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CASE REPORT

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Asthma, PM2.5 Exposure, and Lung Cancer: A Case Report on the Involvement of IL-17A

Nurul ATIKA[1,2,3], Daniel MARANANTHA[1,2,3]

[1] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Hospital, Surabaya, Indonesia
[2] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga/Universitas Airlangga Hospital, Surabaya, Indonesia
[3] Indonesian Society of Respirology, Indonesia

Corresponding Author: Nurul Atika ✉ nurul.atika-2021@fk.unair.ac.id

ABSTRACT

Asthma is an impactful condition resulting in morbidity and incurring significant annual healthcare costs. Exposure to PM2.5 can induce the overexpression of genes encoding transcription factors and cytokines, leading to inflammatory responses and tissue damage. PM2.5 stimulates the release of IL-17A as a driver of severe asthma pathophysiology, where Interleukin-17A and IL-17F can strengthen signaling pathways that are upregulated in the airways of asthma, and their associated cytokines mediate tumor development preventing anti-tumor immunity and by stimulating angiogenesis.

This study presents a case involving a 68-year-old female with worsening shortness of breath over the last week intermittently. The patient also reported weight loss over the past 2 years. The patient was diagnosed with right lung cancer, Small Cell Lung Carcinoma extensive disease (Recist: stable disease) PS 1 VAS 3, and was overweight on the fourth cycle of etoposide-carboplatin chemotherapy. Laboratory examination results showed normal leukocyte count at 5970 µl (neutrophils: 75%, lymphocytes: 13.5%, eosinophils: 1.0%). IL 17A level was 30.429 pg/ml. The highest PM2.5 level reached 28.4 µg/m3.

We establish for our patient a working diagnosis of Small Cell Lung Carcinoma extensive disease with a previous history of asthma. The interaction of PM2.5 with asthma and genetic factors can induce respiratory tract inflammation involving various inflammatory cells and cytokines. Th17 cells and their related cytokines (such as IL-17A, IL-17F, IL-21, IL-22) can strengthen signaling pathways upregulated in the airways of asthma patients and mediate tumor development by preventing anti-tumor immunity and stimulating angiogenesis resulting in the emergence of lung cancer.

The interaction between PM2.5, asthma, and genetic factors can trigger inflammation in the respiratory tract through the activation of IL-17A along with their related signaling pathways, which may mediate the development of lung cancer.

Keywords: Asthma, PM2.5 exposure, lung cancer, IL 17 A

INTRODUCTION

Asthma is prevalent in developed countries, affecting nearly 1 in 10 children and 1 in 12 adults, leading to significant morbidity and substantial annual healthcare costs. Direct and indirect medical costs, including lost productivity, are estimated to exceed $18 billion per year in the United States (1,2).

Lung cancer remains the foremost cause of cancer-related mortality worldwide, accounting for approximately 2.1 million new diagnoses and 1.8 million deaths in 2018. Among its subtypes, small cell lung cancer (SCLC) constitutes around 250,000 new cases and is responsible for over 200,000 deaths globally each year. The incidence of all lung cancer subtypes, including SCLC, is notably higher in high-income countries, a pattern that reflects the greater prevalence of tobacco consumption in these regions (3).

ORCID Nurul Atika / 0009-0009-2017-2516, Daniel Maranantha / 0000-0002-4908-9005

Several studies have demonstrated a significant correlation between asthma and an elevated risk of developing lung cancer, including small cell lung cancer (SCLC). In a meta-analysis conducted by Qu et al., asthma was found to be significantly linked with a higher likelihood of lung cancer occurrence (OR = 1.44; 95% CI, 1.31-1.59; $P < 0.00001$; $I^2 = 83\%$). Notably, even non-smoking individuals with asthma showed an increased susceptibility to lung cancer (4). Furthermore, Charokopos et al. analyzed data from 13,939 smokers enrolled in the National Lung Cancer Screening Trial, utilizing baseline spirometry measurements alongside information on childhood asthma history. Their findings indicated that individuals with coexisting asthma and chronic obstructive pulmonary disease (COPD) exhibited a substantially higher risk of lung cancer compared to those with asthma alone (incidence rate ratio [IRR], 4.5; 95% CI, 1.3-15.8) and to smokers with normal lung function (IRR, 2.3; 95% CI, 1.3-4.2), after adjustment for potential confounding factors (5).

