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ABSTRACT

Introduction: A small-cell lung carcinoma is an aggressive form of lung cancer that is strongly associated with cigarette smoking and tends to early disseminate in the body. It represents about 20 per cent of all lung cancer. Increasing evidence has implicated autocrine growth loops, proto-oncogenes, and tumour-suppressor genes in its development as well as cigarette smoking, exposure to occupational carcinogens such as radon, asbestos, arsenic, crystalline silicon and benzopyrene e.t.c.

Materials and Methods: This case study reports the management of suspected small lung cell cancer in a resource-limited centre diagnosed from transthoracic pleural biopsy in a 26-year-old male who had a history of cigarette smoking from preteen years (9 years). He was stabilized at the emergency with insertion of chest tube, antibiotics, analgesics and oxygen but couldn't commence treatment for lung cancer owing to the late diagnostic test done as a result of severe financial constraints and died three weeks post-hospital admission.

Results: This case shows that early exposure to risk factors associated with lung cancer such as cigarette smoking, exposure to harmful chemicals in Plaster of Paris can lead to aggressive lung cancers like small cell lung cancer in young people.

Recommendations: Increase public awareness of tobacco smoking in all age groups, adequate healthcare financing and insurance schemes and adequate funding for small cell lung cancer research to improve and promote prevention, early detection and proper treatment of the disease.

Keywords: *Cigarette smoking, pleural effusion, dyspnea, small lung cell cancer.*

BACKGROUND

Small cell lung cancers (SCLC) were known as oat cell cancers because of the packed nature of small dense cells. SCLC is a neuroendocrine carcinoma that exhibits aggressive behaviour, rapid growth, early spread to distant sites, exquisite sensitivity to chemotherapy and radiation, and frequent association with distinct paraneoplastic syndromes, including hypercalcemia, Eaton-lambert syndrome, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, and many others. (See Pathophysiology, Etiology, and Presentation).

Worldwide Lung cancer is the most common type of cancer especially in males and is the leading cause of cancer death worldwide killing approximately 1.5 million people in 2012.¹ In the United States, there are over 200,000 new cases per year and over 150,000 deaths per year attributed to lung cancer. SCLC comprises about 15% of cases.² SCLC is a type of lung cancer that is highly malignant which commonly arises from the lungs but can also arise from common sites such cervix, prostate and gastrointestinal tract. It differs from Non-small cell lung cancer (NSCLC) in shorter doubling time, higher growth fraction of tumour and earlier development of metastasis as there are currently no methods with proven efficacy for the early detection of SCLC.

The predominant cause of small cell lung cancer (SCLC) and non-SCLC is tobacco smoking. Of all histologic types of lung cancer, SCLC and squamous cell carcinoma have the strongest correlation to tobacco.³ Approximately 98% of patients with SCLC have a smoking history. SCLC is the most common lung cancer among uranium miners. According to World Health Organization (WHO) statistics, about 1.69 million deaths from lung cancer occur annually throughout the world.⁴ In the US, SCLC once accounted for 20-25% of all newly diagnosed lung cancers; it now comprises only about 13% of all lung cancers and with approximately 31,000 patients diagnosed annually.⁵ The incidence of lung cancer is declining in the US and other developed countries with a gradual increase in developing countries in recent years owing to the rising use of tobacco especially amongst young adults.¹⁶ A 14-year mortality review of cancers in Lagos revealed 2.6% of mortality from lung cancer.⁶

However, data is quite a few in Nigeria about the incidence, prevalence and mortality rate of lung cancer nor any study reviews on SCLC. Moreover, separate data for small cell carcinoma are sparse, especially in Sub-Saharan Africa. Thus, the reason for this case report. Patients with SCLC usually present with a short duration of symptoms, usually only 8-12 weeks before

¹ Basumallik N, Agarwal M. Small Cell Lung Cancer. [Updated 2021 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.

² World Cancer Report 2014. World Health Organization. 2014. pp. Chapter 5.1. ISBN 978-9283204299.

