CASE REPORT

Giant Cell Lung Carcinoma: A Case Report of a Rare Histology Type of Non-Small Cell Lung Cancer

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ABSTRACT

Introduction: Giant cell carcinoma (GCC) of the lung is a subtype of lung cancer, undifferentiated non-small cell carcinoma, in which there are no features of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. Due to its aggressive clinical manifestations and peculiar pathological features, GCC of the lung is a highly anaplastic variant of bronchogenic carcinoma.
Case: A 45-year-old woman was clinically suspected of having a lung malignancy, and a biopsy of the right lower lobe pleura and parietal pleura was performed. The histopathology showed hypercellular tumor cell clusters, forming a syncytia-like sheet pattern. Tumor cells were pleomorphic and contained many giant cells that confirmed the diagnosis of GCC. The patient was diagnosed with GCC of the lung, stage IVB, Karnofsky scores 50-60% with malignant pleural effusion, peritoneal metastases, bone metastases, and grade 3 malignant ascites with bacterial peritonitis. The patient passed away due to septic shock caused by bacterial peritonitis. GCC of the lung is one of the aggressive types of lung cancer. GCC has an unusual tendency to metastasize to the gastrointestinal tract. In this case, the patient had an enlarged abdomen since it was known that she had a malignancy that had continued to grow. From the ascitic fluid analysis, a carcinoma was found to be seeding.
Conclusion: The prognosis of GCC of the lung is generally poor. Our case was diagnosed with GCC of the lung that had already spread to the bone, peritoneal, and had grade ascites. The patient's survival rate was generally poor, and she passed away due to bacterial peritonitis without having received any therapy for her cancer.

INTRODUCTION

Lung cancer is a disease characterized by uncontrolled cell growth in lung tissue. If not treated promptly, these growths can spread beyond the lungs to nearby tissues and other body parts.[1] Lung cancer is malignant worldwide, making up 13% of all cancer diagnoses and ⅓ of all cancer deaths in men.[2] The five-year survival rate for lung cancer is only about 15.6% because patients tend to be at an advanced stage by the point of diagnosis.[3] The incidence of lung cancer in Indonesia has been widely reported. The problem found in public health in Indonesia is caused by the high smoking rate, which also causes lung cancer.[4]

Primary lung cancer is based on cell type and has two main categories, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). The difference is that NSCLC is four times bigger than SCLC.[5] Giant cell carcinoma (GCC) of the lung only occurs in 9-10% of all lung cancers and is part of undifferentiated non-small cell carcinoma. The diagnosis of GCC of the lung is based on the absence of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma.[6] Based on the previously mentioned description, we reported a rare case of GCC of the lung.

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A 45-year-old woman complained of shortness of breath, which worsened when lying. She barely ate and had lost 20 kg in 3 months. She felt that her stomach had been enlarged for the last two months and felt bloated, but there were no problems with defecation and urination. There was no history of smoking for either the patient or their family. The patient had been working as a farmer since she was 20 years old. As a farmer, the patient often used pesticides, with a working time of about an hour, but rarely wore a mask. The patient worked in the fields for 8 hours a day. There was no history of using firewood. There was no family history of cancer.

The patient had an underweight body mass index and looked severely ill. The patient's vital signs showed tachypnea. Physical examination of the lungs revealed decreased vocal fremitus on the 6th intercostal left hemithorax. On percussion, there was dullness on the 6th intercostal left hemithorax. On auscultation, there were decreased vesicular breath sounds at the 6th intercostal left hemithorax, no rhonchi or wheezing was found.

A chest X-ray showed a left-dominant bilateral pleural effusion and an osteoblastic lesion on the right scapula, which suggested metastatic bone disease (Figure 1). The chest computed tomography (CT) scan showed right-left lung compaction and pleural effusion (Figure 2). Ultrasounds of the upper and lower abdomen were within normal limits.

Laboratory examination showed leukocytosis and thrombocytosis. Blood gas analysis showed fully compensated respiratory acidosis. Pleural fluid analysis showed exudate, and the cytological test revealed atypical cells with the impression of seeding adenocarcinoma. The results of the ascitic fluid analysis found an increase in the number of polymorphonuclear cells (PMN) ≥250 cells/mL, and the ascitic cytology showed carcinoma seeding. The epidermal growth factor receptor (EGFR) mutation test revealed wild-type EGFR. Confirmation of the diagnosis of GCC was established through a histopathological examination of an open biopsy of the right lower lobe lung with morphological features of GCC (Figure 3).

