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Follicular B-Cell Lymphoma and Particulate Matter Associated with Environmental Exposure to Wood Dust

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 58-year-old
Final Diagnosis: Lymphoma
Symptoms: Shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Cardiology • Oncology • Pathology

Objective: Unusual clinical course

Background: In humans, wood dust is a carcinogen. Indeed, a strong association between wood dust and lung cancer risk has been reported in woodworkers, as well as in the general population.

Case Report: The patient was a 58-year-old man with follicular B-cell lymphoma. In the 10 years preceding the cancer diagnosis, he lived within 1/4 mile of a paper mill, where wood was processed. Computed tomography of the chest, abdomen, and pelvis revealed right hilar, mediastinal, abdominal, and retroperitoneal lymphadenopathy, bilateral pleural effusions, and a large soft-tissue mass infiltrating the small bowel mesentery. Analysis of the pleural fluid revealed the presence of a web of thin filopodia-like filaments, which trapped clusters of mesothelial cells and atypical lymphocytes. Single tubular filaments, morphologically similar to tunneling nanotubes, were seen originating from atypical lymphocytes and reaching neighboring cells. Furthermore, long, thick, cylindrical fibers of unknown nature, probably from the external environment, were also observed.

Conclusions: Because the patient lived in an unhealthy environment for many years, the possibility that his clinical condition was related to exposure to toxic emissions should be entertained. Considered in this context, the foreign fibers in his pleural fluid could be a direct consequence of inhalation of contaminants in the polluted air.

MeSH Keywords: Air Pollutants • Lymphoma, B-Cell • Pleural Effusion, Malignant

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Background

Exposure to wood dust has been associated with health issues due to chemicals present in the wood or microorganisms (bacteria, molds, and fungi). Wood dust is also associated with a number of toxic effects, including (though not limited to) eye, nose, and throat irritation, dermatitis, decreased lung capacity, and allergic reactions. Chronic exposure to wood dust or other broncho-active substances also can cause chronic obstructive lung diseases [1,2]. Although the toxic effects are related and specific to the different wood species, wood dust is considered a Group I carcinogen in humans [3]. Large longitudinal health studies have identified an occupational threshold of 5 mg/m^3 for inhalable wood dust [4]. In keeping with this finding, a recent meta-analysis showed a strong association between wood dust and lung cancer risk, not only in the general population but also among individuals with wood dust-related occupations [5].

Case Report

The patient was a 58-year-old man with a history of follicular B-cell lymphoma. Prior to being diagnosed with cancer, he had no other medical conditions. His family history was positive only for hypertension in his mother (alive and doing well). In terms of social history, he was married with 3 children, never smoked or used illicit drugs, and drank occasionally in social situations (a glass of wine 3 times a year, on average). Prior to his lymphoma diagnosis, he was functionally very active, walking up to 5 miles a day. In the 10 years preceding the diagnosis, he lived within a half mile of a paper mill where wood processing was conducted.

The patient's presenting symptoms included shortness of breath on exertion, profuse sweating, unintentional weight loss, and abdominal pain. He went to an urgent care facility, where an abdominal radiograph documented the presence of a left lower quadrant mass, which prompted referral to his primary care physician for further workup. Computed tomography of the chest, abdomen, and pelvis revealed right hilar, mediastinal, abdominal, and retroperitoneal lymphadenopathy, bilateral pleural effusions, a liver mass, and a large soft-tissue mass (17×5.1 cm) infiltrating the small bowel mesentery (**Figure 1**). A fluorescence *in situ* hybridization-based diagnostic assay, carried out on the bioptic material from the abdominal mass, was positive for *IGH-BCL2* translocation, but showed no evidence of *MYC* or *BCL6* gene rearrangement. Flow cytometry revealed <1% clonal B cells with a CD20-, CD10- and Kappa-positive phenotype.