³ Pesch B, Kendzia B, Gustavsson P, Jockel KH, Johnen G, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer*. 2012 Sep 1. 131(5):1210-9.

⁴ World Health Organization. Cancer fact sheet no. 297. Available at <http://www.who.int/mediacentre/factsheets/fs297/en/>. 1 February 2018; Accessed: May 22, 2018.

⁵ American Cancer Society. Cancer Facts & Figures 2014. Atlanta, GA: American Cancer Society; 2014.

⁶ Olakanmi R. A, Adekoyejo A. P, Olubanji A. O, Olatunji M. A. "Cancer Mortality Pattern in Lagos University Teaching Hospital, Lagos, Nigeria". *Journal of Cancer Epidemiology*, vol. 2015, Article ID 842032, 6 pages, 2015.

presentation. The clinical manifestations of SCLC can result from local tumour growth, intrathoracic spread, distant spread, and/or paraneoplastic syndromes.

SCLCs are predominantly central in lobar or main bronchi or mediastinal mass involving one hilum and may cause irritation and/or obstruction of the major airways.^{7, 8, 9, 10} Common symptoms resulting from local tumour growth include cough, dyspnea, and hemoptysis. Squamous cell cancer also presents as a central lesion, but unlike SCLC, it frequently exhibits central cavitation.¹² Aggressive dissemination of tumour leads to obstruction of major airways, with distal collapse leading to post-obstructive pneumonitis, infection, and fever. Most patients typically have a systemic disease at the time of diagnosis, symptoms such as weight loss, fatigue, and anorexia may be present (Carter).¹⁰ SCLCs disseminate rapidly and metastasize to mediastinal lymph nodes relatively early in the course of the disease. At presentation, patients may have very large intrathoracic tumours, and distinguishing the primary tumour from lymph node metastases may be impossible.¹² Pressure on mediastinal structures can cause Superior Vena Cava Obstruction and recurrent laryngeal nerve cause hoarseness, dysphagia or even stridor.¹⁰

Paraneoplastic syndrome has been associated with SCLC due to tumour excretion of a bioactive substance such as a hormone or can result from immune-mediated destruction of neural tissue caused by antibody- or cell-mediated immune responses.¹⁰ SCLC can spread to distant organs. The common sites of hematogenous metastases include the brain, bones, liver, adrenal glands, and bone marrow causing seizures, ataxia, changes in mental status, jaundice, pruritus, bone pain.^{10, 14} Patients may present with clinical features suggestive of metastasis or abnormal biochemical parameters like deranged Liver function tests and deranged electrolytes. Radiological imaging can reveal spinal cord compression.

CASE STUDY

Chief Complaints: A 26-year-old male driver presented at the emergency with complaints of Chronic Cough of five months duration and Chest Pain of two months duration.

History of Present illness: His problem dated back to five months ago when he started coughing repeatedly, which has progressively worsened over time. Cough was productive initially of whitish thickened sputum which was noted to have changed in the past week before presentation to be bloody expelling ~5mls per episode. Chest pain commenced two months ago, of sudden onset, along the lower part of his left chest wall up to the back, scored 10 on a scale of 1 to 10. There's an associated history of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, general

⁷ Carter BW, Glisson BS, Truong MT, Erasmus JJ. Small cell lung carcinoma: staging, imaging, and treatment considerations. *Radiographics* 2014;34:1707–21.

⁸ Huber R, Tufman A. Update on small cell lung cancer management. *Breath* 2012; 8:314-30.

⁹ Medscape "Small Cell Lung Carcinoma", May 07, 2021. <https://emedicine.medscape.com/article/280104>. Cited June, 2021.

¹⁰ Kahnert, Kathrin; Kauffmann-Guerrero, Diego; Huber, Rudolf Maria (2016): SCLC-State of the Art and What Does the Future Have in Store? In: *Clinical Lung Cancer*, Vol. 17, No. 5: pp. 325-333.

body weakness with easy fatiguability, history of night drenching sweat, insomnia and significant weight loss.

