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# Atypical Presentation of a Rare Hematological Malignancy in the Lung

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## I. Introduction

Aggressive natural killer cell leukemia (ANKL) is a distinctly rare neoplastic disease of mature natural killer (NK) cells classified as a separate entity in the World Health Organization 2016 classification. [1] The earliest report dates back to 1990 [2] and literature search reveals less than 200 cases reported in the literature. [3] ANKL has a distinct geographic distribution with most reported cases occurring in Asians. The entity commonly affects young to middle aged adults, and is almost always associated with Epstein Barr virus (EBV) infection. ANKL has a rapidly fatal clinical course with a median survival of around 1 month in one of the largest series published.[4] Due to lack of unified diagnostic criteria a combined approach combining clinical features, imaging modalities and pathological studies (with relevant markers) is helpful in diagnosis. Herein we describe a patient who presented to the respiratory OPD mimicking a usual viral lower respiratory infection, but turned out to be lodging this grave disease with a catastrophic course.

## II. Case Summary

A 34 year old gentleman, driver by occupation presented to Pulmonary Medicine outpatient department (OPD) with a history of cough for 10 days. He denied history of any medical illness. He experienced mild left sided pleuritic chest pain for 5 days. There was no history of associated fever, loss of appetite, loss of weight.

On examination, he had expiratory wheeze. Rest of the physical evaluation was unrewarding. Chest X-ray at initial presentation was unremarkable. A diagnosis of viral upper respiratory infection was entertained and he was given a course of bronchodilators with oral steroids. He was advised to follow up in OPD if symptoms persisted for more than two weeks. He presented again in the OPD after three weeks with worsening cough and chest pain. He had lost three kg of body weight in last three weeks and started experiencing poor appetite. His total leucocyte count was 5.2x10 9/l; C –reactive protein was 1.5 mg/dl. His renal, liver and thyroid function tests were within normal limits. Chest-X ray was repeated which showed subtle left lower zone infiltrate. Computed tomography (CT) chest demonstrated focal area of air space infiltrates in left lower lobe abutting pleura with surrounding ground glass opacities consistent with Halo Sign [Figure 1a and b].

Bronchoscopy was performed; lavage was retrieved from left lower lobe segments and was subjected to appropriate microbial tests. BAL cultures grew aspergillus fumigatus in significant titres. Mantoux test was non-reactive. BAL galactomannan was positive. Subsequently he was started on oral antifungals (Voriconozole) and was treated on an outpatient basis as he was stable. He was advised close monitoring.

He presented in emergency department within a week with new onset high grade fever and further three kg weight loss. Chest-x ray showed an increase in left lower zone alveolar shadows. His blood and urine cultures were negative. He was admitted and treated with intravenous voriconozole and broad spectrum antibiotics. Despite five days of antibiotics and antifungals, he had persistent high grade fever. This prompted a detailed evaluation for persistent fever. His serology for Brucella, Chlamydia, PCR throat swab for influenza A (H1N1) were negative. Serology for viral markers (HIV, HBsAG, HCV) were nonreactive. Serum ACE, ANCA and ANA by IFA were negative. Serum LDH and ferritin levels were normal. His repeat CT chest revealed worsening left lower lobe consolidation. CT paranasal sinus was normal. Amphotericin was added to his antifungal regime. A transesophageal echocardiography revealed no evidence of cardiac vegetations.

