Anaplastic Large Cell Lymphoma Presenting as Respiratory Failure: A Case Report

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Abstract

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma involving CD 30-positive T-cells. As the name implies, the lymphoma cells are anaplastic, often with eccentric, horseshoe-or kidney-shaped nuclei (“hallmark cells”). The true incidence of ALCL is unknown but is thought to represent 3% of adult cases of non-Hodgkin lymphoma. ALCL typically occurs in young men with a median age of 34 years. Patients typically present with late-stage disease and non-specific systemic symptoms, most commonly fever. The diagnosis of ALCL is often challenging due to heterogeneous clinical as well as histological features. Here we present a case of a young man who presented with respiratory failure and pneumonitis-like symptoms. He was treated empirically with antibiotics and discharged; however, his symptoms progressed to acute respiratory distress syndrome and he expired in multiple organ failure with presumed systemic inflammatory immune response. At autopsy, he was discovered to have extensive, multiple organ involvement by ALCL, including all lobes of the lung.

Case Report

A 43-year old man with past medical history of Factor V Leiden, hypothyroidism, and a remote history of pulmonary embolism, presented with fever, frontal headache, and upper respiratory symptoms. Initial imaging showed infiltrates on chest x-ray and possible sinusitis. The patient was discharged to home with antibiotics.

Two days later, he returned with no improvement in symptoms. He was noted to have a leukocytosis up to 35,000. Blood cultures were negative for organisms. A lumbar puncture was performed which was also negative for infectious etiology. The differential diagnosis at the time included infectious etiologies (HIV, CMV, EBV, rickettsia, brucella, etc), hematologic malignancies (acute leukemia or lymphoproliferative disorder), and questionable autoimmune causes.

The patient developed increasing bilateral pulmonary opacities on imaging with progressive respiratory failure requiring intubation. His clinical condition continued to deteriorate and he was transferred to University of Maryland Medical Center with the provisional diagnosis of respiratory failure and acute respiratory distress syndrome (ARDS), secondary to multilobar pneumonia with systemic inflammatory response syndrome (SIRS).

The patient was empirically treated for pneumonia and pneumonitis, but continued to worsen clinically and radiographically. Multiple bronchoscopies and cultures were initially negative. He subsequently developed tension pneumothorax requiring multiple chest tubes. Bronchoalveolar lavage and endotracheal aspirates at that time came back positive for *Serratia marcescens*. Multiple organ dysfunction syndrome then ensued, requiring vasopressor support and continuous veno-venous hemofiltration. Head CT and MRI findings were suggestive of ischemic brain injury, and the patient ultimately became unresponsive with no brainstem reflexes. The decision was then made to provide comfort measures only and the patient expired.

Autopsy examination was performed. At autopsy examination, there was diffuse anasarca. The lungs showed bilateral, multilobar pulmonary infiltrates (figure 1) consistent with the clinical history of multilobar pneumonia. There were also scattered mucosal nodules in the esophagus, stomach and colon. The cardiac examination showed mild concentric left ventricular hypertrophy with no significant coronary artery disease. The most striking finding at autopsy was the presence of systemic involvement by malignant cells with anaplastic morphology. Immunophenotyping was positive for both CD30 and ALK, indicative of ALCL. ALCL was identified in numerous lymph nodes including mediastinal, para-aortic and pelvic lymph nodes, as well as the spleen. Other organs involved included all five lung lobes (figure 2), the stomach, esophagus, small bowel, appendix, colon, liver, and right testis. Additional findings at autopsy included acute and organizing diffuse alveolar damage in the lungs (figure 3). The cause of death was respiratory failure, secondary to ALK-positive anaplastic large cell lymphoma.
Figure 1. Multilobar pulmonary infiltrates consistent with clinical history of multilobar pneumonia.

Figure 2. Diffuse involvement of lung with anaplastic large cell lymphoma cells.
Discussion

First identified in 1985 by Harald Stein and Karl Lennert, anaplastic large cell lymphoma (ALCL) is described as a unique large cell lymphoma with anaplastic cytology and an unusual sinus growth pattern. The malignant cells show strong expression of the antigen CD30, in a membranous distribution as well as in the Golgi region. CD30 is an activation antigen and member of the tumor necrosis factor receptor family. The receptor tyrosine kinase, anaplastic lymphoma kinase (ALK) protein is commonly activated through the nonrandom t(2;5) chromosome translocation. ALK is not normally expressed in lymphoid tissue, so anti-ALK antibodies can be used to detect t(2;5).

ALK-positive ALCL, ALK-negative ALCL, and primary cutaneous ALCL (C-ALCL) are three forms of ALCL that have been classified by the World Health Organization, the first two being the systemic variants. ALK-positive ALCL typically affects children and young adults and includes small cell and lymphohistiocytic variants, but carries a better prognosis than ALK-negative ALCL, with 5-year survival rates of 70-80% versus 15-45% respectively. The presence of ALK protein signifies an excellent prognosis when treated with standard chemotherapy; however, this may be due to younger age at presentation because no difference between ALK-positive and ALK-negative was found for isolated patient age of 40 years and older. ALK-positive ALCL accounts for 3% of adult Non-Hodgkin lymphoma (NHL) and 10-15% of childhood lymphomas. Systemic ALCL represents 2-5% of NHL and 12% of T-cell NHL. ALK-negative ALCL makes up 15-20% of all systemic ALCL cases and affects adults, with a slight predilection for males.

Morphologically, all cases of ALK-positive ALCL contain a variable number of cells with eccentric, horseshoe or kidney shaped nuclei with an eosinophilic region near the nucleus (“hallmark cells”) (figure 2). The tumor consists of large cells that may resemble Reed-Sternberg cells. The cells tend to grow around venules and infiltrate lymphoid sinuses, and may be difficult to distinguish morphologically from metastatic carcinoma. ALK-positive ALCL extranodal involvement includes bone, bone marrow, subcutaneous tissue, and spleen at an increased frequency. In 65% of cases, patients with ALK-positive ALCL generally present with stage III or stage IV disease. In 75% of cases, systemic symptoms, such as fever, are present. Lymph node involvement is common, followed by extranodal involvement of soft tissue and bone. Morphologically, ALCL may mimic other types of lymphoma or may grow in a pattern suggestive of nonhematologic malignancies such as sarcomas, carcinomas, germ cell tumors, and melanoma, thus making ALCL particularly challenging to diagnose.

This case is noteworthy for several reasons. The most striking feature was the acute respiratory presentation which suggested infection rather than malignancy. Indeed, the patient was admitted and treated for...
pneumonia. In retrospect, the initial negative cultures on bronchoscopy may have suggested a broader differential diagnosis, although a subsequent culture was positive for *Serratia marcescens*, most likely a nosocomial, ventilator-associated pneumonia. *Serratia marcescens* is an opportunistic gram-negative bacteria that accounts for 2% of nosocomial infections of the bloodstream, lower respiratory tract, urinary tract, surgical wounds, and skin and soft tissue\(^8\).

Because of the atypical presentation, the diagnosis of ALCL was not made during life, thus emphasizing the importance and value of autopsy examination involving natural deaths in the hospital setting. While the autopsy rates are now very low even in academic centers\(^9\), the value of the autopsy in hospital quality assurance and education of medical practitioners continues. The results of this autopsy further shed light on the clinical spectrum of systemic ALCL, and may sensitize clinicians to the possibility, so that proper therapy can be instituted. Based on our report of this case, ALCL should be considered in the differential diagnosis of pneumonia and respiratory failure refractory to treatment.
References