Air pollution is an environmental problem that impacts human health, resulting in a high prevalence of respiratory diseases. Data shows COPD with 209 million cases and 3.2 million deaths, pneumonia with 6,300 cases and 2.6 million deaths, lung cancer with 29 million cases and 1.8 million deaths, tuberculosis with 109 million cases and 1.2 million deaths, and asthma with 477 million cases and 455 thousand deaths (1,6).

PM2.5 is a type of air pollutant with a diameter of ≤2.5 μm. Exposure to PM2.5 can stimulate the overexpression of genes for transcription factors and cytokines that trigger inflammatory responses and injury (7). PM2.5 promotes the secretion of IL-17A as a potential driver of severe asthma pathophysiology, where Interleukin-17A and IL-17F can amplify signaling pathways upregulated in the airways in asthma, and their related cytokines mediate tumor development by stimulating angiogenesis and preventing anti-tumor immunity (8).

CASE REPORT

The 65-year-old woman presented with a history of frequent, worsening shortness of breath episodes that had been present since youth, becoming more problematic over the last decade, especially with strenuous activity and at night. She also reported a persistent cough with difficulty expelling phlegm and unexplained weight loss. The patient had a documented history of moderate asthma, managed with regular fenoterol and budesonide and formoterol inhalers, though the blood pressure was also elevated and inconsistently controlled. Further investigations revealed a significant pulmonary malignancy. On 2021, a CT-guided FNA confirmed adenocarcinoma of the right lung, with subsequent testing showing an EGFR positive exon 19 mutation. The patient underwent Gefitinib chemotherapy until 2022. However, the patient experienced progression of the lung cancer, and a bronchoscopy was performed for diagnostic evaluation. The patient was diagnosed with right lung cancer, Small Cell Lung Carcinoma extensive disease (Recist: stable disease) PS 1 VAS 3, and was overweight on the fourth cycle of etoposide-carboplatin chemotherapy. Relevant social history includes a small home with poor ventilation and a husband with a history of brain cancer in 1994. Physical examination of the lungs revealed asymmetric chest wall movement with reduced excursion on the right, diminished tactile fremitus on the right hemithorax, dullness upon percussion over the upper two-thirds of the right hemithorax, and decreased vesicular breath sounds in the same area. Wheezing was noted in both lung fields. Laboratory examination results showed normal leukocyte count at 5970 μl (neutrophils: 75%, lymphocytes: 13.5%, eosinophils: 1.0%). IL 17A level was 30.429 pg/ml. The highest PM2.5 level reached was 28.4 μg/m3. The patient's spirometry results showed an obstructive ventilatory defect without restriction, and a positive bronchodilator response. Before bronchodilators, FVC was 1.860 L (104%), FEV1 was 0.750 L (57%), and FEV1/FVC was 40%. After salbutamol, FEV1 improved to 0.960 L (73%) with 28% reversibility, confirming significant bronchodilation.

DISCUSSION

Bronchial Asthma

Bronchial asthma is a persistent inflammatory disorder of the respiratory tract characterized by symptoms such as coughing, wheezing, and dyspnea. While asthma commonly manifests during childhood (childhood-onset asthma), it may also arise later in adulthood, referred to as late-onset asthma (1,2).

Asthmatic manifestations arise from the interplay between the innate and adaptive immune responses in conjunction with airway epithelial cells. This interaction contributes to bronchial hyperresponsiveness — a condition in which airway smooth muscle exhibits exaggerated reac-

tions to nonspecific triggers such as cold air or physical exertion — as well as to excessive mucus secretion, structural remodeling of the airway wall, and luminal narrowing. The constriction of the airways results from persistent inflammation involving plasma leakage and infiltration of inflammatory cells, including eosinophils, neutrophils, lymphocytes, macrophages, and mast cells (1,2,9).

