IV lung cancer. This regimen is effective at reducing tumor size and slowing disease progression, although it does not provide a permanent cure [24]. As a conclusion is SCLC transformation can be triggered by gene mutations due to various causes such as fungal infections and vice versa. CT Thorax RECIST is an important evaluation for lung cancer prognosis.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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