Over the past five months, he presented to 4 different hospitals seeking care. The last Hospital where he presented eight days ago before presentation in LUTH, Lagos GH Mainland where he did some investigation: Liver function test that was deranged with markedly elevated liver enzymes, full blood count had leucocytosis of, hypokalemia, hyponatremia, hypocalcemia and hypoalbuminaemia. Retroviral disease screening was negative, Gene Xpert for tuberculosis was negative and a chest X-ray showed massive pleural effusion with left-sided effusion greater than the right side, for which he had left closed thoracostomy tube drainage (CTTD) inserted three days before presentation. He was thus referred to LUTH on account of a leaking chest tube for expert management.

History of past illness: He smoked Maurijauna for the past 5 yrs, previously smoked cigarettes for 10 yrs (started at the age of 9yrs) about 10 packs per day.

He worked in a building construction company for 3-5years in which he was in charge of handling Plaster of Paris and interior wall decoration of houses built by the company. There's a history of cancer in a 1st-degree relative- his late mother.

He has no known chronic medical condition. However, consumption of herbal concoctions was noted, last being two months before presentation at the emergency and he sparingly consumes alcohol.

Physical Examination: A young man acutely ill-looking in both respiratory and painful distress, orthopneic, drenching sweat with Left CTTD Insitu draining serosanguineous effluent ~300mls into urine bag and leaking from sides plastered to the chest wall, anicteric, acyanosed, not pale, afebrile= 36.8°C, presence of differential digital clubbing with bilateral pedal oedema up to the knee and large right supraclavicular lymphadenopathy (4×4cm), non-tender and mobile.

CHEST: Dyspneic, asymmetrical chest wall with a bulge at the left posterior aspect, left chest didn't MWR, RR=38CPM. The chest was very tender with left tender gynecomastia, tactile fremitus increased on the left side with dull percussion notes and reduced breath sounds, diagnostic thoracocentesis had serosanguineous effluent from left pleural space.

SPO₂= 98% at INO₂ 10L/min and 92% in room air.

CVS: PR= 134bpm, BP= 138/87mmHg.

Abdomen: Horizontal umbilicus slit, distended abdomen that MWR, vague generalized tenderness, nil organomegaly palpable and ascites demonstrated by shifting dullness.

ASS: Advanced lung cancer r/o advanced mediastinal tumour.

On admission at the ER, he had the Urine bag attached to the chest tube changed to an underwater seal to enhance the passive flow of Pleural fluid into the sealed bottle and chest tube site dressing changed. He had severe financial constraints and PFA was obtained for cytology, M/C/S and ADA to effectively screen for PTB and r/o malignancy wasn't analyzed by the laboratory as well as chest CT scan and repeat Electrolyte test.

Results of FBC &ESR repeated in LUTH still revealed leucocytosis, neutrophilia and markedly elevated ESR.

PCv= 42.6% WBC= 12.61×10^3 , Neutrophil=73.9%.

Hb=13.5g/dl, ESR=111mm/hr. Viral markers were triple-negative. Chest X-Ray repeated in LUTH revealed pleural effusion of left lung although left pleural fluid was reduced compared to chest X-ray he did at the referral centre. A right supraclavicular mass was also noted. He was commenced on analgesics, antibiotics were changed from IV Augmentin 1.2g to IV Fytobact 1g 12hrly and were said to have mild relief of chest pain. He was admitted into the ward and counselled to do a Chest CT scan and other investigations requested as well as purchase an incentive spirometer.

Owing to the patient's severe financial constraint, he couldn't do outstanding investigations nor regular with his IV medications and was deteriorating clinically with increasing hemoptysis by 4DA. However, LCTTD wasn't active with a dry tap from diagnostic thoracentesis, was extubated and worked up for emergency pleural biopsy (which wasn't done because of lack of funds to procure materials for procedure and non-availability of relatives). He was commenced on medications to relieve symptoms and to slow the progression of suspected lung malignancy: Tabs prednisolone 10mg, Caps Omeprazole 20mg, IV tranexamic acid 500mg, IV Vitamin K 10mg daily x3/7 and 100% O₂. Tabs co-codamol was added as an adjunct to analgesics. He improved clinically and was quite stable. Transthoracic left pleural biopsy was done under LA and the procedure was well tolerated. Pleural samples were obtained put into universal bottles containing formalin and sent to the pathology laboratory.

