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Primary Pulmonary Anaplastic Large Cell Lymphoma Presenting as Progressive Respiratory Failure in a 38-Year-Old Woman: A Case Report of a Rare Entity

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Abstract: We report a case of primary pulmonary *anaplastic lymphoma kinase*-positive anaplastic large cell lymphoma in a 38-year-old woman with a smoking and vaping history. The patient presented with hypoxemia and a history of shortness of breath, cough, and intermittent fevers. Initial imaging and pleural fluid studies suggested possible empyema. Despite being given antibiotics, her respiratory status continued to deteriorate and she was put on extracorporeal membrane oxygenation. Repeat imaging showed increased size of intrathoracic lymph nodes and perilymphatic pulmonary nodules. IV steroids were initiated after bronchoalveolar lavage revealed lipophages suggestive of e-cigarette, or vaping, product use-associated lung injury. A laboratory workup revealed no signs of rheumatologic disease, and negative cultures ruled out a bacterial or fungal cause of the disease. Because of these laboratory results and because the patient did not show clinical signs of improvement, a biopsy of the left lower lobe lymph node was performed. The patient was diagnosed with *anaplastic lymphoma kinase*-positive anaplastic large cell lymphoma based on the results of the biopsy. This case highlights the importance of suspecting pulmonary lymphoma in patients with a history of B-symptoms and compatible imaging findings, despite its rarity.

Keywords: *anaplastic large cell lymphoma, primary pulmonary lymphoma, non-Hodgkin lymphoma, e-cigarette or vaping product use-associated lung injury (EVALI), pulmonary nodules*

Key Points

- Primary pulmonary ALCL (anaplastic large cell lymphoma) is a rare diagnosis with nonspecific presenting symptoms, but compatible radiographic findings can help reduce the number of differential considerations.
- Early identification of a history of B-symptoms can help guide appropriate imaging, tissue sampling, and treatment.

Case Presentation

A 38-year-old woman with a 25 pack-year smoking history and 2 years of vaping product use presented to an outside hospital after experiencing fatigue, shortness of breath, cough, and intermittent fevers for 3 weeks. She was hypoxemic and tachycardiac on examination. Computed tomography angiography (CTA) was performed to exclude pulmonary embolism and revealed a 4.5 cm right pleural effusion and consolidations in the right middle and right lower lobes, scattered sub-centimeter pulmonary nodules, and mildly enlarged thoracic lymph nodes (Figure 1A, 1B). No pulmonary embolism was identified.

Abbreviations
ACE: angiotensin converting enzyme
ALK: anaplastic lymphoma kinase
ALCL: anaplastic large cell lymphoma
BAL: bronchoalveolar lavage
CHOEP: cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone
CT: computed tomography
CTA: computed tomography angiography
ECMO: extracorporeal membrane oxygenation
EVALI: e-cigarette, or vaping, product use-associated lung injury
MALT: mucosa-associated lymphoid tissue
NHL: non-Hodgkin lymphoma
RF: rheumatoid factor
VATS: video-assisted thoracoscopic surgery

A laboratory workup revealed leukocytosis (21 500 WBC/μL [reference range, 4500-11 000 WBC/μL]) with left shift (greater than 94% neutrophils [reference range, 40-60%]). The patient was also revealed to be mildly anemic, with hemoglobin levels of 10 g/dL (reference range, 12.1 to 15.1 g/dL).

The patient underwent thoracentesis, during which 500 mL of exudative hemorrhagic fluid was removed. Blood and pleural fluid cultures were negative. The patient was started on broad-spectrum antibiotics with a presumed diagnosis of pneumonia. Video-assisted thoracoscopic surgery (VATS) and decortication was attempted for suspected empyema, but the procedure was terminated early due to hemodynamic instability. Twelve days after presenting to the outside hospital, the patient was transferred to our institution for higher level of care and possible extracorporeal membrane oxygenation (ECMO) due to progressive respiratory failure.

Repeat CT imaging of the patient's chest revealed an increase in the size of multi-station thoracic lymph nodes, numerous new and enlarging subcentimeter pulmonary nodules in a primarily perilymphatic distribution, ill-defined ground-glass attenuation and consolidative densities in both lungs, small bilateral pleural effusions measuring roughly 1 cm (Figure 2), and the enlargement of a partially visualized spleen.

