



# Aggressive Natural Killer Cell Leukemia: A Case Report and Literature Update

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## Abstract

Aggressive natural killer cell leukemia (ANKL) is an extremely rare type of leukemia characterized by clonal NK cell infiltration of peripheral blood and the bone marrow, cytopenias, and hepato/splenomegaly. ANKL is an aggressive subtype of a large granular lymphocytic (LGL) leukemia. Peripheral blood smear shows LGL cells containing characteristic azurophilic granules in a light pale basophilic cytoplasm and immature nuclei. Immunological studies determine CD3-/CD16+/CD56+ and cytoplasmic CD3+. Tumor cells may have EBV positive. Chemotherapy resistance is caused by a multi-drug resistance gene (MDR); thus, patients die within 2 months after diagnosis. Here, we report a rare case of a patient diagnosed with ANKL.

**Keywords:** NK cell leukemia, aggressive, CD16, CD56, hematopoietic stem cell transplantation

## Introduction

Aggressive natural killer cell leukemia (ANKL) is an extremely rare type of leukemia characterized by clonal natural killer (NK)-cell infiltration in the peripheral blood and bone marrow, cytopenia, and hepato/splenomegaly. ANKL is a subgroup of NK-cell neoplasias that constitutes approximately 15% of large granular lymphocytic leukemias. According to the LGL classification of 2008 WHO, mature T-cell neoplasias (T-LGLs) differ from NK-cell neoplasias (NK-LGLs) in terms of both molecular and clinical features. In the group of NK-cell neoplasias, chronic lymphoproliferative diseases of NK cells are examined independent of NK-cell leukemia, which is highly aggressive (1). If circulating lymphocytes have the feature of CD3+/CD57+ cytotoxic T cells, patients can be followed-up with the expectation of a good prognosis by considering T-cell LGLs. If lymphocytes have the feature of CD3-/CD56+ NK cells, chronic NK lymphocytosis must be distinguished from ANKL. In this study, the case of a patient who was followed-up due to the clinical picture of aggressive leukemia and who was diagnosed with ANKL is presented.

## Case Report

A 63-year-old female patient applied to the emergency unit with complaints of fever, fatigue, weakness, and redness in the right eye. She was then hospitalized in the Clinic of Internal Medicine for follow-up. In her physical examination, there was conjunctival bleeding in the right bulbar. Her liver and spleen were larger than normal and were approximately 2 cm and 5 cm, respectively. The values were found to be 11.2 g/dL (12–16) for Hb, 5.360 10<sup>3</sup>/μL (4.5–10.5) for WBC, 42.000 10<sup>3</sup>/μL (150–400) for Plt, and 28, CRP 75 mg/L (0–5) for sedimentation. The results of *Bruceella* lamina and tube agglutination tests were normal. In a peripheral smear, 70% PNLs, 9% monocytes, and 18% lymphocytes were observed. Many LGLs were found in the smear (Figure 1). During the follow-up period, her anemia and thrombocytopenia were deepened and her leukocyte count increased from 5,000 to 165,000. The proportion of LGLs reached up to 68% in the peripheral smear. The sizes of organs gradually increased (liver: 8 cm, spleen: 20 cm). She developed obstructive icterus due to the compression of 3-cm lymph nodes in the portal hilum. In the immunological examination of the peripheral blood, CD3-/CD16+/CD56+ was found. NK-cell infiltration was detected in the bone marrow and lymph node biopsies (Figure 2, 3). The patient was diagnosed with aggressive NK-cell leukemia. EBV serology was found to be consistent with that of a previous infection. The markers of rheumatic diseases (ANA, RF, and ENA profile) were negative. Because her health state was rapidly deteriorating, it was thought that she would not be able to tolerate aggressive chemotherapy. Therefore, she was given 1 mg/kg/day of methylprednisolone and 10 mg/m<sup>2</sup>/week of methotrexate, which is a mild therapy recommended for chronic T-LGL leukemia treatment. With this treatment, the general status of the patient became partially better. Within a week, leucocyte count regressed to 9,800. The sizes of the liver, spleen, and lymph node began to turn to normal, and an apparent decrease was observed in the levels