The frequent brief relapse of initial symptoms requiring INO₂ to resuscitate patient and patient improves clinically was noted all through admission as well as novel symptoms such as excessive thirst, severe constipation. However, he was reported to be consuming herbal concoctions (ginger juice) and was counselled of its consequence. The medical social worker was notified to help with funds for the patient as his relative couldn't do outstanding investigations and the patient couldn't afford INO₂ with hospital debt bills since admission.

Attention was called to review patients by 2:30 am as he was dyspneic, restless, refusing to restrain in bed and causing a nuisance on the ward with aggression to the nurses. INO₂ was finished and relatives have not been available at the hospital for the past 2/7 owing to nationwide lockdown 24hr curfew restriction. However, efforts were made to get oxygen while he was escorted to bed he was noticed to decompensate and despite being administered Oxygen, his respiratory effort deteriorated. Resuscitation attempted yielded no efforts. He was certified dead.

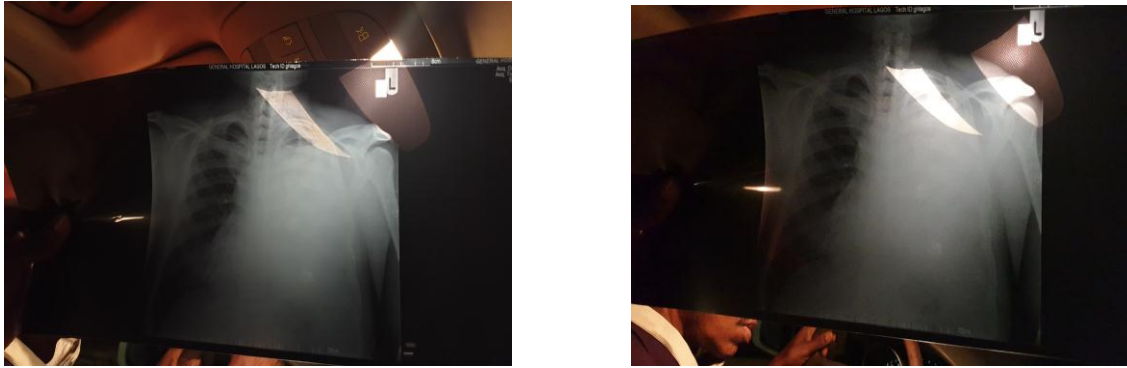


Fig 1. Chest X-ray 3/7 before presentation at the ER with left-sided massive pleural effusion

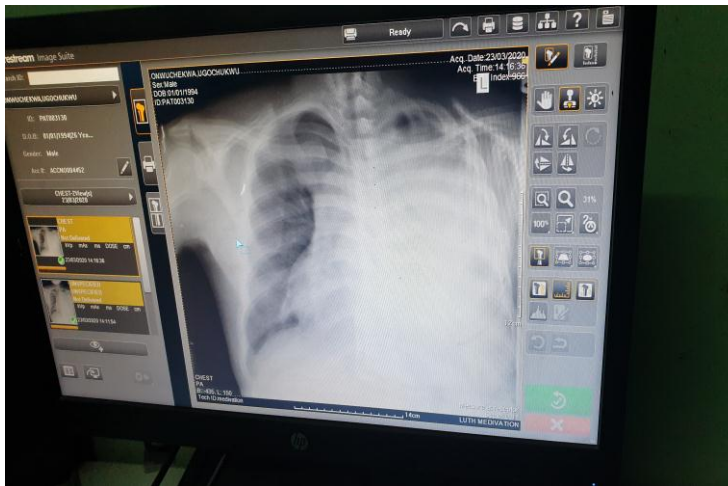


Fig 2. Repeat Chest X-ray post insertion of left CTTD with Right supraclavicular mass noted at the posterior aspect.

