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REVIEW ARTICLE

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Progressive respiratory failure in a patient with wood dust exposure — a case report with an unexpected outcome of adenocarcinoma with *ALK* gene rearrangement

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ABSTRACT

Lung cancer remains the leading cause of cancer-related deaths among both men and women in Poland. There are various types of lung cancer, with non-small cell lung cancer (NSCLC) being the most prevalent. Within NSCLC, adenocarcinoma is the most common subtype. Lung adenocarcinoma poses significant challenges in effective treatment due to its complex molecular profile. Recently, significant advancements have been observed in targeted therapies for lung cancer, which are based on the molecular diagnosis of cancer subtypes. Patients with adenocarcinoma with *ALK* gene rearrangements have the possibility of effective therapy with ALK inhibitors, especially the third generation of these drugs — lorlatinib. Here, a 39-year-old male admitted to the documented clinic with symptoms of respiratory failure is presented. He had a long-term history of employment in the wood industry. The course of the disease was rapid and it did not allow for diagnosis and treatment before the patient's death. In the autopsy material pneumonic type of lung adenocarcinoma (PLADC) was diagnosed, and immunohistochemical method revealed expression of aberrant ALK protein. This case report is the first according to the literature in which *ALK* gene rearrangement was found in a non-smoking, young patient exposed to wood dust.

Keywords: lung adenocarcinoma, occupational diseases, dust, wood, occupational exposure, *ALK* rearrangement

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Introduction

Lung cancer places itself as the one of the most common malignancies. Squamous cell carcinoma (SCC), lung adenocarcinoma (LUAD) and small cell lung cancer (SCLC) are the most common histological types of lung cancer. The first two types constitute non-small cell lung cancer (NSCLC), which accounts for 85% of lung cancer cases. Since the nineties of the twentieth century the increase of lung adenocarcinoma incidence in North America, Europe and Asia was noticed. At the same time the number of SCC cases decreased [1]. This trend has been attributed to several changes such as a more polluted environment or increasing people's awareness of the dangers of smoking cigarettes [2]. Since 1995, wood dust has been reported in the International Agency for Research in Cancer (IARC) list as a human carcinogen and that it might be linked with lung cancer [3].

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An important aspect of lung adenocarcinoma is the tumor heterogeneity, including the occurrence of different driving mutations. The most common genetic abnormalities involve the *EGFR* and *KRAS* genes. The *ALK* gene rearrangements are presented in 3 to 5% of LUAD patients [4]. These patients often exhibit unique clinical characteristics, such as a younger age at onset, a non-smoking history, and adenocarcinoma histology. *ALK* gene rearrangement does not coexist with mutations in the *EGFR* and *KRAS* genes and other driver alterations [5]. The primary techniques currently employed in clinical practice to detect *ALK* abnormalities include among others fluorescence *in situ* hybridization (FISH), immunohistochemistry (IHC) and next generation sequencing [6].

In this report the case of a 39-year-old patient is presented who was diagnosed with lung mucinous adenocarcinoma, in which its occurrence might be linked with wood dust exposure. The diagnosis of lung cancer was made only in the autopsy material due to the fulminant and atypical course of the disease. Expression of ALK abnormal protein was detected by the IHC method in autopsy material.

Case description

A 39-year-old male was admitted to the Department of Pneumonology, Oncology, and Allergology at the University Clinical Hospital No. 4 in Lublin with symptoms of respiratory failure. He reported progressively worsening dyspnea and fatigue over the preceding two months. His medical history was significant for occupational exposure in the wood industry, involving prolonged contact with wood dust. He denied any smoking history or recent infectious symptoms upon admission. His condition was assessed as moderately severe. The initial computed tomography (CT) scans demonstrated extensive interstitial infiltrative changes in both lungs, along with numerous round air-filled bullae or areas potentially representing central necrosis within the infiltrates.

To reduce the elevated hemoglobin concentration (19 g/dL) — indicating chronic hypoxia — a 400 mL blood sample was taken, with normalization of hemoglobin concentration in next days. Physical examination revealed lung crackles and muffled percussion sounds. He was afebrile, had low inflammatory markers, and maintained normal blood pressure.

Due to the worsening dyspnea, the patient required the initiation of high-flow nasal oxygen therapy (HFNOT) on the second day after admission.

A bronchoscopy was performed during which biopsies were taken for histopathological examination. An attempt to obtain bronchoalveolar lavage (BAL) was unsuccessful due to bronchial collapse in the lower lobes. The bronchial aspirate collected for culture and cytology was positive for parainfluenza virus and *Candida spp.* only. A final pathomorphological diagnosis based on the biopsy material was not achieved.