The patient was diagnosed with GCC of the lung, stage IVB, Karnofsky scores 50-60% with malignant pleural effusion, peritoneal metastases, bone metastases, and grade 3 malignant ascites et causa metastases with bacterial peritonitis. The patient had water seal drainage (WSD) installed for the pleural effusion and ascitic fluid drainage. The patient continued to experience a worsening condition with increasing shortness of breath, weakness, and an ever-expanding stomach. The patient experienced decreased consciousness and was shocked seven days after being admitted before undergoing chemotherapy. The patient passed away with the direct cause of death being septic shock and the intermediate cause of death being sepsis due to bacterial peritonitis.

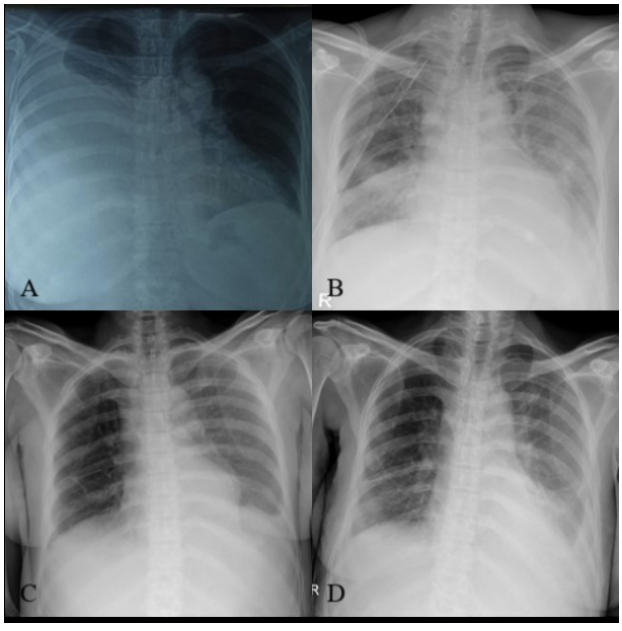

Figure 1. Sequential chest X-ray of the patient. A) At first hospitalization (April 2022), effusion in the right hemithorax. B) In May 2022, the patient had pneumonia and bilateral effusion. The patient had a chest tube installed, and the X-ray showed the chest tube attached with the tip pointing to the cranial projection at the 3rd right posterior intercostal. C) In June 2022, the second hospitalization showed reduced bilateral pleural effusion and fibrosis in the lower zone of the right lung, suspected to be part of the aging process. D) In August 2022, when the third hospitalization showed bilateral effusion with left-sided domination, metastatic type effusion was suspected, and an osteoblastic lesion of the right scapula was found, with metastatic bone disease suspected.

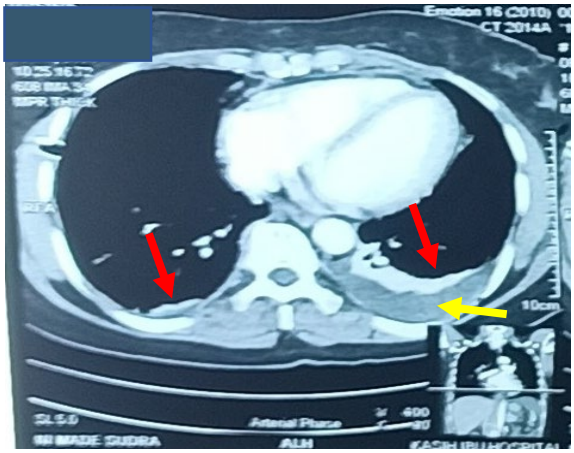

Figure 2. A CT scan of the thorax with contrast revealed right-left lung compaction with a fibrotic atelectasis component (red arrow) and pleural effusion (yellow arrow)

