Acute Monocytic Leukemia Linked to Pulmonary Infiltrates and the Importance of Early Induction Chemotherapy

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Abstract
Currently there is no consensus on the approach to evaluating lung infiltrates in patients with newly diagnosed acute myeloid leukemia (AML), a rare disease with an incidence of 3-4 cases per 100,000 people. The CT findings of pulmonary infiltrates in patients with AML are nonspecific and can range from confluent air-space opacities with patchy consolidation to interstitial markings and multiple subpleural small nodules. Biopsy will most often reveal bacterial or fungal infection and rarely malignant infiltrates. Here is a case of a patient with newly diagnosed AML, specifically of the monoblastic subtype, who was admitted to the hospital for induction chemotherapy and underwent transthoracic lung biopsy that confirmed monoblastic leukemic infiltrates. Following chemotherapy there was complete resolution of the lung infiltrates.

Key Words
AML, Acute myeloid leukemia, Acute monocytic leukemia, Acute monoblastic leukemia, Leukemic lung infiltrate

1. Introduction
Currently there is no consensus on the approach to evaluating lung infiltrates in patients with newly diagnosed acute myeloid leukemia (AML), a rare disease with an incidence of 3-4 cases per 100,000 people. More specifically, it remains unclear if there is a need to obtain a lung tissue biopsy prior to the initiation of induction chemotherapy. Here we describe a case of such lung infiltrates in which a newly diagnosed AML patient underwent a diagnostic lung biopsy before receiving chemotherapy, was shown to have leukemic infiltration of lung tissue, and subsequently had complete resolution of lung infiltrates following initiation of chemotherapy.

2. Case Presentation
A 60 year-old female with a past medical history of psoriasis, hyperthyroidism, and a 40 pack-year smoking history presented with chest pain preceded by an upper respiratory tract infection and was found to have diffuse ST segment elevations on electrocardiogram and a moderate sized pericardial effusion on echocardiogram. She was diagnosed with and treated for pericarditis.
Lab studies revealed leukocytosis with a white blood cell count of 41.3 x 10^3/µL with a predominance of monocytes and monoblasts. While karyotypic analysis was normal, molecular testing revealed both a nucleophosmin (NPM1) mutation and internal tandem duplication of the fetal liver tyrosine kinase 3 gene (FLT3-ITD). Bone marrow biopsy was consistent with the FAB subtype of monoblastic (M5) AML (Figure 1A) or AML with recurrent genetic abnormalities based on the more recent WHO classification criteria.

She was re-admitted for induction chemotherapy. At that time, her only complaint was of a persistent dry cough. She denied fever, hemoptysis, or other symptoms of infection. Lung exam was remarkable for coarse bilateral rales.

Given the persistence of her cough and lung exam findings, a chest CT scan was performed which revealed multiple bilateral nodular opacities measuring up to 1.6 cm, concerning for infection vs. leukemic infiltrate vs. secondary malignancy including non-small cell lung cancer (Figure 1B). Induction chemotherapy was delayed for 3 days while the patient underwent transthoracic fine needle aspiration (FNA) of one of the peripheral nodules.

The FNA revealed atypical mononuclear blastoid cells consistent with her monoblastic AML (Figure 1C). Prior to these results being available and without further delay, the patient started induction chemotherapy with daunorubicin and Ara-C. On day fourteen, bone marrow aspirate showed post-ablation hypocellularity. On day twenty-eight, she underwent repeat bone marrow biopsy, which showed increased cellularity due to myeloid hyperplasia, particularly monocytic elements. Immature and mature monocytes accounted for 8% and 15% of the cellularity respectively. Blast equivalents (myeloblasts and promonocytes) accounted for 12% of the cellularity. Flow cytometric analysis showed a myeloblast population (accounting for 1.4% of all nucleated cells) that was positive for CD34, HLA DR, CD117, and CD13. Interestingly, repeat molecular testing did not show an NPM1 mutation, confirming remission of AML and re-establishment of a likely pre-existing chronic myelo-monocytic leukemia (CMML)-like process\[1\].