Due to a rapid increase in inflammatory markers [leucocytes — 23 660 cell/mm^3 (norm: 4 500–11 000 cells/mm^3), C-reactive protein — 218.9 mg/L (norm: 0–5 mg/L), interleukin 6–18.6 pg/mL (norm: < 4.4 pg/mL)], the initiating therapy with clarithromycin, and fluconazole was started. Later, fluconazole was replaced by voriconazole. Additionally, a pulse steroid regimen of 500 mg methylprednisolone was administered for life-threatening indications.

Tumor marker tests revealed elevated cancer antigen 19-9 (CA 19-9) concentration, prompting an abdominal ultrasound which showed a probable hemangioma. A testicular ultrasound did not reveal any abnormalities.

The CT scan of the chest, abdomen, and pelvis was ordered which revealed further progression of bilateral multi-lobar ground-glass opacities and a new area of lung tissue destruction near the right atrium. Minimal aeration of the lungs was preserved at the left upper lobe. A bilateral collapse of segments 4 and 5 was present along with interlobular septal thickening, a crazy-paving pattern and multifocal lung tissue destruction. There was a single enlarged lymph node at the right hilum measuring 16 × 13 mm. Neither pleural effusion nor evidence of liver or bone metastasis was revealed. The altogether scan was inconsistent due to possible overlapping of infection (including possible *Staphylococcus aureus,* mucormycosis or cryptococcosis), and interstitial disease (Fig. 1A–C).

On the following day of the hospitalization the patient's condition rapidly deteriorated, with oxygen saturation dropping to 84% despite HFNOT. An arterial blood gas analysis showed a non-compensated metabolic alkalosis and severe hypoxemia. The patient began coughing with hemoptysis, respiratory effort and tachypnea. However, inflammatory markers remained low. Additional sputum tests were conducted, revealing positive results for parainfluenza and adenovirus, although causative treatment was not available. Dyselectrolytemia was observed. The patients received another pulse dose of 500 mg methylprednisolone, and non-invasive ventilation (NIV) was initiated. Due to the lack of effect of these treatment methods, invasive mechanical ventilation was started. After intubation, a large amount of blood-tinged secretion was suctioned from the airways. The patient was placed in the prone position, with only minimal improvement observed in gas exchange parameters. The cardiovascular system required support with a norepinephrine infusion. The methylprednisolone pulses were continued and acyclovir in inhalation was started. Unfortunately, the medical interventions were unsuccessful. The patient died less than 3 months after the first symptoms appeared and 20 days after the beginning of hospitalization.