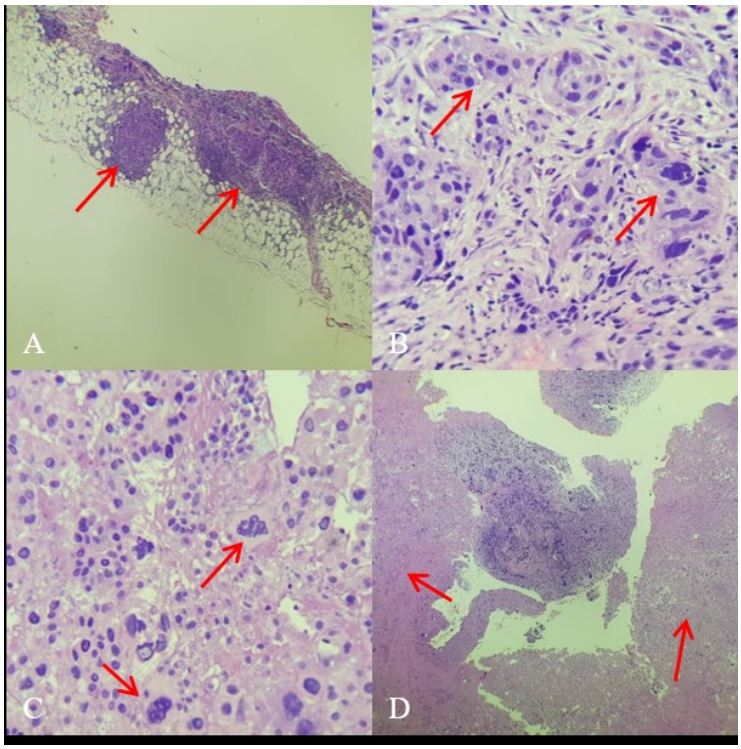

Figure 3. Histology of the tumor. A) Tumor cells formed a solid mass-invaded pleural tissue. B & C) Infiltrative malignant cells with many malignant giant cells. D) Tumor with extensive necrosis (H&E).

DISCUSSION

The true incidence, prevalence, and mortality of GCC of the lung are generally unknown because this tumor is a scarce variant of cancer.[6–9] Males are more often diagnosed with GCC of the lung than females, with a high male-to-female ratio (12:1 or greater).[9] Our case was a woman aged 45 years old. It is known that women usually have a better life expectancy than men with lung cancer.

The risk factors of lung cancer include cigarette smoke (smoking), air pollution, radiation, uranium, asbestos and other hazardous industrial materials, and genetic mutations.[10] Previous studies have shown that K-ras activation plays a role in tumor progression due to lung cancer. Abnormal mutations due to oncogenic factors like Myc, c-Raf, a tumor suppressor gene retinoblastoma (Rb), and p53 play a part in the process of lung cancer.[11,12]

Smoking is believed to be the leading cause of lung cancer.[10] However, not everyone who develops lung cancer is a smoker. Many people with lung cancer are ex-smokers, but others have never smoked. This patient was a second-hand smoker. Cigarette smoking is the leading cause of lung cancer. It is believed that men and women may have different susceptibilities to the carcinogenic effects of smoking, resulting in various deoxyribonucleic acid (DNA) repair mechanisms. In addition, gender differences in response to specific biological therapies (such as tyrosine kinase inhibitors and anti-angiogenic factors) have been observed.[5] The

genetic differences observed showed differences in K-Ras frequency and mutations in the EGFR.[8]

In this case, the patient had worked as a vegetable farmer for over 20 years, often spraying pesticides. The process can take 1-2 hours per week, and the patient did not routinely use a mask. According to the United States Environmental Control Act, pesticides refer to all substances or mixtures of substances used to regulate the growth or drying of plants and to control, prevent, or fend off pest disturbances. Pests include insects, rodents, nematodes, weeds, viruses, bacteria, and microorganisms.[13] Pesticides consist of various types, including insecticides, herbicides, fungicides, rodenticides, and fumigants.[14]

Pesticide exposure occurs during the production, transportation, preparation, and use of pesticides.[5] The acute toxic effects of pesticides can be identified based on toxicology and clinical studies. Respiratory problems develop because excessive toxic effects interfere with cell regeneration.[15] A study of workers involved in pesticide packaging showed that compared with a sample of controls, the workers exposed to pesticides had a significantly higher risk of developing respiratory disorders.[16]

The signs and symptoms of GCC of the lung are usually the same as other NSCLCs. The most common symptoms were cough (including hemoptysis), weight loss, and shortness of breath.[5] In this case, the patient initially experienced excessive weakness for one month, breathing difficulty, and weight loss. GCC has no distinct radiological features. The picture depends on the tumor's location, usually in the peripheral areas of the lung, except for basaloid carcinoma. The cancer can be detected using a transthoracic fine needle aspiration biopsy and during a bronchoscopy.[17] In this case, the patient was suspected of having malignancy due to the pleural effusion found on a chest X-ray, and pleural fluid cytology showed seeding adenocarcinoma. The chest CT scan with contrast showed a mass in the lower lobe of the right lung.

GCC of the lung has an unusual tendency to metastasize to the small intestine, leading to obstruction, severe bleeding, and/or intussusception. Its clinical characteristics have been seen in cases that have lasted more than half a century.[6,8] The jejunum appears to be the most common site for GCC metastases in the small intestine.[9] In this case, the patient had an enlarged abdomen since it was known that she had a malignancy that continued to grow. From the ascitic fluid analysis, a carcinoma was found seeding. The patient also often complained of body aches, and based on a chest X-ray showing an osteoblastic lesion on the right scapular bone, it was suspected to be metastatic bone disease.