The patient was placed on ECMO 3 days after transfer and continued to receive broad-spectrum antibiotics. Samples collected with bronchoalveolar lavage (BAL) demonstrated positive cytology for lipophages (lipid laden macrophages) on oil red O staining. Given her history of vaping product use and a possible diagnosis of e-cigarette, or vaping, product use-associated lung injury (EVALI), the patient received 500 mg of methylprednisolone once per day for 3 days, followed by a tapering regimen.

Despite receiving broad spectrum antibiotics, the patient continued to experience intermittent fevers. Results from an extensive laboratory workup, including atypical and fungal infection serologies, repeat blood cultures, and BAL cultures, remained negative. The patient's angiotensin converting enzyme (ACE) level was within the reference range. A serology workup was performed to rule out autoimmune disease, but the only significant result was a low-level positive rheumatoid factor (RF) of 16 (reference, < 14). The patient had no signs or symptoms of connective tissue disease.

Despite treatment with steroids, the thoracic lymph nodes continued to enlarge, which was suggestive of a neoplastic process. Bronchoscopy was repeated to perform a biopsy of the left lower lobe lymph node. Histologic and immunohistochemical analyses revealed tumor cells that were positive for CD30 and *anaplastic lymphoma kinase* (*ALK*), features consistent with a diagnosis of *ALK*-positive anaplastic large cell lymphoma (ALCL) (*ALK*+ ALCL).[1]

The patient was started on her first cycle of chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone (CHOEP). Subsequent laboratory tests and imaging revealed a decrease in the size of the mediastinal lymph nodes and spleen as well as the resolution or decrease of the pulmonary nodules that were first identified at the time of presentation.

Discussion

Lymphomas comprise approximately 5% of all malignancies and are generally divided into

Hodgkin's lymphoma (HL), which consists of B-cells and characteristic Reed-Sternberg cells, and the more common non-Hodgkin lymphoma (NHL), which can consist of B-cells, T-cells, or NK cells.[2,3] Lymphomas are further classified based on the subtype of cell involved and the stage of maturation.[1]

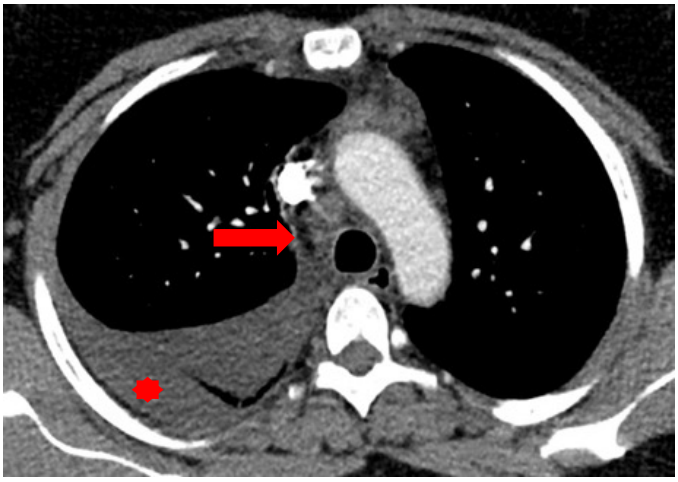
Pulmonary involvement of lymphoma is common in systemic disease, whereas primary pulmonary lymphoma is extremely rare and represents only 0.5% of primary lung neoplasms.[4] "Primary pulmonary lymphoma represents a monoclonal lymphoid proliferation affecting the lungs in a patient with no detectable extrathoracic lymphoma for at least 3 months after the initial diagnosis."[4] Primary "lymphomas arising in the lung are estimated to be less than 1% of all lymphomas."[5] The most common subtypes of primary pulmonary lymphoma include extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) origin, diffuse large B-cell lymphoma, and lymphomatoid granulomatosis.[4] Radiographic features of primary pulmonary lymphoma are variable and can include multiple bilateral nodules or consolidations, a single nodule or mass, cavitation, and/or peribronchovascular infiltrates.[4,6] HL is more often a cause of secondary pulmonary lymphoma, with 85% of HL cases having pulmonary involvement, compared to only 24% in NHL.[6] Radiographic features of secondary lymphoma include pulmonary nodules, lymphangitic spread, pleural effusion, and intrathoracic lymphadenopathy.[4]