Repeat chest CT showed complete resolution of infiltrates (Figure 1D). The patient was given one course of consolidation chemotherapy with high-dose Ara-C while a search was conducted for a suitable allogeneic stem cell donor. An unrelated match was identified and she subsequently successfully underwent allogeneic stem cell transplantation. She is alive and well with no evidence of relapse ten months following her diagnosis. Bone marrow biopsy at 30 days and 100 days post-bone marrow transplantation revealed all donor chimerism, no evidence of AML, and no mutations in NPM1 and FLT3.
3. Discussion

AML, particularly of the former classification system FAB subtypes myelomonoblastic or monoblastic morphology (M4 or M5), can infiltrate the lung. Generally the infiltrates are less likely attributable to leukostasis if the leukocyte count is <100 x 10³/µL, which was the case in our patient[2]. Leukemic infiltrate should be considered in the differential when the peripheral smear shows >40% blast cells[3]. In a retrospective study looking at 278 patients diagnosed with AML, 19% had pulmonary complications based on clinical, laboratory, and chest film data. Among these patients with pulmonary infiltrates, high-resolution thoracic computed tomography (CT) scan and other appropriate medical tests were used to further delineate the etiology of the infiltrate. 56.6% of the cases were confirmed likely bacterial or fungal infections, 9.4% were likely cardiac disease, and 7.5% were due to pulmonary embolism. There were only 2 cases (3.8%) of malignant infiltrates, both were AML with predominantly myelomonoblastic or monoblastic cells[4]. Interestingly, another case series looking at 1020 acute leukemia patients at a single-center between 1994-2002 showed that among these patients, the 20 who presented with pulmonary infiltrates and acute respiratory failure all had the same subtype of AML, subtype M5. All 20 showed further deterioration in their respiratory status after chemotherapy initiation and 10 died in the ICU primarily due to acute lysis pneumopathy[5]. This is suggestive that the subtype M5, the same subtype as our patient, may be linked to both pulmonary leukemic infiltrates and severe respiratory failure.
Based on a prospective study of 65 patients with newly diagnosed acute leukemia, a large percentage or 46% had respiratory signs or symptoms ranging from cough to pulmonary infiltrate on chest radiography. Among those with respiratory signs or symptoms, regardless of etiology, a strong predictor of mortality by 45 days post-induction chemo was the inability to achieve complete remission\(^6\). One paper suggests that empiric use of dexamethasone in patients with the M5 AML subtype and evidence of ARDS resulted in reduced mortality and reduced rate of respiratory deterioration without a significant increase in rate of infection\(^7\).

The CT findings of pulmonary infiltrates in patients with AML are nonspecific ranging from confluent air-space opacities with patchy consolidation to interstitial markings and multiple subpleural small nodules\(^8\). Biopsy of the infiltrate is therefore a way to differentiate between infection and malignancy. Transthoracic FNA is considered a relatively safe approach to obtaining lung tissue with high diagnostic yield; however, lung biopsies are not without risks. In a large pooled study looking at the diagnostic accuracy and complications of transthoracic FNA, the most common complications were pneumothorax (PTX) with an incidence of 20.5%, 7.3% of which required chest tube placement. Less commonly, 2.8% of patients developed significant hemorrhage with hemothysis, hemothorax, or a chest wall hematoma. Diagnostically the FNA approach had both high sensitivity (92.1%) and specificity (100%) for detecting malignancy\(^9\). One case report discusses using the alternative approach of intubation and bronchoscopy to obtain a bronchoalveolar lavage sample to rule out infection and to rule in monoblast cells of the AML M5 subtype via cytology\(^10\).

Our case is unique in that a lung biopsy was performed which definitively demonstrated monocytic cells in the lung infiltrate prior to initiation of chemotherapy. The effectiveness of chemotherapy for AML lung infiltrates was demonstrated with resolution of nodular opacities on repeat imaging. While this patient ultimately had a good outcome, an important issue raised by this case report is whether lung biopsies should be routinely performed in patients with the AML presenting with lung infiltrates characteristic of leukemic lung involvement and in whom no convincing evidence of pulmonary infection is found. As it is important to rule out infection, lung biopsy if deemed appropriate should be done in an expedited manner and results need not delay chemotherapy which may ultimately prevent respiratory failure in cases of leukemic infiltrates. Perhaps one alternate approach is to keep leukemic infiltrate higher on the differential when the AML morphology is predominantly of myelomonoblastic or monoblastic elements, and to closely monitor these patients for respiratory failure during chemo induction.

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