International Journal of Occupational Medicine and Public Health
Prodi Kedokteran UNTIRTA

PNEUMONIA IN LUNG CANCER PATIENTS: CLINICAL CHALLENGES, DIAGNOSTIC PITFALLS, AND MANAGEMENT STRATEGIES

Muhammad Nurman Ariefiansyah[1], Yana Aurora Prathita[2], Heidy Agustin[3]

[1]Faculty of Medicine, Universitas Islam Negeri Syarif Hidayatullah, Indonesia
[2]Faculty of Medicine and Helath Science, Sultan Ageng Tirtayasa University, Banten, Indonesia
[3]Departemen of Pulmonology and Respiratory, Faculty of Medicine Universitas Indonesia, Indonesia

(Correspondency: m.ariefiansyah@gmail.com, +6281275426794)

ABSTRACT

Lung cancer is a condition that has a risk of co-infection. Conditions such as immunodepression, neutropenia, and other co-morbidities such as smoking and COPD are also risk factors for infection, especially lower respiratory tract infections. Pneumonia is an infection that often occurs in lung cancer. Impaired immunity, malnutrition and anatomical abnormalities in lung cancer can cause pneumonia-causing pathogens to enter and colonize the lower respiratory tract. Streptococcus pneumoniae, Haemophilus influenza and gram-negative bacilli are bacteria that often cause pneumonia. Fever, productive cough with purulent sputum and shortness of breath are classic symptoms of pneumonia which also occurs in lung cancer with pneumonia. Radiographic images, laboratory analysis and microbiological tests are modalities in establishing the diagnosis. Antibiotics are the main therapy in the management of lung cancer with pneumonia adjusted to each individual and the accompanying risks.

Keywords: Lung cancer, pneumonia

INTRODUCTION

The highest mortality rate from cancer in men and women worldwide are caused by lung cancer. Deaths in men are estimated at 87,000 deaths or 28% of all cancer deaths and 72,220 deaths or 26% of all cancer deaths in women.[1] Lung cancer patients can experience comorbid infections and have a high risk of recurrent infections. Some risk factors for infection in lung cancer patients are age, smoking habits, chronic obstructive pulmonary disease (COPD) and cancer therapy that causes immune system suppression. The most common infection in lung cancer is pneumonia caused by bacterial infections.[2,3]

Conditions that patients with lung cancer have such as immunodepression, neutropenia and COPD. The incidence of pneumonia is estimated at around 2-20% in lung cancer patients undergoing lung resection.[4] The frequency of respiratory tract infections in lung cancer patients treated in hospitals is around 21.9%-49%. Research conducted in the Netherlands in 2015 by Janssen-Heijnen showed that the characteristics of lung cancer patients have the potential for respiratory tract infections. The

occurrence of pneumonia in lung cancer patients results in poor outcomes. This literature review will discuss the risk of pneumonia in lung cancer, recent diagnosis and management.

PREDISPOSING FACTORS AND CLINICAL SIGNIFICANCE

The lungs are the main site of infection in cancer patients. Immunocompetent and immunosuppressed conditions in cancer patients are initial conditions that can cause pneumonia due to invasion of microorganisms that develop in the lung parenchyma. In immunocompetent patients, the body's defense system can eliminate pathogens. Post-obstructive pneumonia can occur in lung cancer. Obstructive conditions caused by cancer cause mechanical consequences that cause damage to the immune system, resulting in lung infection. Patients with an Eastern Cooperative Oncology Group (ECOG) score ≥2 d are at risk of pneumonia.[5]

Systemic inflammation is a hallmark of cancer that causes metabolic changes. Tumor cells release cytokines and inflammatory mediators and activate immune cells to release cytokines and chemokines. Tumors and the gastrointestinal tract together mediate immune cell activation. Barrier dysfunction in the gastrointestinal tract and bacterial translocation are associated with cancer. Release of lipopolysaccharides and bacterial toxins activate cytokine synthesis and immune cell release. Cytokines cause activation of transcription factors in cells related to fat and muscle tissue reduction.[6] Solid tumors have an indolent presentation and long therapy so that accompanying malnutrition and cachexia can worsen the patient's condition.[7]