Asthma represents the most prevalent phenotype, typically characterized by early onset, allergen sensitization, and Th2-driven IgE (immunoglobulin E)-mediated mechanisms. Type 2 immune responses encompass the involvement of Th2 lymphocytes, IgE-secreting B cells, group 2 innate lymphoid cells (ILC2s), as well as smaller populations of IL-4-producing natural killer (NK) and NK-T cells, basophils, eosinophils, and mast cells, which serve as key cytokine producers. A dynamic interaction exists between type 2 cytokines (IL-4, IL-5, IL-9, and IL-13), primarily secreted by these immune cells, and epithelial-derived alarmins (IL-25, IL-33, and TSLP). In contrast, non-allergic or intrinsic asthma encompasses a group of patients exhibiting non-Th2-mediated inflammation. The pathogenesis of non-type 2 asthma is thought to arise from dysregulated innate immune mechanisms, including intrinsic neutrophilic dysfunction and activation of IL-17-dependent signaling pathways (Figure 1) (9).

Eosinophilic inflammation of the airways is a defining feature of both early-onset allergic asthma and late-onset non-allergic asthma phenotypes. As mentioned, eosinophilic asthma arises from complex immunological and proinflammatory mechanisms, primarily regulated by Th2 lymphocytes that release IL-5, IL-4, and IL-13. Besides being driven by adaptive immune mechanisms, Th2-mediated airway eosinophilia can also be linked to relevant innate immune responses dependent on cell-to-cell communication involving dendritic cells, bronchial epithelial cells, and innate lymphoid cells. Distinct subsets of Th cells are implicated in driving neutrophilic airway inflammation, which is frequently linked to the more severe asthma phenotypes. Among these, the Th17 subset—a specialized lineage of effector CD4⁺ T lymphocytes characterized by IL-17 production—plays a pivotal role in promoting airway neutrophilia. Environmental exposures, including allergens, cigarette smoke, and diesel exhaust particles, have been demonstrated to elicit Th17-dependent inflammatory responses within the airways of individuals with asthma (10).

