

# Aggressive natural killer cell leukemia: a case report

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**Abstract:** Aggressive natural killer (NK) cell leukemia is a rare hematological malignancy. It often presents with a rapidly declining clinical course and a poor prognosis with a median survival of a few months. We report the case of a 23-year-old man with high fever, enlarged lymph nodes, splenomegaly, cytopenia, liver dysfunctions, coagulation disorders and hemophagocytosis. Computed tomography scan showed right lung shadow. Lung involvement was considered. Histological examination of the lung was not performed because of low platelets and coagulation disorders. Bronchoscopic examination revealed positive Epstein-Barr virus in bronchoalveolar lavage fluid. Bone marrow and lymph node phenotype showed CD56+ CD3- NK cells type. He died of respiratory failure a week after diagnosis.

**Keywords:** hemophagocytosis, Epstein-Barr virus, CD56+ CD3- NK cells, aggressive natural killer cell leukemia

## Introduction

Diseases originating from mature natural killer (NK) cells include extranodal NK/T-cell lymphoma-nasal type, aggressive natural killer cell leukemia (ANKL) and chronic lymphoproliferative disorders of NK cells.<sup>1</sup> ANKL is the rarest and worst malignancy. ANKL is an Epstein-Barr virus (EBV)-associated tumor most prevalent among Asian young adults (median age of 42 years).<sup>2</sup> There is no standard treatment currently available for patients.

## Case presentation

A 23-year-old man with no prior medical history was admitted to the Department of Respiratory Medicine. The symptoms were fever for 1 month and a weight loss of 5 kg in the last 1 month. Physical examination revealed enlarged spleen and lymph nodes. The blood cell counts were as follows: leukocyte (white blood cell [WBC])  $5.2 \times 10^9/L$ , neutrophilic granulocyte (NEU) 44.4%, lymphocyte (LYM) 49%, hemoglobin (HGB) 128 g/L, platelet  $159 \times 10^9/L$ . Biochemistry showed marked increased level of lactate dehydrogenase to 551.6 U/L, alanine transaminase to 577.2 U/L, direct bilirubin to 64.3  $\mu\text{mol/L}$ , and indirect bilirubin to 30.7  $\mu\text{mol/L}$ . Examinations also revealed the following levels: albumin 31.2 g/L, serum creatinine 59  $\mu\text{mol/L}$ , triglyceride 2.06 mmol/L, ferritin >1500 ng/mL,  $\beta_2$ -microglobulin 5.68 mg/L, erythrocyte sedimentation rate 10 mm/h, C-reactive protein 5 mg/L, prothrombin time 12.4 s, prothrombin activity 82%, international normalized ratio 1.13, partial thromboplastin time 45.9 s, and fibrinogen 2.18 g/L.

Serum detection revealed positive EBV IgG and negative IgM. Computed tomography (CT) scan showed no neoplasm in the nasal cavity and oropharynx.

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CT scan showed right lung large lesions, partial pleural effusion, splenomegaly and mild hepatomegaly. Bronchoscopic examination revealed positive EBV in bronchoalveolar lavage fluid.

Fifteen days after hospitalization, the following were found: WBC  $2.3 \times 10^9/L$ , HGB 110 g/L, PLT  $24 \times 10^9/L$ , NEU 28%, LYM 47%, abnormal cells 25% in peripheral blood. A hematological neoplasm was suspected. Bone marrow smears showed 10% abnormal cells with varying size, irregular shape, dark blue cytoplasm, azurophilic granules and some hemophagocytes. Bone marrow flow cytometry showed the following phenotype: CD56+, CD2+, CD8dim+, CD159a+, CD94bri+, CD16+ (partially), CD161+ (partially), KI-67(15%), CD4-, CD3-, CD5-, CD30-, CD158a/h-, CD158b-, CD159c-, TCR-ab-, TCR-rd-, CD117-, CD57-. Bone marrow biopsy showed clustered abnormal cells. Lymph node biopsy immunohistochemistry showed CD56+, CD2+, CD8dim+, CD94bri+, CD161+, CD16+, CD159a+ (partially), CD7+ (partially), CD4-, CD3-, CD5-, CD159c-, TCR-, IgH-. A diagnosis of ANKL was made. Only glucocorticoid was given. Other chemotherapy drugs were not administered because the patient did not agree. The patient sustained high fever and presented with dyspnea and nasal bleeding. A week after diagnosis, the patient died of respiratory failure.

The patient's next of kin provided written informed consent to publish this case report.

## Discussion

ANKL is recognized by the WHO classification as a distinct neoplasm that constitutes approximately 10% of all large granular lymphocyte (LGL) lymphoproliferative disorders.<sup>3</sup> ANKL occurs in younger adults and is more common in males. Presentations usually have fever, B symptoms, jaundice, lymphadenopathy, hepatosplenomegaly, circulating leukemic cells and cytopenia, disseminated intravascular coagulation, hemophagocytic syndrome and liver dysfunction. Morphologically, mature NK cells are large granular lymphoid cells, which are characterized by the presence of pale cytoplasm containing azurophilic granules. Unlike T-cell large granular lymphocytes, they are negative for CD3. Furthermore, clonal rearrangement of the T-cell receptor (*TCR*) gene is also absent in NK cells. ANKL was diagnosed in our case based on clinical manifestations and LGL with positive CD56, CD16 and negative CD3, CD4, CD5, CD57, TCR. T-cell LGL leukemic cells typically co-express CD3+, CD8+ and CD57+ markers and hence were excluded. CT scan showed no mass in nasal cavity and oropharynx, and so NK/T cell lymphoma-nasal type was also excluded. Flow cytometric immunophenotyping is a primary laboratory tool for the accurate identification of NK cells, which

are expressed by cells such as CD2, CD7, CD16 and CD56, and antigens, which are not expressed by cells such as sCD3 and CD5.<sup>4</sup> Flow cytometric immunophenotyping studies for ANKL revealed that all cases have bright CD56 expression and lack CD57 expression. The vast majority of cases do not express CD16 or CD8; some cases are CD16 positive.<sup>5</sup> Standard therapies such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) are ineffective when used to treat ANKL.<sup>6</sup> Intensive acute lymphocytic leukemia-like therapies with central nervous system prophylaxis should be considered as an initial treatment for ANKL. Consolidation therapy with hematopoietic cell transplantation should also be considered for those patients achieving responses to induction therapy.<sup>7</sup> A multicentric study of 15 patients with relapsed, refractory or disseminated extranodal NK/T-cell lymphoma, nasal type and ANKL treated with L-asparaginase-containing regimens showed that seven patients reached complete remission and only two relapsed. L-asparaginase-based regimen should be considered as a salvage treatment, especially for patients with disseminated disease.<sup>8</sup> SMILE protocol (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) achieved 67% response and 50% complete response.<sup>9</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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