Anaplastic large cell lymphoma is an aggressive form of non-Hodgkin lymphoma with rapid proliferation of mature T-cell lymphocytes termed hallmark cells, which have unique horseshoe-shaped nuclei and strong immunohistochemical staining for CD30.[11] ALCL is further divided into several subtypes, the two most common of which are defined by the expression or absence of *anaplastic lymphoma kinase*, denoted as *ALK*+ or *ALK*-, respectively. The primary organ of involvement is not always identified. However, being of T-cell lineage,[11] the lymphoma is usually of peripheral origin involving lymph nodes and extranodal sites including skin, bone, soft tissues, lung, and liver.[12]

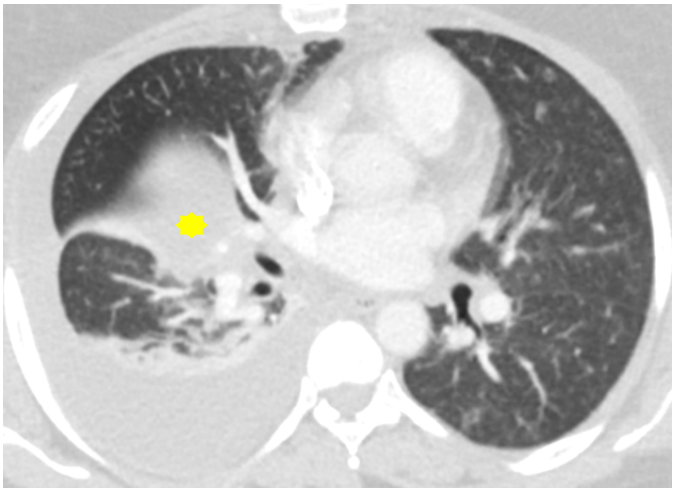
ALCL limited to the lungs without extrapulmonary involvement, as in our case, is defined as primary pulmonary ALCL. This is an exceedingly rare diagnosis with only a few cases described in the literature. Reports describe similar imaging findings as those encountered here: diffuse lung nodularity, marked thickening of the bronchovascular structures and interlobular septae with mediastinal and hilar lymphadenopathy, while others have reported a more mass-like initial presentation.[7–9]

Figure 1. Computed Tomography (CT) Images of the Chest of a 38-Year-Old Woman with Primary Pulmonary Anaplastic Large Cell Lymphoma at the Time of Presentation.

A CT of chest from the mediastinal window, axial view



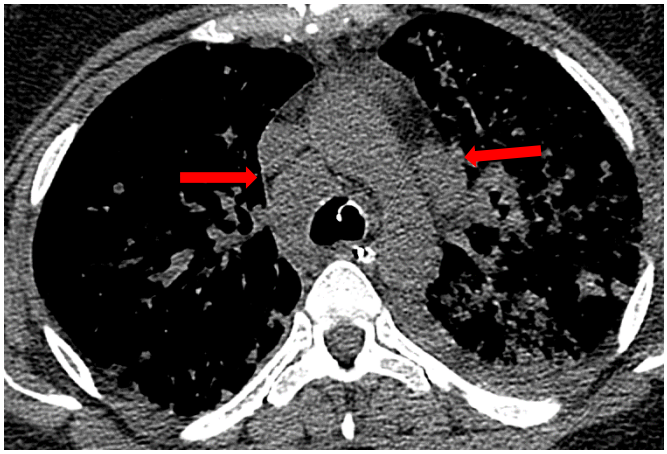
B CT of chest from the lung window, axial view



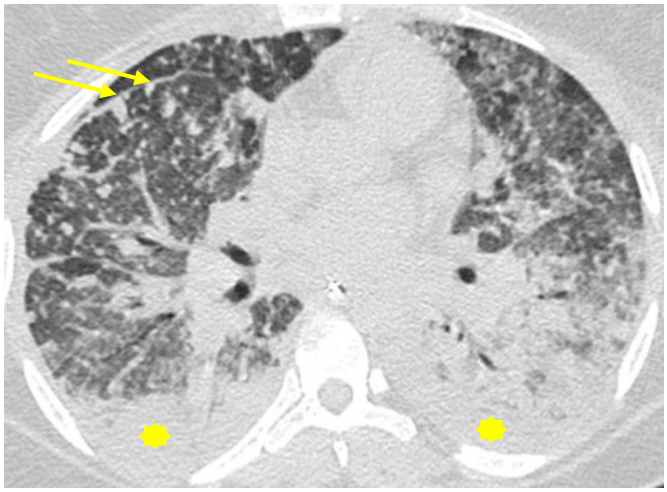
(A) An axial CT image of the chest from the mediastinal window demonstrates mildly enlarged mediastinal lymph nodes (A, red arrow) and a moderate-sized right pleural effusion, measuring 4.5 cm at the widest segment (A, red star). (B) An axial CT image of the chest from the lung window demonstrates subsegmental atelectasis of the right lower and right middle lobes (B, yellow star).