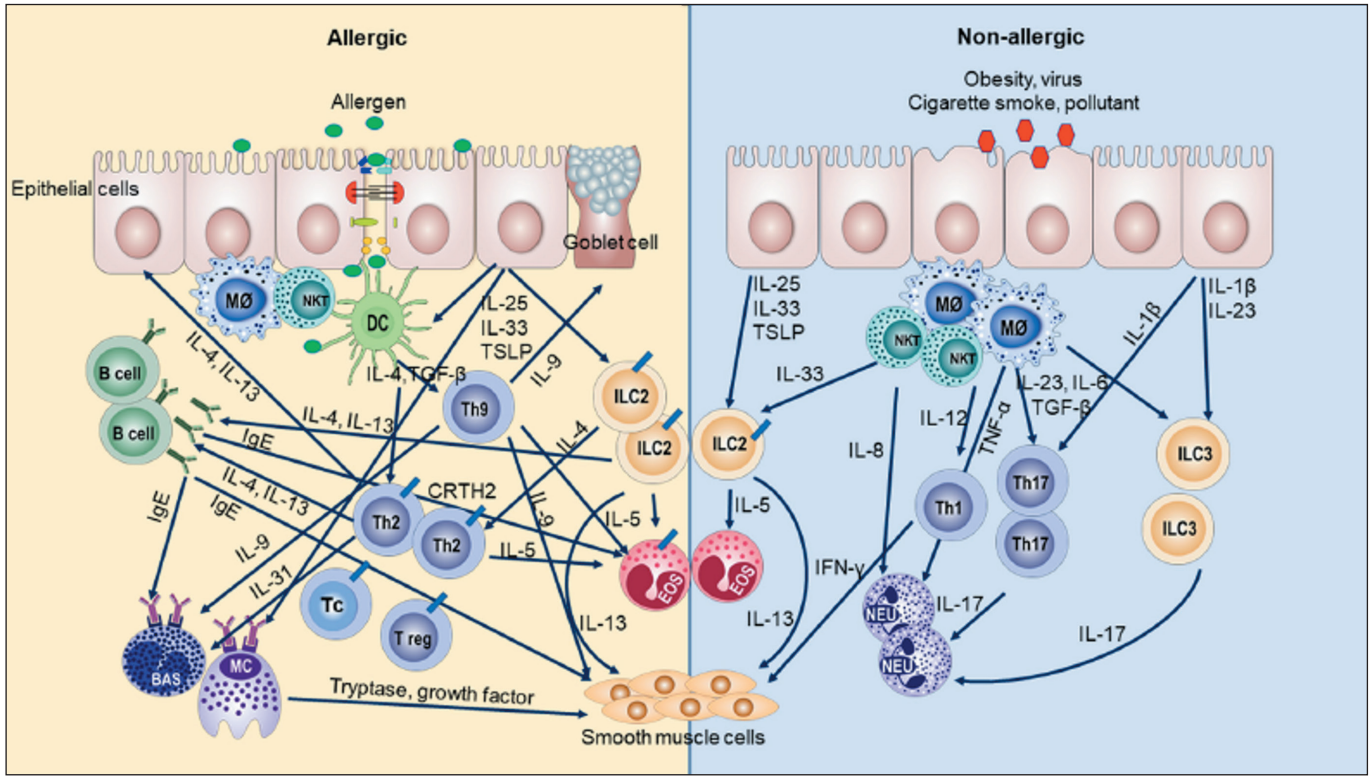

Figure 1: Immunological mechanisms of asthma

In this case, the patient experienced recurrent shortness of breath since a young age, especially with strenuous activity, corroborated by the patient's complaints of shortness of breath and cough. Physical examination revealed wheezing in both lung fields. Laboratory results showed elevated neutrophils (75%) and eosinophils (1.0%), along with an elevated IL-17A level of 30.439 pg/mL (increased from normal values). Pulmonary function tests showed an obstructive pattern with a positive bronchodilator response.

PM2.5

PM2.5 refers to fine particulate matter with an aerodynamic diameter of ≤2.5 μm, distinguished by its minute size, extensive surface area, and high capacity to adsorb toxic substances. These particles predominantly affect the distal airways and alveolar regions. Compositionally, PM2.5 represents a complex mixture of solid and liquid components, including black carbon, trace metals, nitrates, sulfates, polycyclic aromatic hydrocarbons, and emissions derived from vehicle exhaust.

The World Health Organization (WHO) ambient air quality guidelines recommend an annual average PM2.5 concentration limit of 10 μg/m^3 and a 24-hour average of 25 μg/m^3 (11). The Indonesian Agency for Meteorology, Climatology, and Geophysics (BMKG) categorizes PM2.5 levels into five categories as shown in Table I (12).

The measurements from the seven facilities showed average PM2.5 levels exceeding the standard concentration (>25 μg/m^3), with the highest levels found in public facilities (75.7 μg/m^3), followed by child activity facilities (41.9 μg/m^3), transportation facilities (36.3 μg/m^3), and healthcare facilities (33.1 μg/m^3). Data from Indonesia from 2016 to 2023 indicates that the highest PM2.5 levels reached was 15.51 μg/m^3 - 28.4 μg/m^3 (13). The above data suggests that inhaled air pollutant levels can cause respiratory disorders.

Table I. PM2.5 categories according to BMKG.