At that point, the patient was referred to an oncologist for management. Analysis of pleural fluid obtained by thoracentesis

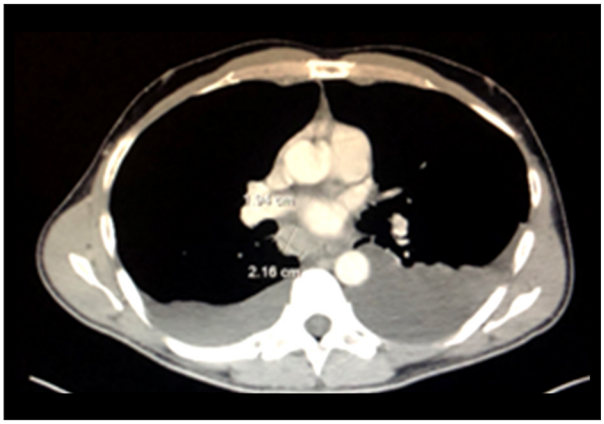

Figure 1. Computed tomography scan of the chest. The size of the heart is within normal limits. Moderately small bilateral pleural effusions are visible, which are larger on the left than on the right side. The right hilar lymph node measures 2.2×1.9 cm.

was positive for high-grade B-cell lymphoma of follicle center origin. A baseline echocardiogram also was obtained and showed normal left and right ventricular volumes, preserved left and right ventricular function (with a left ventricular ejection fraction [LVEF] of approximately 60%), no valvular issues, and mild pericardial effusion. Before receiving any chemotherapeutic agents, the patient developed oliguria and acute respiratory distress secondary to tumor lysis syndrome. Therefore, he was admitted to the Medical Intensive Care Unit, where he successfully underwent therapeutic thoracentesis and renal replacement therapy. During the same hospitalization, which lasted 12 days, he was started on chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).

The day after completing the eighth R-CHOP cycle, the patient's clinical condition progressively worsened. He developed ingravescent symptoms (severe shortness of breath, cough, inability to lie flat, leg heaviness, and ankle swelling) indicative of acute decompensation of congestive heart failure. After readmission to the hospital, he was found to be in acute systolic heart failure and to have atrial fibrillation (AFib) with rapid ventricular response, for which prompt cardioversion under deep sedation was required to reestablish a normal sinus rhythm. A repeat echocardiogram showed a severe reduction in left ventricular systolic function with an LVEF of 15%, severe generalized hypokinesis, right ventricular dysfunction, dilation of both the left and right atria, moderate to severe mitral regurgitation, and mild to moderate pulmonary hypertension. The patient was started on heart failure management, as well as anticoagulation to reduce the risk of stroke secondary to AFib. To rule out underlying myocardial ischemia as a potential cause of heart failure, the patient underwent a left heart catheterization, which showed normal coronary arteries. His clinical