Figure 2. Computed Tomography (CT) Images of the Chest of a 38-Year-Old Woman with Primary Pulmonary Anaplastic Large Cell Lymphoma 13 Days After Initial Imaging.

A CT of chest from mediastinal window, axial view



B CT of chest from the lung window, axial view



(A) Axial CT imaging of the chest from the mediastinal window demonstrates a significant increase in the size of intrathoracic lymph nodes (A, red arrows) from the time of initial imaging (Figure 1). (B) Axial CT imaging of the chest from the lung window demonstrates numerous subcentimeter nodules and micronodules with perilymphatic distribution (B, yellow arrows), and small bilateral pleural effusions (B, yellow stars).

A systematic review by Padhi et al[10] analyzed 39 cases of pulmonary ALCL and found that 21 cases involved endobronchial lesions and 18 cases involved parenchymal lesions. Radiographic findings were as follows: 25 cases with mass or mass-like findings, 11 with nodular infiltrates, 15 with associated collapse/atelectasis, 6 with pleural effusions, 3 with hilar and/or mediastinal adenopathy, 1 with consolidation, 1 with a cavitary lesion, and 1 with ground-glass opacities. The three most common symptoms were fever, cough with or without sputum production, and dyspnea. Twenty-three cases (59%) had associated B-symptoms, and, notably, 7 cases (17.9%) had worsening dyspnea/respiratory failure.[10]

Consistent with the aforementioned reports, our patient presented with a history of B-symptoms, cough, and worsening respiratory failure. Radiographic findings included pleural effusion, nodular infiltrates, interlobular septal thickening, and progressive intrathoracic lymphadenopathy.

Though the imaging features of this diagnosis are nonspecific and tissue sampling is required, there are several key imaging findings which are useful in narrowing the differential considerations and in guiding the clinician to the appropriate diagnostic test. Recognizing the presence of nodular peribronchovascular infiltrates and interlobular septal thickening is crucial, as there are relatively few possible causes other than ALCL, including lymphoma, sarcoidosis, lymphangitic carcinomatosis, tuberculosis, and endemic mycoses.[13] Disseminated mycotic infection was the primary differential consideration given the acute nature of the patient's disease and the high rate of coccidioidomycosis in the southwestern United States, where she presented. This diagnosis was appropriately excluded with negative serologic markers and culture following BAL, as were tuberculosis and the other endemic mycoses. Sarcoidosis was also excluded due to the rapid progression of disease and an ACE level within normal limits.[14]

The *ALK*+ subtype, defined by a t(2;5)(p23;q35) translocation involving the *ALK* gene and the *nucleophosmin* (*NPM*) gene, carries a more favorable prognosis with 5-year survival reaching 70-90%.[11] Interestingly, this type is far more common in younger populations (mean [SD] age, 22 [10.8] years) and has a 3-fold male predominance, making this case in a 38-year-old woman even more unusual.[12,15]

Patients usually present with advanced stage disease (stage III or IV), so detecting ALCL and beginning treatment quickly after presentation is crucial for improving survival.[16] Despite the rarity of this diagnosis, the need for rapid identification and treatment means that it is important that primary pulmonary lymphoma remain a diagnostic

consideration when the imaging features are present and the clinical presentation supports the diagnosis.