Range $PM_{2.5}$	Category
0-15.5 μg/m^3	Good
15.6-55.4 μg/m^3	Fair
55.5-150.4 μg/m^3	Unhealthy
150.5-250.4 μg/m^3	Very Unhealthy
≥250.5 μg/m^3	Hazardous

The impact of PM2.5 on mortality has been extensively examined in both national and international studies over the past several decades. Contemporary epidemiological evidence demonstrates a strong association between fine particulate matter exposure and the development of respiratory diseases. PM2.5 has been identified as a contributing factor in the aggravation of chronic inflammatory disorders of the lungs, as well as in conditions such as pulmonary hypertension, cardiovascular disease, and autoimmune disorders. Various mechanisms have been proposed to explain the physiological effects of PM2.5 on the human respiratory system. These include the activation of molecular signaling pathways—such as extracellular signal-regulated kinases (ERK), protein kinase B (Akt), mitogen-activated protein kinases (MAPK), and signal transducer and activator of transcription 1 (STAT1)—following exposure, and the interaction of pathogenic antibodies with pro-inflammatory cell receptors, which collectively amplify chronic inflammatory responses (14-17).

Exposure to PM2.5 can induce the overexpression of genes encoding transcription factors and cytokines, thereby initiating inflammatory cascades and cellular injury. Damage to vascular endothelial cells has been associated with PM2.5-related cardiovascular disorders, contributing to elevated morbidity and mortality rates. Contact with PM2.5—whether as a whole suspension, water-soluble fraction, or insoluble fraction—has been shown to promote cell death, enhance reactive oxygen species (ROS) generation, disrupt mitochondrial membrane potential, and activate the transcription factor NF-κB in human endothelial cells. Activation of NF-κB by PM2.5 particulates subsequently leads to cytotoxic effects mediated through apoptosis. Furthermore, human macrophages exposed to ex vivo cigarette smoke exhibited increased production of proinflammatory cytokines (IL-6 and IL-8), alongside a dose-dependent reduction in phagocytic activity and oxidative burst capacity (15-18).

Oxidative stress serves as a major pathological mechanism in the development of lung diseases and is closely linked to exposure to environmental contaminants such as ozone (O_3), nitric oxide (NO), and fine particulate matter (PM2.5). The toxic effects of PM2.5 are largely attributed to its ability to induce oxidative stress, primarily through the direct generation of reactive oxygen species (ROS) on its particle surface. Moreover, oxidative imbalance may stem from mitochondrial impairment, dysregulation of nicotinamide adenine dinucleotide phosphate (NADPH)

function, or activation of inflammatory cells that release ROS and reactive nitrogen intermediates (15-18).

PM2.5 has been shown to enhance IL-17A secretion from γδT and Th17 cells, thereby intensifying inflammatory responses. Elevated IL-17A expression is a recognized feature during pulmonary injury. Accumulating evidence indicates that both γδT and Th17 lymphocytes contribute to the aggravation of inflammation through IL-17A release. In the early phase of infection, γδT cells represent the predominant source of IL-17A, whereas Th17 cells are mainly involved in mediating its protective functions. Moreover, PM2.5 exposure stimulates IL-17A production, activates transforming growth factor (TGF) signaling cascades, and facilitates epithelial-mesenchymal transition (EMT) in bronchial epithelial cells, ultimately leading to pulmonary fibrosis. IL-17A is intricately associated with signaling pathways implicated in fibrosis development, while TGF-β plays a pivotal role in regulating fibroblast migration, invasion, and proliferative remodeling within the lungs. Thus, PM2.5 can cause several diseases with chronic airway inflammatory pathogenesis, one of which is asthma (8).

Haikerwal et al. investigated the relationship between daily mean PM2.5 levels and emergency department (ED) visits for asthma from December 2006 to January 2007. The 2006-2007 wildfire season represented one of the most widespread and prolonged fire events in Australia's history, resulting in elevated concentrations of PM2.5. After accounting for variations in temperature and relative humidity, an interquartile range increase of 8.6 μg/m³ in PM2.5 levels was correlated with a 1.96% rise (95% CI: 0.02-3.94) in emergency department visits for asthma on the corresponding day of exposure (15).

Acute exposure to fine particulate matter has been implicated in the onset of asthma. Short-term exposure to PM2.5 can provoke both local and systemic reactions through the release of proinflammatory mediators, such as cytokines and transcription factors, from airway epithelial cells. These processes are triggered by oxidative stress, which subsequently results in tissue injury and the worsening of asthma symptoms (14).