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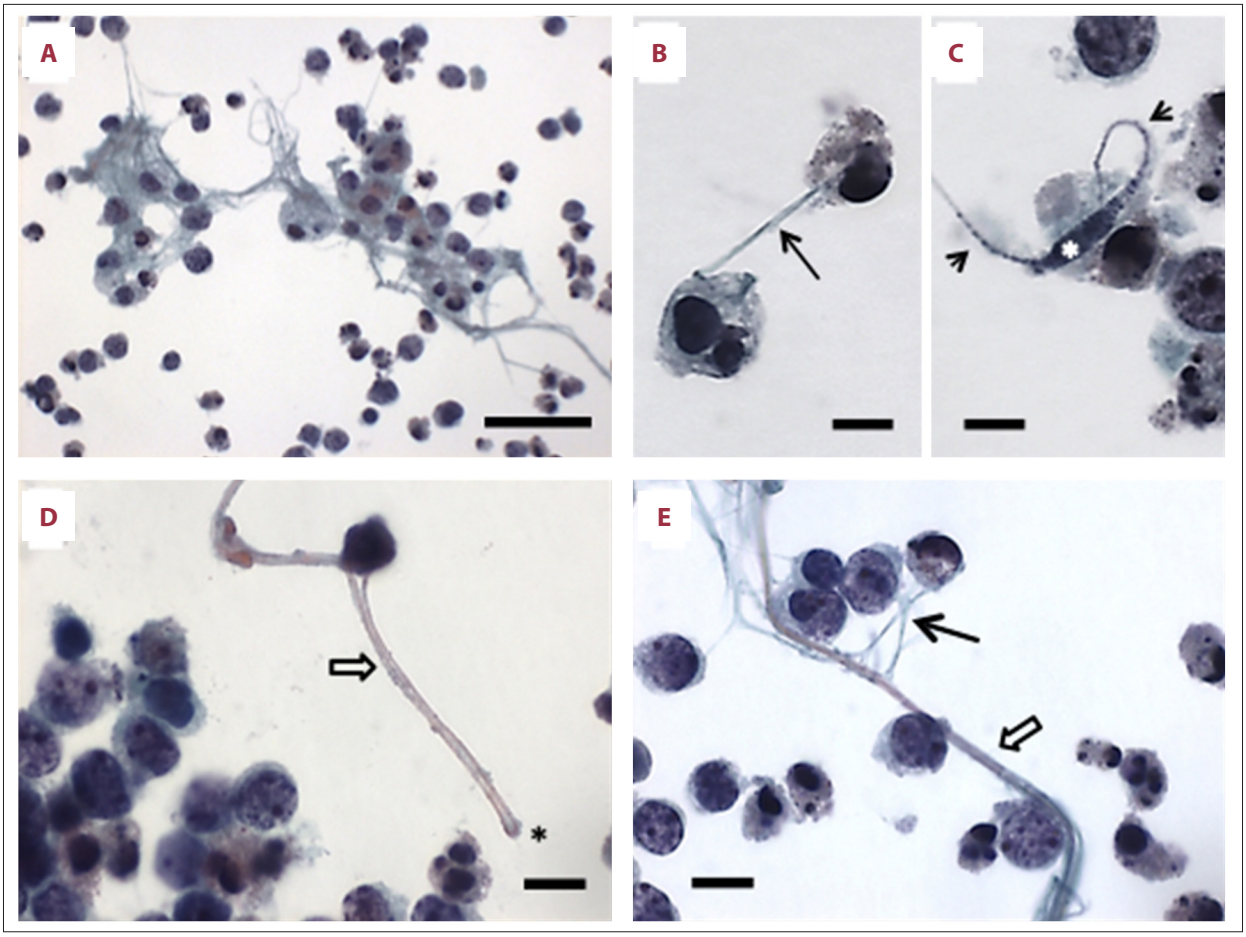

Figure 2. A pleural fluid sample. (**A**) A cluster of atypical lymphocytes. The cells have distinct nuclear bodies and a high nucleus-to-cytoplasm ratio. From these cells originates a net of filaments (filopodia-like filaments) that reach and trap surrounding cells (scale bar=50 µm). (**B**) A nanotube-like filament connects 2 atypical lymphocytes (arrow). Small particles of intensely-stained material are present in the cytoplasm as well as at the periphery of the nucleus and close to the cell membrane (scale bar=5 µm). (**C**) Densely-stained material similar to nuclear chromatin (white asterisk) is seen in the cytoplasm of atypical lymphocytes. The material gives rise to 2 thin tubes containing small particles of condensed material (short arrows), which probably were created when the main mass fragmented (scale bar=5 µm). (**D, E**) Unusually long, large-caliber cylindrical fibers (white arrows), many with truncated ends (asterisk in **D**), are seen in the pleural fluid. The black arrow points to the filopodia-like filaments (scale bar=10 µm).

condition slowly improved and he was finally discharged home with a wearable defibrillator (LifeVest), to reduce the risk of sudden cardiac death.