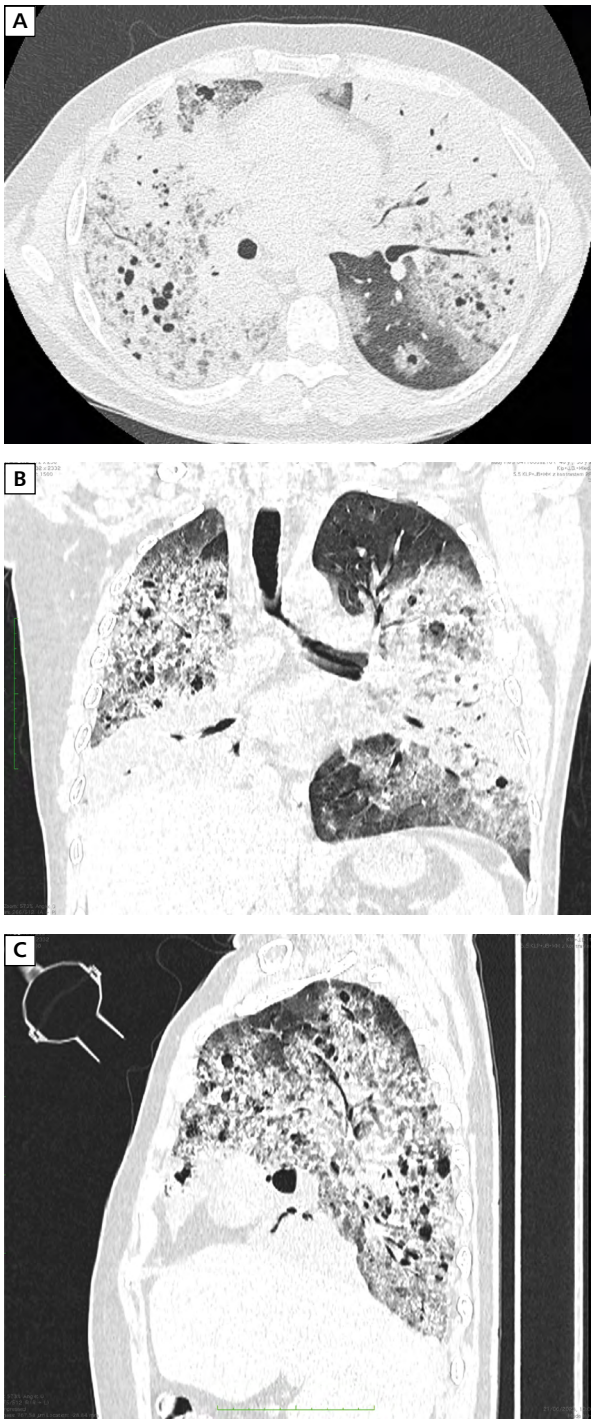

Figure 1. A. Computed tomography (CT) in the axial projection; **B.** CT in the frontal projection; **C.** CT in the sagittal projection of the right lung

The postmortem pathological examination revealed diffuse infiltrating mucinous adenocarcinoma in both lungs with lymphatic and vascular invasion. The tumor tissue showed a micropapillary and cribriform subtype. Clusters of tumor cells spread through air space (STAS). The results of the immunohistochemical staining revealed the expression of cytokeratin 7, and lack of expression of TTF1 and napsin A. Presence of aberrant ALK protein was detected by the IHC method with anti-ALK antibody clone D5F3 (Ventana) (Fig. 2A–C). The result of *ALK* gene rearrangement testing using the FISH method (ZytoVision break apart probe) was non-diagnostic due to DNA fragmentation in the autopsy material.

Discussion

Lung cancer is the leading cause of cancer-related mortality worldwide due to late diagnosis of the disease [7]. Early and rapid diagnosis of lung cancer (LC) remains a problem in modern medicine. There are no specific LC biochemical markers that can detect the disease. However, testing for various available tumor markers could be useful in ruling out the presence of a primary tumor outside the lung, as was done in the current patient. Computed tomography is an essential tool in LC diagnosis and staging. However, CT is not an ideal diagnostic method given, the heterogeneity of LCs, their growth patterns and the possibility of unusual radiological presentation. Typically, LUAD is localized in the lung periphery [8]. However, there is also a subtype of LC presenting as non-obstructive pulmonary consolidations, known as pneumonic type LUAD (PLADC), which was strongly expressed in the present patients. Huo et al. reported that patients with diffuse PLADC were predominantly male, smokers with respiratory manifestations and elevated inflammation parameters, whereas the most frequent histological subtype of PLADC is mucinous carcinoma [9].

The radiological signs of LUAD could be misleading since the possible presentation is ground glass opacity (GGO), consolidations with or without air bronchogram, pleural retraction, pleural effusion and lymphadenopathy. The consolidations and GGO might also be a sign of infection, especially in line with an elevated C-reactive protein level. In light of the environmental exposure to organic dust (wood processing), those disseminated and bilateral signs could be also connected with pulmonary toxicity or hypersensitivity pneumonitis and intestinal lung diseases [9–11]. The patient was employed in a private enterprise and the level of exposure to wood dust was unknown. The patient reported that employees often did not follow the rules for protection against exposure to wood dust (e.g., lack of appropriate protective masks). Further studies are being conducted on the effect of wood dust on the occurrence of respiratory diseases, especially interstitial lung diseases [12]. In the case of the current patients, lung cancer diagnosis was less likely compared with diseases mentioned above.