PM2.5 exposure contributes to oncogene activation and the silencing of tumor suppressor genes by inducing microRNA dysregulation and alterations in DNA methylation patterns in lung cancer (3). Changes in the tumor microenvironment are also detected in PM2.5-induced inflammatory cells. Gene mutations induced by PM2.5 have been widely investigated. In one study, there were 970 and 492 gene changes after exposure to 200 and 500 μg/ml PM2.5 in human bronchial epithelial cells, respectively. An in vivo experiment demonstrated that exposure to PM2.5 in mice resulted in mutations in 57 genes, with 14 showing upregulation and 43 showing downregulation. Multiple studies have established a preliminary foundation for exploring the role of microRNAs in oncogene activation associated with PM2.5-induced lung carcinogenesis. Further research has also examined the relationship between PM2.5-induced alterations in long non-coding RNAs (lncRNAs) and lung cancer, revealing that PM2.5 can upregulate lncRNA loc146880 via reactive oxygen species (ROS), thereby enhancing autophagy and the malignant potential of lung cancer cells (18).

T-helper 17-IL17

Th17 cells are derived from naive $CD4^+$ T lymphocytes, which also serve as precursors for Th1, Th2, and regulatory T (Treg) cells. The differentiation of these naive $CD4^+$ T cells into distinct subsets is determined by the surrounding cytokine milieu following antigenic stimulation. In the case of Th17 cells, cytokines such as transforming growth factor (TGF)-β and interleukin (IL)-6, together with IL-21 and IL-23, contribute to their induction and activation. Th17 cells further reinforce their own differentiation by secreting IL-21 and IL-6 or by stimulating nearby cells, thereby creating an amplification loop through autocrine and paracrine signaling. Additional proinflammatory cytokines, including IL-1β and tumor necrosis factor (TNF)-α, also facilitate the development of Th17 cells. Moreover, the upregulation and activation of specific transcription factors are pivotal for Th17 lineage commitment. In particular, signal transducer and activator of transcription 3 (STAT3) and retinoic acid-related orphan receptor-γt (RORγt) have been recognized as key regulators essential for Th17 cell differentiation and cytokine synthesis (19-21).

Interleukin-17A can specifically contribute to neutrophilic airway inflammation through upregulation of CSF3 and CXCL chemokines, mucosal membrane hyperplasia, airway hyper-reactivity, and corticosteroid resistance (22). In normal individuals, serum IL-17A levels are typically undetectable by instruments or close to 0 pg/mL (23,24). This contrasts with the case report where an elevated IL-

17A result of 30.429 pg/mL was found. This finding indicates an increased inflammatory response in the patient, marked by elevated IL-17A, which can serve as an inflammatory marker for asthma. This suggests that every asthmatic patient undergoing IL-17A examination shows an increase in IL-17A levels (25). Several studies have demonstrated neutrophil involvement in severe asthma. Given that IL-17A can promote the recruitment of neutrophils to sites of inflammation through both direct and indirect mechanisms, its relationship with airway neutrophilia deserves attention. In individuals with asthma, elevated IL-17A expression has been shown to correlate with increased levels of C-X-C motif ligand (CXCL) 8 and enhanced neutrophilic inflammation within the airways. Furthermore, the observed association between IL-17A expression, airflow obstruction, and sputum neutrophil counts indicates that IL-17A may play a key role in the pathogenesis of neutrophilic asthma (20).