Malnutrition weakens the immune response, both adaptive and innate. The skin and mucosal barriers as a natural immune system against infection as well as phagocytosis, natural killer (NK) cells and complement are damaged by (directly and indirectly) cancer and its therapy. 8 Cancer in cachexia is triggered by tumor-derived factors, namely lipid mobilization factors and proteolysis-inducing factors. Myostatin, a protein as a ligand for Tumor Growth Factor-β (TGF-β), is also associated with reduced muscle mass in different catabolic conditions.[6]

Mitochondrial dysfunction results in altered skeletal muscle metabolism and further contributes to the exacerbation of cancer-wasting syndrome. Mitochondrial dysfunction that occurs during cancer cachexia results in reduced adenosine triphosphate synthesis and uncoupling of oxidative phosphorylation. Inflammatory cytokines also contribute to the activation of proteolysis. Cytokines that play a role in muscle mass reduction in cancer include Tumour Necrosis Factor-α (TNF-α), TNF-like weak inducer of apoptosis (TWEAK), TNF receptor-associated factor 6 (TRAF6), Interleukin-6 (IL-6), Interferon-γ (IFN-γ) and Leukemia Inhibitory Factor (LIF). These cytokines act through two intracellular pathways.[6]

Surgery in patients with solid tumors can damage normal physiological barriers during the procedure so that normal tissues that were originally sterile and vulnerable organs can be colonized and infected by pathogens.[7,8] Chemotherapy and radiation cause a decrease in circulating neutrophils.[7] Radiotherapy and chemotherapy as cancer therapies are also causes of changes in immunity.[5] These therapies suppress the immune system so that there is a decrease in the number of circulating neutrophils. Solid tumors also have a damaging effect on the adaptive immune system. A decrease in the number of Cluster Differentiation (CD) 4 and CD 8 lymphocytes is seen in solid tumors but abnormal clinical symptoms are not clearly visible. Severe lymphopenia can increase the risk of life-threatening infections such as P. jivoreci pneumonia.[7]

The risk of infection in cancer patients depends on the integrity of the body's defense mechanisms (anatomical barriers and adaptive immunity) and the intensity of exposure to pathogenic microorganisms. Chemotherapy and radiotherapy treatments and invasive procedures generally damage the anatomical barriers[9] Smoking is a risk factor for the development of pneumonia in lung cancer patients receiving chemotherapy. There is a relationship between smoking and community-acquired pneumonia, namely smoking affects cilia, inhibits alveolar macrophages, causes hypertrophy of mucous glands and increases goblet cells. This causes the bronchial mucosal epithelium to become inflamed and facilitates infection.[10]

Advanced lung cancer is more likely to cause infection due to abnormal bronchial permeability which causes increased pressure on the bronchial wall due to enlarged tumor mass or lymph nodes.[10] Almost half of patients with central tumors present with peripheral lung collapse or obstructive pneumonia.[11] Lung cancer often involves lung damage due to possible comorbidities such as COPD, emphysema and idiopathic pulmonary fibrosis (IPF). These conditions cause mucociliary abnormalities and damage to the anatomical barrier, thus predisposing to the development of lower respiratory tract infections.[12]

MANAGEMENT STRATEGIES

Initial management of pneumonia is based on the individual and their associated risks. Cancer patients who do not have risk factors for opportunistic pathogens can be given targeted antibiotic therapy based on the main respiratory pathogens according to the recommended guidelines for community-acquired pneumonia in immunocompetent individuals. Patients with specific risk factors such as neutropenia require broader spectrum therapy including microbiology results. Infections with drug-resistant pathogens such as MRSA (often found in patients who are frequently hospitalized) or Pseudomonas aeruginosa (patients with chronic lung disease) are given empirical therapy targeting the pathogen.[13]

Antibiotic therapy is the main therapy for community-acquired pneumonia including severe pneumonia. Starting from empirical therapy because the causative organism is not identified at the beginning and the delay in providing adequate antimicrobials is associated with mortality in pneumonia patients,

especially severe pneumonia.[14] Empirical antibiotics in early hospitalized acquired pneumonia should include protection against S pneumoniae, methicillin-resistant S aureus, haemophilus influenzae and Enterobacteriaceae.[15] Patients with pneumonia who are hospitalized late or ventilator-associated pneumonia should be ensured antibiotics and include Gram-negative bacilli.[16]