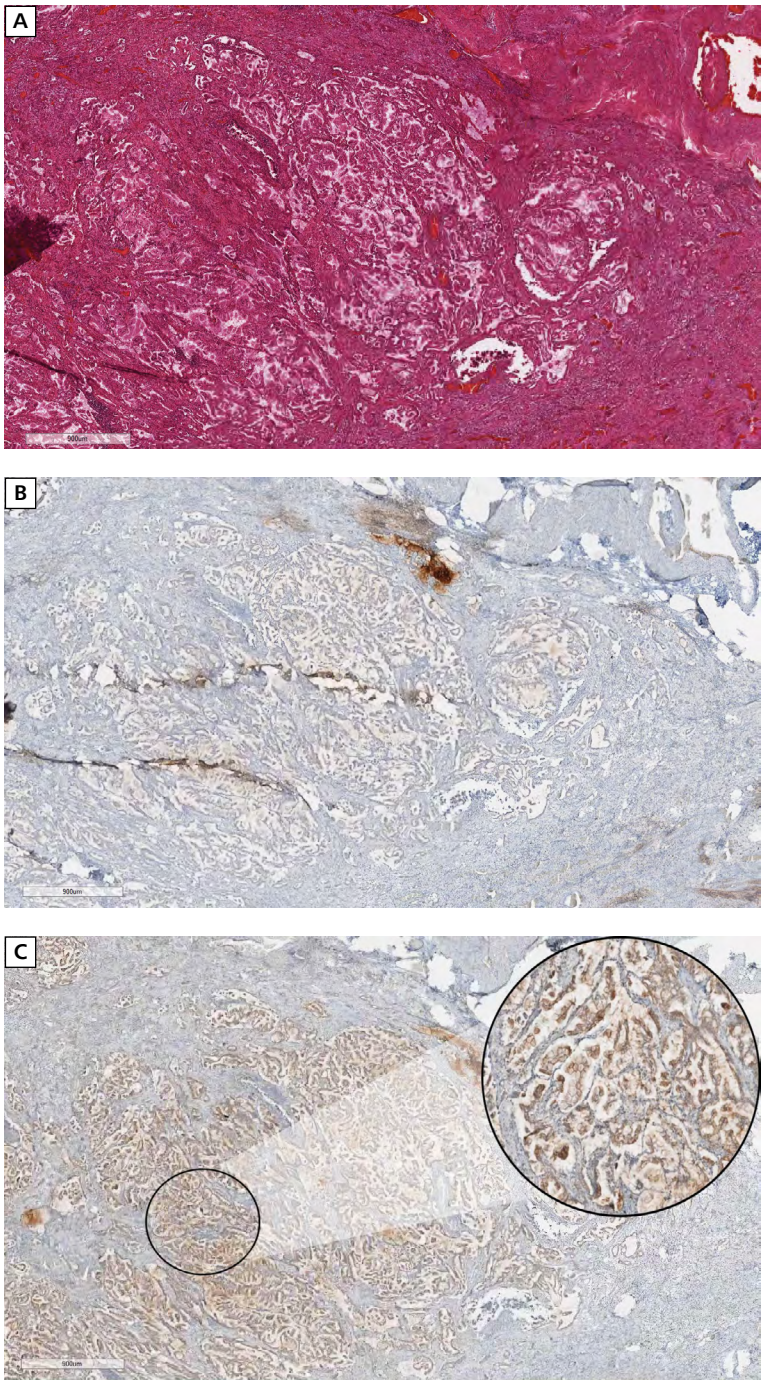

Figure 2. A. Hematoxylin and eosin (H&E) staining for visualization of cancer cells; **B.** Negative control for ALK protein staining in the immunohistochemistry (IHC) method; **C.** Positive staining of the ALK abnormal protein with D5F3 antibody in the IHC method

Due to the extremely short and aggressive course of the patient's diseases, it was impossible to establish a correct diagnosis before the patient's death and only post-mortem studies revealed possible targets for molecularly targeted therapy of the LUAD.

The ALK, a member of the insulin receptor tyrosine kinase family, is physiologically expressed in the nervous system during embryogenesis, participating in its development, and gradually diminishes after birth [13–17]. The *ALK* gene rearrangement occurs in about 4.5% of NSCLC patients, almost exclusively in young, non-smoking patients with adenocarcinoma. The presence of this genetic abnormality promotes the development of metastases to the central nervous system (CNS). The *ALK* gene rearrangement involves gene fragment containing the tyrosine kinase domain.

There are several partners of fusion for the *ALK* gene, however it is most often the gene encoding echinoderm microtubule-associated protein-like 4 (EML4). The fusion protein remains active without the need for stimulation by ligands and causes neoplastic transformation and excessive cells proliferation [18]. The ALK protein is not expressed on normal cells in adults, but active kinase can appear in cancer cells due to *ALK* gene rearrangements. Most *ALK* rearrangements in NSCLC patients (approximately 85% of cases) are caused by fusion of *ALK* gene with echinoderm microtubule-associated protein-like 4 (EML-4) gene. However, there have been described nearly 30 other possible fusion partners [19–21]. The oncogenic, constitutively active ALK cause ligand-independent hyper-activation of signaling pathways, including Janus kinase — signal transducer and activator of transcription protein family (JAK-STAT), phosphoinositide 3-kinases — protein kinase B (PI3K-PKB also known as AKT), phosphoinositide phospholipase C γ (PLCγ), and mitogen-activated protein kinase/mitogen-activated protein kinase (MAPK/ERK) [19, 21, 22].