The histopathological examination of the tissue following surgery can establish a specific diagnosis of GCC and its variants.[18] In this case, a definite diagnosis was obtained from a histopathologic examination from an open biopsy of the right lower lobe pleura with morphological features consistent with GCC. Under macroscopic pathological examination, GCC appears as a sizeable peripheral mass and may involve the subsegmental or large bronchi, often invading the chest wall or surrounding structures. A soft, brownish-white group is seen in the cross-section, often accompanied by necrosis, bleeding, and cavitation. Large cell neuroendocrine carcinoma is usually located in the periphery, while basaloid carcinoma has bronchial growth characteristics that are exophytic.[13] GCC is diagnosed microscopically after removing squamous cell carcinoma, adenocarcinoma, or small cell carcinoma. The tumor cells are large, irregular, and odd, with protruding vesicular nuclei arranged in layers or nests of moderately sized polygonal cells.[6,8]

Cytological specimens can be obtained from sputum, bronchial secretions, bronchial brushes, fine needle aspiration biopsy (FNAB), or pleural fluid.[19] Under the microscope, the background of GCC contains many neutrophils and lymphocytes. The tumor cells are large, multinucleated, and bizarre, with the tumor cell sizes varying more than 5-fold. The tumor cells are also abundant, thick, and have a distinct cytoplasm. The nucleus is oval or irregular in shape and has centrifugal force. Multinucleated giant cells were observed more frequently than anucleated cells. The nuclei are more than five times larger than normal lymphocytes. The nuclear membrane is thin, and the nuclear chromatin is coarsely granular, but the nucleoli are discrete and round.[20] The cytology examination of this case revealed that almost all of the tumors were large, bizarre, and multinucleated.

There are no randomized clinical trials for treating GCC due to their rarity, and all available information comes from small retrospective institutional series or multicenter meta-analyses. Surgical resection can be performed for the early stages and provides adequate local control. Most physicians have used platinum-based chemotherapy to treat GCC of the lung, but a study showed that GCC generally responds poorly to chemotherapy.[21] It also showed the efficacy of radiotherapy in treating GCC.[21] Due to the higher resistance rate to conventional chemotherapy than other NSCLCs, patients with GCC need more treatment options, such as targeted molecular therapy. However, the molecular structural features of GCC remain enigmatic.[5] A clinical study with 42 pleomorphic carcinomas investigated somatic mutations in EGFR and TP53.[22] EGFR mutations were detected in 23.8% (10/42) cases, including exons 19 and 21

transformations. TP53 mutations were detected in 28.6% (12/42) of patients. This pleomorphic cancer has been shown to benefit from treatment with a tyrosine kinase inhibitor.[19] Recently, pembrolizumab was shown to have a significant antitumor effect over platinum-based chemotherapy against NSCLC with high PD-L1 expression (TPS ≥ 50%).[23] Little is known about PD-L1 protein expression in GCC of the lung, although one report showed positive PD-L1 expression in 6 out of 10 tumors. Immunohistochemistry showed that PD-L1 was expressed in 37 of 41 pleomorphic lung cancers (90.2%), with a higher expression in sarcomatoid areas than in carcinoma areas.[6] Patients with PD-L1-positive giant cell lung cancer in a study conducted by Nakayama, *et al*. (2018) were successfully treated with the anti-PD-L1 antibody pembrolizumab.[8]

Patients with bronchogenic carcinoma should undergo complete pretreatment and staging, and treatment decisions should be based on the extent and stage of the disease.[2] The prognosis of GCC of the lung is generally poor even after complete resection in stage I or II. Survival rates have been estimated to range from 0% to 21%.[23] In this case, the patient passed away three months after being diagnosed. She passed away due to bacterial peritonitis without having received therapy for her cancer.

CONCLUSION

Diagnosis of GCC must be made by histopathologic examination. Early-stage GCC of the lung can be managed by surgical resection but not by radiotherapy. Due to the higher resistance to conventional chemotherapy than other NSCLCs, more treatment options are needed, such as molecular target therapy for GCC. Pembrolizumab can be used as an option in GCC of the lung with a high expression of PD-L1 (TPS ≥ 50%). GCC of the lung has an unusual tendency to metastasize to the small intestine, leading to obstruction, severe bleeding, and/or intussusception. The prognosis for GCC of the lung is generally poor, with an estimated survival rate of 0-21% despite complete resection in stage I or stage II.

Consent

Written informed consent was obtained from the patient.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conception: KSAP, IAJDK. Data collection and manuscript writing: KSAP, IAJDK, NPS. Review and revision: KSAP, IAJDK, NPS, NLGYK. All authors contributed and approved the final version of the manuscript.

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