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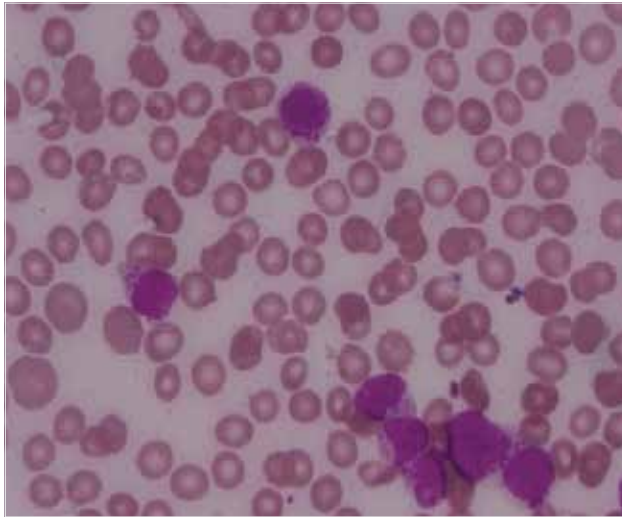
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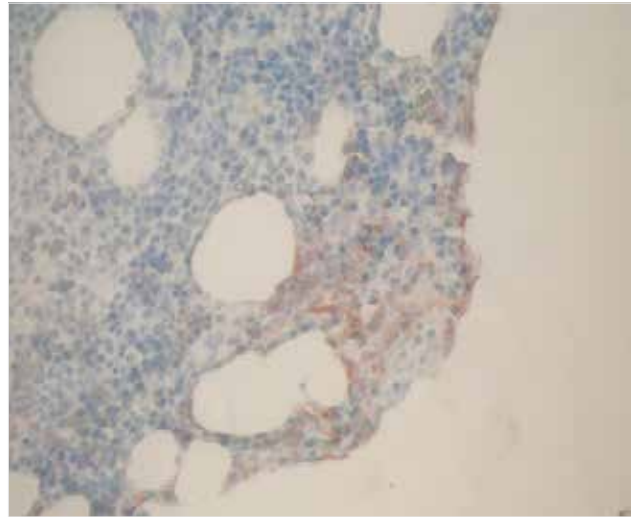
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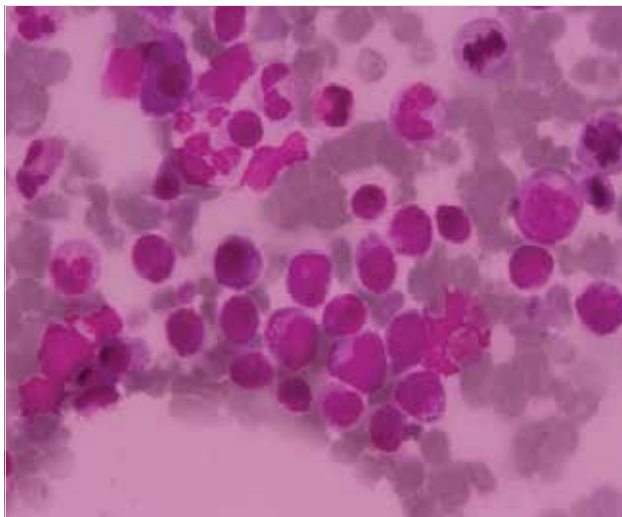
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**Figure 1.** LGLs in the peripheral smear; HE  $\times 100$   
LGLs: large granular lymphocytes



**Figure 3.** LGLs in the bone marrow; CD56  $\times 40$   
LGLs: large granular lymphocytes



**Figure 2.** LGLs in the bone marrow; HE  $\times 100$   
LGLs: large granular lymphocytes



**Figure 4.** LGLs in the lymph node; CD3  $\times 10$   
LGLs: large granular lymphocytes

of bilirubin. However, in the 4<sup>th</sup> week of the treatment, LGLs were still notable in the peripheral smear of the patient. The dose of methylprednisolone was decreased a month later, and the therapy was then discontinued. Then, neutropenic fever developed in the patient. She died due to pneumonia and septic shock 39 days after the beginning of the treatment.

## Discussion

Lymphocytes are a lymphocyte subgroup constituting 10–15% of lymphocytes in peripheral blood, and its morphologies are characteristically different. In normal people, their absolute counts in the peripheral blood vary between 200  $\mu\text{L}$  and 400  $\mu\text{L}$ . They mainly originate from two classes of cells: cytotoxic effector T cells activated by CD3+/CD56–/CD57+ *in vivo* antigens and CD3–/CD56+ NK cells. Benign non-clonal secondary LGL increases can be particularly seen in viral infections such as EBV, HBV, HCV, HIV, and CMV, connective tissue diseases, immune thrombocytopenia, non-Hodgkin lymphoma, various skin diseases, and hemophagocytic syndrome. In this condition, CD3+ reactive T-cell increases are observed (2). Myelodysplastic syndrome and solid tumors can

sometimes lead to increased NK-LGLs. Proliferative NK-cell impairments are also observed in living people who had been exposed to the atomic bomb (3).

Aggressive NK-cell leukemia is a more aggressive neoplasia than T-cell LGL leukemia and chronic NK-cell lymphocytosis. Patients are younger and their mean age is 39 years. Initial findings include massive hepatosplenomegaly as well as symptoms such as fever, night sweating, and weight loss, which are referred to as B symptoms. Gastrointestinal involvement is seen in many patients. Cerebrospinal, acid-peritoneal involvements were reported (2). In the differential diagnosis, extranodal NK/T-cell lymphomas, blastic NK-cell lymphomas, and NK-like T-cell lymphomas should be evaluated.

Aggressive NK-cell leukemia originates from neoplastic NK cells. In a study conducted in Japan, *in situ* hybridization analyses revealed EBV RNA, EBV nuclear antigen-1, and EBER-1 in leukemic cells in more than 50% of ANKL patients (4). This information suggests that EBV can directly affect NK-cell transformation. In our case, EBV serology was found to be positive. Aggressive NK-leukemia cells are normally morphologically larger than LGLs. They have great azu-

rophilic granules in a light pale basophilic cytoplasm. The nucleus includes a slightly immature chromatin pattern (Figure 1). Hemophagocytosis is common. The surface in immunological studies is CD2+/CD3-/CD4-/CD8+/CD16+/CD56+/CD57-. In many cases, cytoplasmic CD3 is positive (5). In our case, CD3-/CD16+/CD56+ and cytoplasmic CD3+ were detected (Figure 3, 4).

During treatment, the patients were given a chemotherapy regimen including CHOP, hyper-CVAD, or third-generation anthracycline. However, the prognosis is poor despite chemotherapy. Resistance to chemotherapy develops over p-glycoprotein, which is an MDR-1 gene product (6). It is difficult to administer aggressive therapy in patients with poor performance, as in our patient. Therefore, steroid and methotrexate therapies, which are known to be effective in T-LGL treatment, were used for our patient. Partial improvement was obtained in the course of the disease because of this treatment. However, the patient died due to pancytopenia complications. Successful results have been reported in the treatment of ANKL with hematopoietic stem-cell transplantation (7).

## Conclusion

Further studies are needed on the treatment methods of aggressive NK-cell leukemia for patients whose general health states are poor. For this purpose, it will be important to involve patients in well planned and scientifically updated clinical study groups.

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