According to the consensus guidelines recommend the use of two antibiotics, namely β-lactam and macrolide or respiratory fluoroquinolone (levofloxacin or moxifloxacin). Combination therapy can reduce mortality from severe pneumonia. Research conducted by Postma, et al. in 2015 stated that the administration of beta-lactam monotherapy also has the same effectiveness without a combination with macrolide or fluoroquinolone.[17] In patients who have risk factors for drug resistance S pneumoniae including comorbidities such as immunosuppression, heart disease, liver disease or diabetes, respiratory fluoroquinolone should be given or beta lactam plus macrolide. Administration for 3-5 days is estimated to be sufficient as the duration of antibiotic administration.[14] All antibiotic selection must consider culture data, severity of pneumonia, local antibiotic sensitivity profile, previous antibiotic exposure and patient immune status.[18]

Lung cancer patients with febrile symptoms suspected of being due to infection should be initiated on empiric therapy immediately and include protection against strains of S. aureus and P. aureruginosa.[19] Antimicrobial prophylaxis has shown some benefits, especially during the initiation of chemotherapy. This aims to protect patients during vulnerable periods such as during neutropenia and mucositis. Administration of ciprofloxacin and roxithromycin during chemotherapy for COCs reduces the frequency of febrile leukopenia, the number of infections and hospitalizations. The use of levofloxacin prophylaxis for 7 days is also known to have benefits. Although the use of antibiotics can cause new resistance, the benefits of antibiotic prophylaxis outweigh the emergence of infections and increased morbidity. Fluoroquinolones can be selected and used in lung cancer patients who are at high risk for infection.[8]

FUTURE DIRECTIONS AND RESEARCH GAPS

Early detection of pneumonia is important, especially in patients with lung cancer. Methods for diagnosing pneumonia can be done in several ways such as laboratory-based, auscultation examination, radiology, and examination of several physiological parameters.[20] Biomarkers can also be used to determine the patient's response to infection and treatment. In pneumonia, biomarkers are an indication of inflammation released after par tissue injury due to infection.[21] Several laboratory tests used to diagnose pneumonia include complete blood count, blood culture, polymerase chain reaction (PCR), C-reactive protein (CRPs). Culture of pleural fluid and fluid obtained from bronchoscopy can also be used to determine severe cases of pneumonia. The method of recording lung sounds using a digital stethoscope and analyzing them is useful in teleclinic cases such as COVID 19. The use of imaging such as chest X-ray, computed tomography (CT) scan and lung ultrasonography (USG) can see changes

that occur anatomically in the lungs that are infected. These methods can provide a good picture but sometimes cannot be done in health facilities that do not have these tools.[20]

CT scan examination can provide better accuracy although not all health facilities have it. Community-acquired pneumonia (CAP) can be diagnosed based on the following three appearances such as peribronchial nodules, alveolar/lobar consolidation, or ground glass opacity (GGO).[20] CT scan examination to determine cases of pneumonia in lung cancer patients must be differentiated because of their similar appearance. In cases of lung tumors such as adenocarcinoma, focal GGO will be seen on CT scan examination. The appearance of consolidation in lung tumors often looks single solid or like a mass with an invasive appearance. In cases of metastasis, nodules can be seen scattered randomly.[22] Fast and accurate radiological examination to determine the diagnosis, especially in cases of pneumonia, is currently very important. Several studies have shown that chest radiography for pneumonia-related consolidation or opacities identified by artificial intelligence (AI) has a sensitivity of up to 95.4% and a specificity of 66%. The combination of AI and a radiologist can shorten the time, speeding up the care of patients with pneumonia.[23]

Cancer patients need prevention of bacterial pneumonia by minimizing exposure, addressing risk factors for infection and vaccination. Infection control is very important especially in neutropenic patients. Speech therapy and dietary modification can reduce the risk of aspiration and oral care is important as an effect of chemotherapy and radiotherapy related to immune dysfunction.[13] Pneumococcal vaccination is recommended in cancer patients. In the pandemic era, SARS-Cov-2 vaccination is important in cancer patients. Booster vaccines have been shown to increase antibodies that can fight omicron variants in patients with solid tumors.[13] Current S. pneumoniae vaccines are effective but depend on the age of the individual in preventing pneumonia and also have problems related to high costs. Post-pandemic conditions are expected to provide developments in improving vaccines especially for infectious diseases.[24]

CONCLUSION

Conditions such as malnutrition or cachexia, chemotherapy and radiotherapy, in cancer patients cause decreased cellular and humoral immunity, increasing the risk of pneumonia. Dysfunction of the immune response such as decreased numbers of T cells and NK cells and damage to the anatomical defense of the respiratory tract cause pathogens that cause pneumonia to enter the lower respiratory tract. Symptoms that often occur in pneumonia with lung cancer are classic symptoms of pneumonia and are related to the causative pathogen. Supporting examinations such as chest X-ray, CT scan, ultrasound and microbiological examination can help establish the diagnosis of pneumonia in lung cancer. Antibiotics are given empirically or according to the target pathogen according to the condition of each individual.

