

## Aggressive NK cell leukemia presented with secondary hemophagocytic lymphohistiocytosis

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**Background:** Aggressive natural killer cell leukemia (ANKL) is a rare neoplasm of mature natural killer (NK) cells, almost always associated with Epstein-Barr virus (EBV) infection. It is known for a fatal clinical course with poor prognosis. We report a case of aggressive NK cell leukemia presented with EBV-associated secondary hemophagocytic lymphohistiocytosis (sHLH). Case A previously healthy 23-year-old male presented with fever, abdominal pain and watery diarrhea that began 5 days ago. Initially he was presumed to have traveler's diarrhea, however the symptoms were deteriorated. He visited emergency department, was accompanied by a high fever of 39.3°C, scleral jaundice, hepatosplenomegaly, and lymph node enlargement. Laboratory examination revealed WBC 2500/uL, platelet 46,000/uL, triglyceride 303mg/dL, total bilirubin 9.7mg/dL, AST 763U/L, ALT 222U/L, creatinine 1.87mg/dL, fibrinogen 83mg/dL, LDH 3566U/L (100-225U/L), and serum ferritin 144942ng/mL. Whole blood EBV DNA level was markedly elevated (46,516.678copies/mL). Four out of eight HLH-2004 diagnostic criteria were satisfied, raising the possibility of EBV-associated HLH. Clinically, it was necessary to differentiate sHLH due to chronic EBV infection versus EBV-associated T- or NK-cell lymphoproliferative disorder. Dexamethasone was used to control HLH activity after a bone marrow examination (BME) and axillary lymph node biopsy. After steroids use, his vital signs and symptoms showed a gradual improvement. Lymph node biopsy (Fig.1) revealed atypical lymphoid hyperplasia with EBV+, CD3+, CD56+, and granzyme B+ small lymphoid cells. BME (Fig.2) showed Normocellular Marrow with increase of CD3+/CD56+ granular Lymphoid cells with many hemophagocytic histiocytes. Karyotype was 46,X,add(Y)(q12),del(6)(q21q25),add(7)(q32),del(9)(p21)[8]/46,XY[12]. He was finally diagnosed with ANKL associated with sHLH. He started the chemotherapy with SMILE protocol, consisting of methotrexate, ifosfamide, etoposide, dexamethasone, and L-asparaginase. **Conclusion:** Aggressive clinical course, high EBV viral loads, and leukemic presentation associated with sHLH should be concerned NK/T-cell neoplasms such as ANKL.

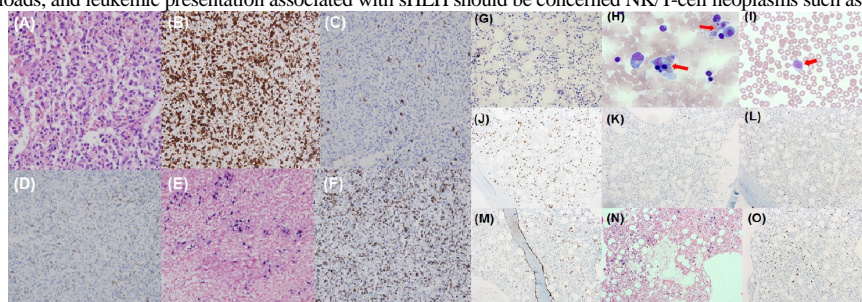


Fig1. Axillary lymph node biopsy  
(A) H&E stain; (B) CD3; (C) CD20;  
(D) CD56; (E) EBV; (F) Granzyme B

Fig2. Bone marrow examination  
(G) H&E stain x400; (H) H&E stain x1000, Arrow-hemophagocytic  
histiocyte; (I) PB x1000, Arrow-Large granular lymphocyte;  
(J) CD3; (K) CD20; (L) CD4; (M) CD56; (N) EBV; (O) Granzyme B

## Hypergranulocytosis in patient with polycythemia vera and bone marrow metastasis of melanoma

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Melanoma is one of the secondary malignancies in patients with myeloproliferative neoplasm (MPN), and its risk in MPN cohort is 2-folds higher compared to normal population. We report a case of unusual manifestation of bone marrow (BM) metastasis of melanoma in a patient with pre-existing polycythemia vera (PV). An 80-year-old-man had been diagnosed with PV and had been stable for 10 years. Two years ago, he had been diagnosed with acral melanoma at right 1st toe and undergone toe amputation with inguinal lymph node dissection. His last follow up, 1 year ago, had shown no evidence of disease. He visited emergency department with general weakness 8 months ago. Laboratory finding showed anemia (hemoglobin 2.9mg/dL) and thrombocytopenia (49,000/uL). BM examination revealed melanoma infiltration instead of post-PV myelofibrosis (post-PV MF) or leukemic transformation (Fig 1A). BM hematopoietic cells harbored JAK2 V617F mutation and its karyotype was normal. Positron emission tomography (PET) also showed multiple systemic metastases. He started pembrolizumab (Pem) for relapsed melanoma. Anemia and thrombocytopenia were improved with Pem. But neutrophilia developed since 2nd cycle of Pem and progressed without any evidence of systemic infection (Fig 1B). Second BM examination reported diffuse myelofibrosis, granulocytic hyperplasia and melanoma infiltration (Fig 1C). BM hematopoietic cells were transformed to cells with complex karyotype. He died of BM failure 2 months after the last BM examination. Some case reports have described paraneoplastic granulocytosis in metastatic melanoma patients and suggested it could result from ectopic granulocyte colony stimulating factor production of melanoma cells. However, they are limited reports in patients with primary melanoma without pre-existing MPN before programmed cell death protein 1 (PD-1) signaling inhibition era. In this case, clonal evolution and post-PV MF were also detected with hypergranulocytosis in BM after Pem therapy. PD-1 signaling inhibition has shown efficacy in melanoma and some lymphoid malignancies, yet not in myeloid neoplasms. Further investigation is needed for these issues.

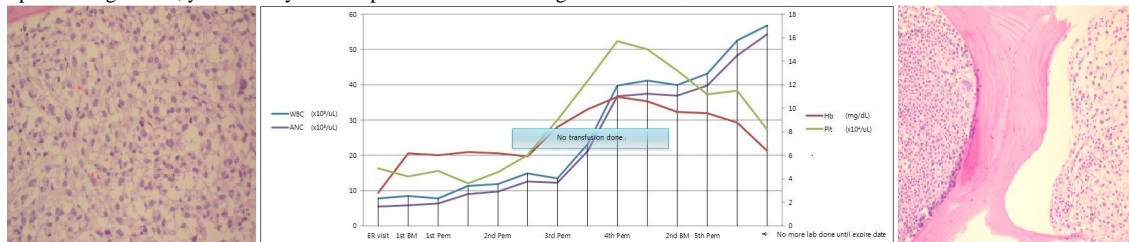


Fig 1A

Fig 1B

Fig 1C