Microscopic examination of the pleural fluid revealed the presence of a web of threadlike filaments (filopodia-like filaments, caliber ≤0.1µm) trapping clusters of mesothelial cells and atypical lymphocytes (**Figure 2A**). Many of the single tubular filaments that arose from the atypical lymphocytes reached the neighboring cells (**Figure 2B**), whose cytosols (and/or nuclei) contained small, dark inclusions of unclear origin (**Figure 2C**). Long, cylindrical, larger-caliber fibers (approximately 1.5 µm), many of which had truncated ends, also were observed in the pleural fluid (**Figure 2D, 2E**).

Discussion

Wood dust is a known carcinogen that can cause cancers, mainly in the upper respiratory tract. More recently, however, wood dust exposure has been associated with a significantly increased risk (69%) of lung cancer alone and increased risks (82–93%) of squamous cell, small cell, and adenocarcinoma of the lung, especially in individuals with regular exposure to wood dust over a long period of time [6].

The patient in our case lived for many years in a geographic area (West Point, Virginia, United States) that is home to approximately 20 large chemical plants, 3 power stations, and more than 30 paper mills. Because of the attendant pollution, the West Point area has been listed as the Virginia locality with

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the most toxic air emissions [7]. Given the gravely unhealthy environment, the possibility that our patient's clinical condition was related to the toxic and particulate emissions in the air should be considered.

Among the pollutants in the area where the patient lives, wood dust is predominant. Wood dust generated by industrial woodworking consists mainly of particles that measure less than 5 µm, which tend to become trapped in the upper respiratory tract. Particles smaller than 5 µm are very hazardous because they infiltrate the non-ciliated epithelium in the lower respiratory tract, where their removal is especially slow (half-life >1 month) [8].

There is evidence that a fraction of all airborne particles, known as particulate matter, (PM) reaches the pleural cavity. According to the United States Environmental Protection Agency (US EPA, www.epa.gov), PM such as dust, fibers, and chemicals is defined as very small airborne particles, either directly emitted by burning or forming in the air as a result of reactions among chemical pollutants pollutants. If inhaled, PM can affect the heart and lungs, causing serious health problems, including cancer. Indeed, fine PM ($PM_{2.5}$) has been associated specifically with mortality from cancers of the lung, stomach, colorectum, liver, breast, cervix, and bladder, as well as for Hodgkin and non-Hodgkin lymphomas and leukemia [9].

Clearance of exogenous particles from the pleural space occurs by means of an inherent mechanism that involves the stomata in the parietal pleura. Lymphatic stomata are small lymphatic openings in the serous membrane, communicating with the serous cavity the serous cavity [10]. It has been shown that airborne PM that reaches the lung alveoli enters the pleural space and crosses the interstitium. From there, the inhaled PM that access the stomata of the parietal pleura can pass into the lymphatic flow, leading to lymph nodes in the mediastinum and the central lung [11]. The stomata also are the main retention sites for long fibers such as carbon nanotubes, asbestos, and cellulose, and when they are retained, they become a pathogenetic trigger for inflammation and pleural pathology, including cancer [11,12].

Most of the tubular filaments in our patient arose from atypical lymphocytes and exhibited morphology typical of tunneling nanotubes (TnTs), which are long, actin-based, cytoplasmic extroversions used to shuttle molecular cargo between cells [13]. Indeed, similar structures are involved at different levels in communications between immune system cells [14,15], especially the spread of cancer from cell to cell [13,16]. Inside these nanotubes, we observed small particles of densely-stained material, which often appeared to originate from the fragmentation of nuclear chromatin. Conversely, the nature of the larger-caliber, long, cylindrical, truncated fibers in the pleural liquid is unknown. It is plausible that these are foreign fibers derived from the external environment and are likely related to the presence of PM in the air.

Conclusions

Air pollution and toxic and PM emissions represent a major public health concern. Accordingly, the discovery of foreign fibers in the pleural fluid of our patient might be a direct consequence of his inhalation of contaminants present in the polluted air around him. Large-scale studies are warranted to better characterize the risk attendant to wood dust with the ultimate goal of protecting the population from the hazardous and poisonous effects of pollutants.

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