REFERENCES

1. Cruz C et al. Epidemiology of lung cancer. In: Elias JA, Fishman. Fishman's Pulm Dis Disord 4th ed. 2015;1667–83.
2. Belluomini L et al. Infections and immunotherapy in lung cancer: A bad relationship? Int J Mol Sci. 2021;22(1):1–19.
3. Patel AJ et al. Characterising the impact of pneumonia on outcome in non-small cell lung cancer: Identifying preventative strategies. J Thorac Dis. 2020;12(5):2236–46.
4. Dancewicz M et al. Bronchial bacterial colonization in patients with lung cancer. Adv Respir Med. 2009;77:242–7.
5. Valvani A et al. Postobstructive pneumonia in lung cancer. Ann Transl Med. 2019;7(15):357–357.
6. Argilés JM et al. Mediators of cachexia in cancer patients. Nutrition. 2019;66:11–5.
7. Sutton SH. Infections associated with solid malignancies. Vol. 161, Cancer Treatment and Research. 2014. 371–411 p.
8. Akinosoglou K et al. Infectious complications in patients with lung cancer. Eur Rev Med Pharmacol Sci. 2013;17:8–18.
9. Albano D et al. Imaging side effects and complications of chemotherapy and radiation therapy: a pictorial review from head to toe. Insights Imaging. 2021;12(1):76.
10. Heo JW et al. Smoking is associated with pneumonia development in lung cancer patients. BMC Pulm Med. 2020;20(1):1–8.
11. Hsu-Kim C et al. The microbiology of postobstructive pneumonia in lung cancer patients. J Bronchol Interv Pulmonol. 2013;20(3):266–70.
12. Nagy A et al. Worse lung cancer outcome in patients with lower respiratory tract infection confirmed at time of diagnosis. Thorac Cancer. 2019;10(9):1819–26.
13. Pollock J et al. Respiratory infections and cancer. Vol. 2022, ERS Monograph. 2022. p. 15–30.
14. Garnacho-Montero J et al. Severe community-acquired pneumonia: current management and future therapeutic alternatives. Expert Rev Anti Infect Ther [Internet]. 2018;16(9):667–77. Available from: https://doi.org/10.1080/14787210.2018.1512403
15. Wong JL, Evans SE. Bacterial Pneumonia in Patients with Cancer: Novel Risk Factors and Management. Clin Chest Med [Internet]. 2017;38(2):263–77. Available from: http://dx.doi.org/10.1016/j.ccm.2016.12.005
16. Lynn J et al. Risk factors associated with complications in patients with chemotherapy-induced febrile neutropenia in emergency department. Hematol Oncol. 2013;31:189–96.
17. Postma DF et al. Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults. N Engl J Med. 2015;372(14):1312–23.
18. Rabello L et al. Clinical outcomes and microbiological characteristics of severe pneumonia in cancer patients: a prospective cohort study. PLoS One. 2015;10(1):1–13.
19. Vuotto F et al. Risk factors, clinical features, and outcome of Pseudomonas aeruginosa bacteremia in patients with hematologic malignancies: a case-control study. Am J Infect Control. 2013;41:527–30.
20. Kanwal K et al. Current Diagnostic Techniques for Pneumonia: A Scoping Review. Sensors.

2024;24(13):1–30.

21. Karakioulaki M, Stolz D. Biomarkers in pneumonia-beyond procalcitonin. Int J Mol Sci. 2019;20(8):1–18.

22. Guarnera A et al. COVID-19 Pneumonia and Lung Cancer: A Challenge for the Radiologist Review of the Main Radiological Features, Differential Diagnosis and Overlapping Pathologies. Tomography. 2022;8(1):513–28.

23. Becker J et al. Artificial Intelligence-Based Detection of Pneumonia in Chest Radiographs. Diagnostics. 2022;12(6):1–10.

24. Silva PH et al. Non-capsular based immunization approaches to prevent Streptococcus pneumoniae infection. Front Cell Infect Microbiol. 2022;12(September):1–11.