Non-small cell lung cancer patients with *ALK* gene rearrangement can be treated with ALK inhibitors (ALKi). There are three generations of ALKi. Crizotinib belongs to the first generation of ALKi. This drug is relatively rarely used due to insufficient efficacy and poor penetration into the CNS. Second-generation ALKi (alectinib, brigatinib and ceritinib) are used in the first line of treatment or after failure of crizotinib therapy in patients with advanced NSCLC. Additionally, alectinib can be used in adjuvant therapy after radical surgery in patients with early stages of NSCLC. Lorlatinib is a third-generation ALKi. It can be used in the first line of therapy or after failure of first- or second-generation ALKi in patients with advanced NSCLC [18].

In the light of the development of novel targeted therapies and their promising results, comprehensive molecular testing in cancer is necessary to introduce the suitable targeted treatment in cancer patients [23]. Driver alterations in NSCLC can be investigated with several methods, including real-time polymerase chain reaction (PCR), FISH, next generation sequencing (NGS), or immunohistochemistry however in recent years, NGS became a preferred method in molecular testing of NSCLC patients [14, 23, 24]. NGS enables the simultaneous analysis of multiple frequently altered genes, including *EGFR, ALK, ROS1, BRAF, MET*, and *RET* [23, 25, 26]. Next generation sequencing is characterized by quite high sensitivity and material savings because all alterations are examined at the same time in one sample. There are, however, several drawbacks and limitations of NGS, including high requirements for material quality, limited accessibility, and high device costs [23].

Taking advantage of the fact that ALK is physiologically not highly expressed in healthy lung tissue, the use of IHC is a convenient method for detection of ALK protein expression [13]. The ALK-detecting IHC methods are rapid, accessible, reliable, and cost-effective. IHC do not require high-quality material (proteins do not degrade as quickly as DNA or RNA) [23, 27, 28]. Nevertheless, in cases where sample quality is not optimal and other advanced molecular methods might be unsuccessful, IHC could be used successfully, as demonstrated in the described case (the autopsy material was stored for months in a freezer).

In light of the development of molecularly targeted therapies, the treatment of choice in *ALK*-rearranged LUAD patients are ALK tyrosine kinase inhibitors (TKIs). The preferred first line treatment according to the European Society for Medical Oncology (ESMO) guidelines would by third-generation of ALK TKI — lorlatinib. However, sequential treatment with the second-generation of ALK TKIs (ceritinib, alectinib, or bryagtinib) in the first line, followed by third-generation (lorlatinib) in the second line of treatment is still used. Crizotinib, a first-generation agent, is currently not preferred as an initial therapy in patients with *ALK* gene rearrangement because of its lower efficacy compared to second- and third-generation drugs. In the CROWN trial, lorlatinib compared to crizotinib, which is showing superiority in terms of progression risk reduction, intracranial overall response rate and time to intracranial progression [27].

The influence of environmental factors on the occurrence of driver alterations in NSCLC patients is poorly studied. Ruano-Ravina et al. [29] found that the frequency of *ALK* rearrangements depends on the exposure of radiation from radon in the work and living environment. Intense radiation above 100 Bq/mm^3 caused a much more frequent occurrence of *ALK* rearrangement. However, the intensity of radiation did not affect the increased frequency of *EGFR* mutations. The study included 92 Spanish patients [29]. The present case report is the first, according to available literature, in which *ALK* gene rearrangement was found in a non-smoking patient exposed to wood dust. Moreover, the course of the disease was fulminant and consistent with PLADC type of adenocarcinoma. Establishing a hygienic standard for wood dust exposure is challenging since workers are rarely exposed to wood dust alone. Exposure often includes natural wood chemicals with irritant or allergenic properties, bacteria, molds, and wood preservatives like solvents or formaldehyde [30]. The nasal cavity and paranasal sinuses are the primary deposition sites for wood dust. However, wood processing produces particles capable of reaching the lower respiratory tract and depositing in the lungs [31].

Further research is needed concerning wood dust exposure and the later occurrence on adenocarcinoma. More attention should be drawn to studies on the dependence between adenocarcinoma and wood dust exposure. It is essential to promote knowledge on this topic and highlight the significance of this issue.

Article Information and Declarations

Ethics statement

The study received approval from the Bioethics Committee at the Medical University of Lublin: KE-0254/160/2021.

Author contributions

J.W., A.R., P.K.: conceptualization; P.K., J.M.: validation; J.W., A.R., A.K.: formal analysis; J.W., A.R.: investigation; P.K., T.K., D.L.: resources; J.W., A.R., J.P., W.P., J.K., P.D.: writing — original draft preparation; A.K., P.K.: writing — review and editing; J.M., M.A.K.: supervision; J.W., P.K., A.K.: project administration.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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