Post Demise:

Histology report retrieved revealed small lung cell cancer and autopsy was withheld by the hospital at that time because of the COVID- 19 pandemic.

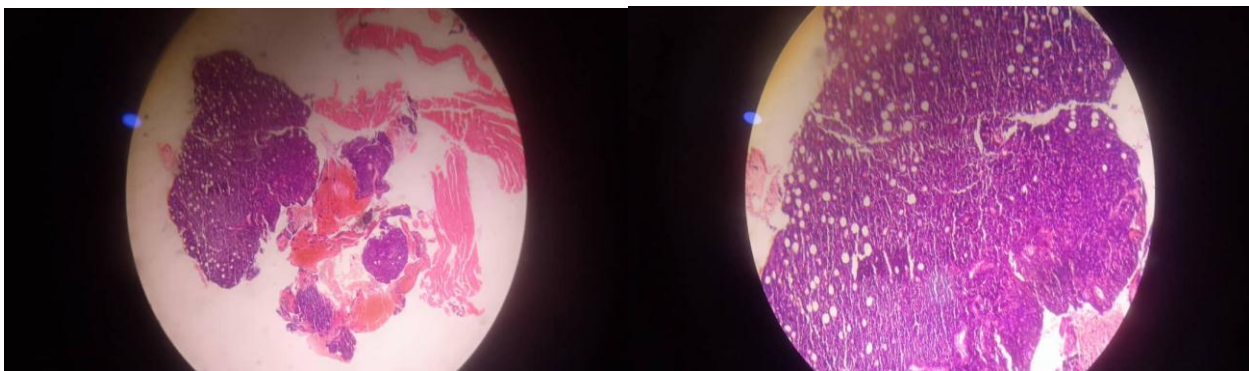


Fig 3. Macroscopy

The specimen consists of pieces of greyish white tissue measuring 0.5x 0.5 x 0.5cm, processed whole.

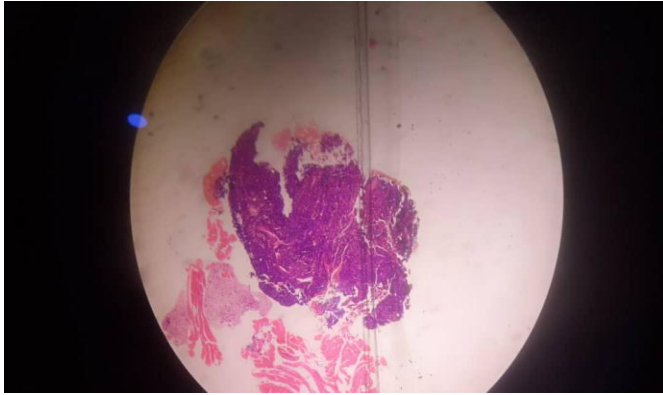


Fig 4. Microscopy

The histologic section of tissue shows round blue cells disposed in sheets within fibrocollagenous stroma. Individual cells show coarse chromatin and scant cytoplasm. The tissue is crushed in areas. Features is that of NEUROENDOCRINE TUMOUR MOST LIKELY SMALL CELL CARCINOMA.

DISCUSSION

The incidence and mortality of small-cell lung cancer worldwide make this disease a notable healthcare issue. Diagnosis relies on histology, with the use of immunohistochemical studies to confirm difficult cases. Typical patients are men older than 70 years who are current or past heavy smokers and who have pulmonary and cardiovascular comorbidities. Patients often present with rapid-onset symptoms due to local intrathoracic tumour growth, extrapulmonary distant spread, paraneoplastic syndromes, or a combination of these features. Most patients eventually die of recurrent disease despite treatment. According to the 17th World Conference on Lung Cancer (WCLC), long term survival of more than 5 years can be achieved with proper treatment.¹¹

Surgical intervention has a limited role as primary therapy because of the high propensity of small cell lung cancer to metastasize early, although the disease is highly sensitive to chemotherapy and radiation, a cure is difficult to achieve. The combination of platinum (carboplatin) and etoposide is the accepted standard chemotherapeutic regimen. It is also the accepted standard therapy in combination with thoracic radiotherapy (TRT) for limited-stage disease recommended by the American College of Chest Physicians (ACCP). Adding TRT increases absolute survival by approximately 5% over chemotherapy alone.¹² Thoracic

¹¹ Medscape "Exceptional SCLC Survivors: 5-Year Median Survival", Dec 20, 2016. | <https://www.medscape.com/viewarticle/873492>. cited on the 14th July 2021.