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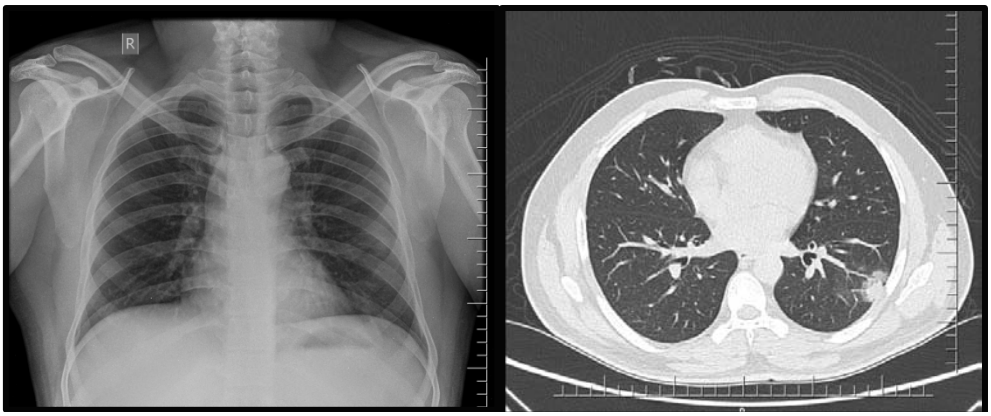
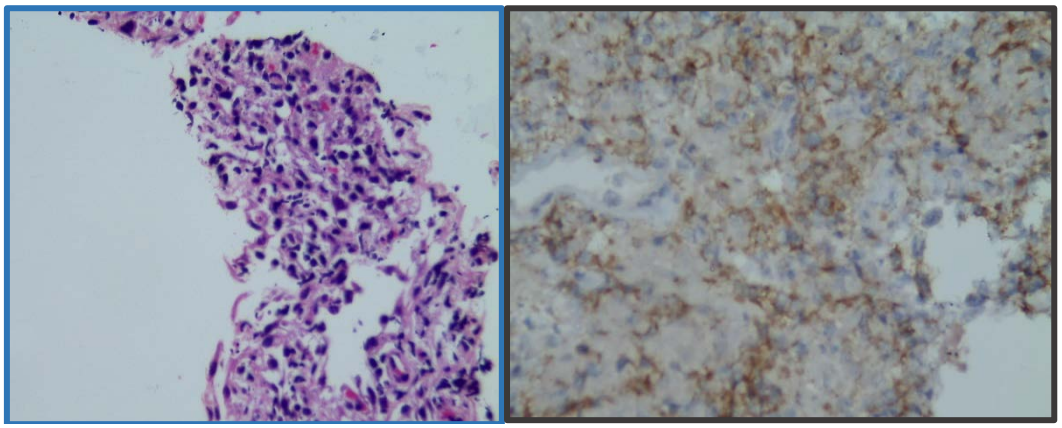


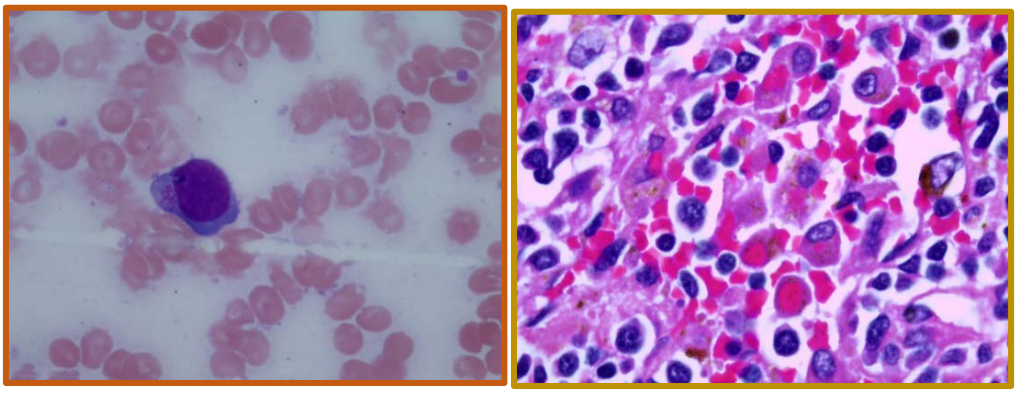
1 (A) 2 (B)

*Figure 1:* Chest radiograph showing subtle left lower zone infiltrate. Computed tomography image showing Halo sign



2 (A) 2 (B)

*Figure 2:* A, B Lung biopsy: H&E, 400 x shows interstitial infiltration by atypical lymphoid cells Lung biopsy: Immunohistochemistry, 1000 x shows CD 56 positive lymphoid cells



3 (A) 3 (B)

*Figure 3:* A, B Bone marrow aspirate: Leishman, 1000 x shows atypical large cells with blastoid morphology and cytoplasmic granulation Lymph node biopsy: H&E, 1000 x shows haemophagocytic histiocytes

CT abdomen revealed mild splenomegaly and portocaval lymph node (LN). Leucopenia and thrombocytopenia started to set in at this juncture and (BM), positron emission tomography (PET CT) and abdominal lymph node biopsy were suggested. PET CT he started to get hypoxic. A multidisciplinary discussion was conducted with Internal Medicine and infectious disease experts. Biopsy of lung lesion, bone marrow demonstrated F-18 fluorodeoxy glucose (FDG) avid large portocaval LN, non FDGavid small axillary nodes,

demonstrated F-18 fluorodeoxy glucose (FDG) avid large portocaval LN, non FDGavid small axillary nodes, bilateral cervical, aortocaval LN; heterogenously avid humeral and femoral marrow and left lower lobe lung lesion. CT guided biopsy of left lower lobe lesion, surgical biopsy of caval lymph node and bone marrow studies were undertaken. Since he started developing altered mentation, a cerebrospinal fluid (CSF) study was also performed which showed lymphocytic pleocytosis with few atypical cells, cultures were unrewarding. Quantitative EBV titres were 1,888,738 copies/ml in his blood sample. BM showed normal karyotype.BM immunophenotypic (IHC) and flow cytometry (Table 1) profile was suggestive of NK /Large granular lymphocytic leukemia (NK/LGL) [Figure 3a]. The same was correlated with histopathology and IHC of lung [Figure 2a, b] and lymph node [Figure 3b].CSF immunophenotyping was done to rule out any invasion but showed no definite CD3 negative / CD8 positive population in CSF.