T cells also play diverse roles in immune responses and are highly relevant to lung cancer biology (26). Th17 cells and their associated cytokines—such as IL-17A, IL-17F, IL-21, and IL-22—contribute to tumorigenesis, including lung cancer, through two principal mechanisms: enhancing angiogenesis and suppressing anti-tumor immune responses. Angiogenesis, the generation of new blood vessels, plays an essential role in the growth and persistence of primary solid tumors as well as in metastatic spread. Among the cytokines secreted by Th17 cells, IL-17A has been prominently identified as a key promoter of tumor-related angiogenesis. Given the influence of angiogenesis on tumor advancement, metastasis, and clinical prognosis, this process has garnered substantial scientific attention. Elevated expression of vascular endothelial growth factor (VEGF)—a central mediator of angiogenesis—has been consistently documented across multiple malignancies and is frequently associated with poor outcomes. It has been demonstrated that IL-17 enhances VEGF production by tumor cells and fibroblasts. Moreover, IL-17 functions as a potent pro-angiogenic cytokine, fostering neovascularization and tumor progression through direct induction of VEGF synthesis and angiogenin-2 release from stromal (myeloid and fibroblast) and epithelial cells. Beyond VEGF-dependent mechanisms, IL-17 may also facilitate tumor angiogenesis by modulating tumor-associated stromal cell activity (21,27,28).

Although existing studies have demonstrated the presence and differentiation of Th17 cells in lung cancer, their precise physiological role in tumor immunity remains incompletely understood. Evidence indicates that Th17 cells do not exhibit direct cytotoxic activity against tumor cells in vitro. Instead, they exert their influence indirectly by stimulating tumor-resident cells to release chemokines such as CCL2 and CCL20, which promote the recruitment of dendritic cells, granulocytes, $CD4^+$ and $CD8^+$ T lymphocytes, as well as natural killer (NK) cells to the tumor microenvironment. Following Th17 cell transfer, the resulting increase in dendritic cells enhances tumor antigen presentation in the lungs and facilitates their migration to lymph nodes, where they activate cytotoxic $CD8^+$ T cells. These tumor-specific $CD8^+$ T cells mediate tumor cell destruction independently of interferon-γ, likely through perforin-mediated mechanisms. Collectively, these findings imply that Th17 cells contribute to anti-tumor immune responses by promoting the infiltration and activation of effector T cells within tumor sites, highlighting their potential as a target for Th17-oriented immunotherapeutic strategies in lung cancer (27-29).

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer remains among the most commonly diagnosed malignancies and is a primary contributor to cancer-associated mortality across the globe. Roughly 85% of all lung cancer cases fall under the collective category of non-small cell lung cancer (NSCLC), which encompasses several histological variants, including adenocarcinoma (characterized by glandular differentiation), squamous cell carcinoma, and large cell carcinoma. The histopathological classification of lung cancer continues to evolve, with refined terminology and diagnostic criteria employed to accurately distinguish squamous cell carcinoma from adenocarcinoma, particularly in cases exhibiting poor differentiation (30,31).

Smoking is a major risk factor for lung cancer development. Globally, 80% of men and 50% of women with lung cancer are smokers. Tobacco use continues to rise in low- and middle-income nations, and a corresponding surge in lung cancer incidence is anticipated within these populations. It is estimated that approximately 10-25% of lung cancer cases occur among never-smokers, defined as individuals who have smoked fewer than 100 cigarettes over their lifetime. In addition to active smoking, several other etiological factors have been identified. Exposure to secondhand tobacco smoke has been recognized as a human carcinogen by the International Agency for Research

on Cancer and is linked to an elevated risk of lung cancer. Moreover, epidemiological evidence demonstrates a significant correlation between lung cancer and ambient air pollution, particularly with fine particulate matter less than 10 μm in diameter, which has been associated with a higher likelihood of developing lung adenocarcinoma (30).

Summary

The interaction of PM2.5 with asthma and genetic factors can lead to airway inflammation involving various inflammatory cells and cytokines. Th17 cells and other associated cytokines (i.e., IL-17 F, IL-17A, IL-21, IL-22, etc.) can amplify signaling pathways that are upregulated in the airways in asthma, in addition to mediating tumor development by stimulating angiogenesis and preventing antitumor immunity, ultimately leading to the emergence of lung cancer.

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Consent

Written informed consent was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the Editor-in Chief of this journal on request.

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Ethical Approval

Ethical approval was not required for this case report, however written informed consent was obtained from the patient and is available for review under request

Conflict of Interest

The authors declare no conflict of interest.

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Authorship Contributions

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