¹² Taimur Sher, Grace K. Dy, Alex A. Adjei, Small Cell Lung Cancer, Mayo Clinic Proceedings, Volume 83, Issue 3, 2008, Pages 355-367, ISSN 0025-6196, <https://doi.org/10.4065/83.3.355>.

radiotherapy administered concurrently with chemotherapy is more efficacious than sequential therapy. Furthermore, the survival benefit is greater if TRT is given early rather than late in the course of chemotherapy and not chemotherapy alone irrespective of the stage of the disease. Prophylactic cranial radiation prevents central nervous system recurrence and can improve survival- google scholar. SCLC has not been shown to respond well to most targeted therapies in contrast with non-SCLC, for which identification of molecular targets and targeted therapies such as vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) inhibitors have yielded poor survival rates (bevacizumab, aflibercept, and vandetanib). Recently, FDA granted accelerated approval of nivolumab for metastatic SCLC in patients with progression after platinum-based chemotherapy and at least 1 other line of therapy¹⁰ and the FDA also approved Atezolizumab (Tecentriq) to be included in Cisplatin Etoposide first-line regime following a 30% decrease in disease progression or death.¹³ Accurate staging of lung cancers is paramount in management, such that patients do not experience the morbidity of surgical resection without the possibility of a definitive cure.

Patients with small-cell lung cancer (SCLC) require close monitoring for adverse effects to therapy using biochemical investigations such as FBC with differential and electrolyte function, is needed before each cycle of chemotherapy to ensure marrow recovery before the next dose of chemotherapy is administered. LS SCLC has had few cases of either total response or slow progression of the disease.¹⁴ A study in South Korea used adjuncts like photodynamic therapy to chemoradiation treatment in LS-SCLC.¹⁷

Studies done in Nigeria has identified smoking as a major risk factor for lung cancer with high prevalence rates (42%)¹⁵ but most of these cases present late with extensive disease.⁹ However our patient, a young man who was exposed to smoking cigarettes preteen years presented with a right supraclavicular mass with worsening respiratory symptoms and severe financial constraints couldn't get adequate management in the hospital with patient's diagnosis (via tissue biopsy) of SCLC available after his demise is pathetic and disheartening in hurdles to care in a resource-limited centre.

CONCLUSION

Small cell lung cancer an aggressive metastatic disease can occur in a young adult with tobacco smoking a major risk factor as well as exposure to carcinogens, in which mortality is imminent if there's late detection and commencement of appropriate treatment.

¹³ Concurrent Tecentriq Adds First Survival Benefit Seen in Small Cell Lung Cancer in 20 Years | <https://www.curetoday.com/articles/concurrent-tecentriq-adds>. Cited June, 2021.

¹⁵ Ezemba, Ndubueze & Ekpe, Eyo & Eze, John. (2012). Challenges of lung cancer management in a developing country. Nigerian journal of medicine: journal of the National Association of Resident Doctors of Nigeria. 21. 214-7.

RECOMMENDATIONS

- I) An increase in public awareness about the carcinogenic effect of tobacco smoking, abuse of cannabis in all age groups including children and teenagers which instil proper knowledge about health early in life.
- II) Medical and Scientific bodies to address potential barriers to SCLC research and create opportunities in the field to improve learning and management of SCLC.
- III) Implementation of health insurance scheme policies in developing countries by government, individuals working in health financing organisations and partnership with non-governmental organizations to mitigate impediments accessing proper care in resource-limited centres.