Conclusion

This case report describes a 38-year-old woman with a history of smoking and vaping who presented with respiratory failure and was ultimately diagnosed with *ALK*-positive anaplastic large cell lymphoma (*ALK*+ ALCL) involving the lungs and intrathoracic lymph nodes. While primary pulmonary ALCL is a rare diagnosis with nonspecific presenting symptoms, compatible radiographic findings can help reduce the number of differential considerations. It is important for clinicians to recognize the key imaging features and consider lymphoma in the differential diagnosis of nodular peribronchovascular infiltrates and interlobular septal thickening. Because this disease can progress rapidly, and because patients often present with advanced stage disease, early identification of a history of B-symptoms can help guide appropriate diagnostic interventions and treatment. Tissue sampling is required for definitive diagnosis, and treatment generally involves chemotherapy and/or radiation therapy.

Author Contributions

Conceptualization, P.A.; Acquisition, analysis, and interpretation of data, P.A.; Writing – original draft preparation, P.A.; Review and editing, P.A., D.R., and L.P.; Supervision, L.P. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

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References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms [published correction appears in Leukemia. 2023 Sep;37(9):1944-1951]. *Leukemia*. 2022;36(7):1720-1748. doi:10.1038/s41375-022-01620-2
2. SEER Cancer Stat Facts. National Cancer Institute. https://seer.cancer.gov/statfacts/index.html. Published 2022. Accessed July 19, 2023
3. Mugnaini EN, Ghosh N. Lymphoma. *Prim* Care. 2016;43(4):661-675. doi:10.1016/j.pop.2016.07.012
4. Hare SS, Souza CA, Bain G, Seely JM, Gomes MM. The radiological spectrum of pulmonary lymphoproliferative disease. *Br J Radiol*. 2012;85(1015):848-864. doi:10.1259/bjr/16420165
5. Lee KS, Kim Y, Primack SL. Imaging of pulmonary lymphomas. *AJR Am J Roentgenol*. 1997;168(2):339-345. doi:10.2214/ajr.168.2.9016202
6. Berkman N, Breuer R, Kramer MR, Polliack A. Pulmonary involvement in lymphoma. *Leuk Lymphoma*. 1996;20(3-4):229-237. doi:10.3109/10428199609051612
7. Hu Y, Liu P, Gao L, Mu X, Wang G. Diffuse pulmonary infiltration by anaplastic lymphoma kinase negative anaplastic large cell lymphoma: A case report and literature review. *Respir Med CME*. 2010;3(4):260-262. doi:10.1016/j.rmedc.2009.09.024
8. Han SH, Maeng YH, Kim YS, et al. Primary anaplastic large cell lymphoma of the lung presenting with acute atelectasis. *Thorac Cancer*. 2014;5(1):78-81. doi:10.1111/1759-7714.12027
9. Carvalho J, Marques DP, Oliveira I, Claudino C. A Rare Case of Primary Pulmonary Anaplastic Large Cell Lymphoma. *Eur J Case Rep Intern Med*. 2019;6(9):001249. Published 2019 Sep 9. doi:10.12890/2019_001249
10. Padhi S, Panigrahi MK, Mohapatra S, et al. Pulmonary anaplastic large-cell lymphoma: A case-based systematic review of world literature. *J Cancer Res Ther*. 2021;17(6):1297-1306. doi:10.4103/jcrt.JCRT_1089_19
11. Kadin ME, Carpenter C. Systemic and primary cutaneous anaplastic large cell lymphomas. *Semin Hematol*. 2003;40(3):244-256. doi:10.1016/s0037-1963(03)00138-0
12. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. *Blood*. 1999;93(8):2697-2706.
13. Kang EY, Grenier P, Laurent F, Müller NL. Interlobular septal thickening: patterns at high-resolution computed tomography. *J Thorac Imaging*. 1996;11(4):260-264.
14. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. [published correction appears in Nat Rev Dis Primers. 2019 Jul 16;5(1):49]. *Nat Rev Dis Primers*. 2019;5(1):45. Published 2019 Jul 4. doi:10.1038/s41572-019-0096-x

15. Sibon D, Fournier M, Brière J, et al. Long-Term Outcome of Adults With Systemic Anaplastic Large-Cell Lymphoma Treated Within the Groupe d'Étude des Lymphomes de l'Adulte Trials. *J Clin Oncol*. 2012;30(32):3939-3946. doi:10.1200/JCO.2012.42.2345

16. Kadin ME. Primary Ki-1-positive anaplastic large-cell lymphoma: A distinct clinicopathologic entity. *Ann Oncol*. 1994;5 Suppl 1:25-30. doi:10.1093/annonc/5.suppl_1.S25