*Table 1:* Flow cytometry profile

| Marker | Percentage of gated population |
|---|---|
| T cell markers | |
| CD2 | 99 |
| CD3 | 17 |
| CD4 | 06 |
| CD5 | 38 |
| CD7 | 47 |
| CD8 | 64 |
| B cell markers | |
| CD10 | 00 |
| CD19 | 02 |
| CD19+CD5 | 00 |
| CD20 | 08 |
| CD23 | 00 |
| NK cell markers | |
| CD56 | 43 |
| CD16 | 16 |
| Myeloid markers | |
| CD13 | 03 |
| CD33 | 00 |
| CD64 | 00 |
| CD117 | 00 |
| Other markers | |
| CD45 | 100 |
| CD34 | 00 |
| CD38 | 82 |
| CD57 | 31 |
| CD11B | 13 |
| TCR gamma -delta | 00 |
| CD11C | 66 |
| HLA DR | 83 |
| FMC 7 | 05 |
| cCD3 | 88 |
| Note – Test performed on 4 colors BD FACS using single page analysis through Lyse wash preparation | |

Based on all aforementioned results, a diagnosis of aggressive NK cell Leukemia was arrived at. He was initiated on L-asparaginase based chemotherapy regimen. He developed febrile neutropenia and succumbed to his illness. The total disease course from initial presentation to death spanned less than eight weeks.

## III. Discussion

Natural killer (NK) cells constitute the third lymphoid lineage other than T-cell and B-cell lineages. Both NK-cells and T-cells arise from a common lymphoid progenitor, thus justifying their grouping under a common heading in the WHO classification of neoplasms. [5]

Aggressive natural killer cell leukemia/lymphoma (ANKL) is a rare and highly aggressive neoplasm. Men and women are equally affected and the disease usually manifests in the third or fourth decades. The neoplastic cells are almost invariably infected with Epstein Barr virus (EBV). Blood EBV antibody titres and EBV DNA loads are very high.

Pulmonary involvement in ANKC leukemia is rare with only a few cases reported so far. [6] The significant majority of case reports have been from South East Asian countries. Patients present with fever, cough, dyspnea, and other symptoms with no antibiotic response. Radiologically, the lesions can present as focal alveolar infiltrates (consolidation), or distinct lesions (pulmonary nodules and masses). As the lesions are angiocentric and angioinvasive, bleeding is often observed and the halo sign may be seen as in our case.

The diagnosis of ANKL neoplasms is often difficult. It requires high index of clinical suspicion and a multidisciplinary approach. A dedicated and detailed pathological evaluation based on morphological, immunophenotypic and molecular studies is mandatory.[4] Most cases of ANKL were diagnosed from the presence of NK neoplastic cells in peripheral blood, bone marrow or tissue. NK cells appear as large granular lymphocytes with pale cytoplasm and abundant azurophilic granules. Peripheral blood cytopenias may be found in about 10-15% of cases of NK cell lymphomas and are mainly due to active hemophagocytosis in the marrow. The hemophagocytic cells are activated reticuloendothelial cells and the presence of these cells by itself does not equate to marrow infiltration. NK T cell lymphoma and ANKL tumor cells nearly always express CD2 and less often CD7 and CD8. Most useful and frequently positive marker is CD56. CD 16 is positive in about 75% of ANKL, which helps to differentiate it from extranodal NK T cell lymphoma.[7] Practical approach to a successful diagnosis is based on suggestive IHC and EBV-encoded small RNA (EBER) detection in a BM biopsy.

Even with the best of treatment chances of survival in aggressive NK cell leukemias is dismal. L-asparaginase based regimens (SMILE protocol-dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) followed by consolidation HSCT showed relatively prolonged survival than antracycline regimes in some cases.[8] In a large series involving L-asparaginase based chemotherapy followed HSCT, two patients are alive and in clinical remission after 2 years.[9] Rapidly growing lung mass and positive EBER herald a poor prognosis. The recurrence rate is very high and most cases succumb in weeks.

## IV. Conclusion

Aggressive natural killer cell leukemia is a rare malignancy caused by proliferation of mature natural killer cells. Pulmonary involvement in this rare neoplasm is exceedingly rare. In the absence of uniform diagnostic criteria, the diagnosis rests on morphological tests and immunological sequencing of the pathological specimen of an involved site. Response to therapy is dismal and median survival time spans a few weeks only. Awareness about the entity and multidisciplinary assessment is crucial for diagnosis and prognostication.

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