CASE REPORT

Aggressive NK cell leukemia. Presentation of a case

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ABSTRACT

Aggressive natural killer (NK) cell leukemia, is a systemic neoplastic proliferation, usually associated with Epstein-Barr Virus and aggressive clinical course. The objective was characterize a case of aggressive NK cell leukemia and the usefulness of flow cytometry. A 29-year-old woman with a history of Systemic lupus erythematosus (SLE). One month before her admission, she started with abdominal pain predominantly in the epigastrium and left upper quadrant, received two pulses of methylprednisolone. Five days before admission he presented unquantified thermal rise so he went to the hospital, She was admitted to the emergency department of the Almanzor Aguinaga Asenjo Hospital in Chiclayo, Peru. Reporting on admission appears to be in generally good condition (GGC), apparent normal nutritional status (NNS), apparent normal level of hydration (NH), ventilating spontaneously, oral cavity with lesions, presence of purpuric petechiae in anterior trunk and abdomen, rhythmic heart sounds, capillary filling <2", tachypnea, supraclavicular pulls, decreased vesicular murmur in PCA bases, no rales, with oxygen support, depressible abdomen, not painful, positive borborygmi, hemogram with leukocytosis, anemia and severe thrombocytopenia, 36% of "immature cells", 64 normoblasts per 100 leukocytes, hypochromia, anisocytosis, a reactive HBcAb. On the tenth day she had a diagnostic impression of SLE with severe hematologic involvement. On the twenty-fifth day, a flow cytometry was performed, finding an aggressive NK cell leukemia, adding sepsis with respiratory focus and progressive liver dysfunction, she died one month after admission. Aggressive NK cell leukemia is uncommon and of aggressive clinical course, the cellular origin of its normal counterpart is not precisely known, flow cytometry was useful to identify, characterize and quantify NK cells with aberrant antigen expression. (www.actabiomedica.it)

Key words: leukemia, killer cells, natural, flow cytometry (source: DsCS-MESH).

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Introduction

Aggressive natural killer (NK) leukemia is a systemic neoplastic proliferation, almost always associated with Epstein-Barr Virus and with an aggressive clinical course. Patients are commonly young to middle-aged, with an average age of 42 years; with a slight male predominance, according to the World Health Organization, there may be overlap with extranodal NK/T-cell lymphoma showing multiorgan involvement, it is unclear whether aggressive NK cell leukemia represents the leukemic counterpart of NK/T-cell lymphoma (1). There are significant variations in the morphology of aggressive NK cell leukemia (ANKL) with tumor cells ranging from typical large granular lymphocyte morphology to highly atypical features with basophilic cytoplasm containing azurophilic granules. The main sites involved are hepatosplenic lesions, bone marrow and peripheral blood; nasal or cutaneous lesions are rare. Fever and liver dysfunction with an often rapidly progressive course are the main clinical symptoms, including hemophagocytic syndrome and disseminated intravascular coagulation (2). Aggressive NK cell leukemia is believed to originate from mature NK cells. Neoplastic NK cells are typically CD2+, surface CD3 -, cytoplasmic CD3ε+, CD56+ and EBV+, with germline configuration of T-cell receptor (TCR) and immunoglobulin (Ig) genes. The exclusive expression of CD2 and CD56 and the absence of CD3 and TCR in ANKL reflect its NK cell origin. A high rate of CD16 expression (75%) is also characteristic of ANKL. CD16 is generally not expressed in other NK neoplasms, suggesting that it is a specific marker for ANKL. ANKL cases are also positive for cytotoxic molecules and have elevated serum levels of CXCR1, CCR5 and soluble Fas ligand, suggesting that the chemokine system plays an important role in systemic infiltration of leukemic NK cells and liver dysfunction (3). ANKL is a fatal disease with almost uniform mortality. Survival is measured in days to weeks. The median overall survival is less than 2 months (4). Regarding genetic alterations it is reported, that the 6q21 region encompassing POPDC3, PREP, PRDM1, ATG5, AIM1, LACE1 and FOXO3, was the most frequently deleted region in the entire genome. Both FOXO3 and PRDM1 expression were down-regulated in most NK cell neoplasms compared to normal NK cells. All seven candidate genes were transduced into NK cell lines and forced re-expression was induced. Re-expression of FOXO3 and PRDM1 in NK cell lines suppressed cell proliferation, but this was not the case after re-expression of the other genes. Therefore, PRDM1 and FOXO3 are considered to be tumor suppressor genes that play an important role in the pathogenesis of NK cell neoplasms (5). The purpose of this report is to describe and characterize a case of aggressive NK cell leukemia and the usefulness of flow cytometry in its identification and characterization.

Case report

29-year-old female patient from the city of Trujillo. History of systemic lupus erythematosus, diagnosed since 2012, in regular treatment with prednisone 25 mg c/ 12h; Hydroxychloroquine 400mg, 2tablets c/ 24h; mycophenolate 500mg, 1 tablet c/12h. One month before his admission, he started with abdominal pain predominantly in the epigastrium and left upper quadrant, as well as nausea and diaphoresis. She went to a private rheumatologist who ordered an abdominal ultrasound scan showing hepatosplenomegaly. He received two pulses of methylprednisolone, the last pulse two weeks before his admission to the emergency room, but without clinical improvement. Five days before his admission, an unquantified thermal rise was added, so he went to a tertiary level hospital in northern Peru. Among the clinical findings reported, the physical examination on admission showed blood pressure: 106/73 mmHg, mean arterial pressure: 86, HR: 107 l/min, RR: 30 resp/min, T: 37.1°C, SpO2: 98%, FiO2: 0.40, General Ap: AMEG, AREN, AREH, ventilating spontaneously Oral cavity: Lesions in labial commissures, Skin: Purpuric petechiae in anterior trunk and abdomen. Cardiovascular Ap: Rhythmic heart sounds, capillary filling <2", no vasoactive drugs required. Respiratory Ap: tachypnea, supraclavicular tugging, decreased Vesicular Murmur in PCA bases, no rales, with oxygen support. Abdomen: flat, soft, depressible, not painful, RHA (+);

Renal: maintains spontaneous diuresis, Neurological: Glasgow 15 points, isochoric pupils 2 mm photoreceptors, no focalization. Ancillary tests on admission revealed a complete blood count with leukocytosis, anemia and severe thrombocytopenia. Leukocytes: 19 530 cells/mm3, Hb: 8.7 g/dl, Plaq: 8 000 cells/mm3. Peripheral lamina reports 36% of "immature cells", 64 normoblasts per 100 leukocytes, hypochromia, anisocytosis. C-reactive protein: 40 mg/L, urea: 58 mg/dl, TGP: 8 IU/L, TGO: 66 IU/L, GGTP: 40U/L, total proteins: 4.99 g/dl, albumin: 3.04 g/dl, globulins: 2. 0 g/dl, LDH: 3350 IU/L, Total Bilirubin: 0.88 mg/dl, Direct Bilirubin: 0.29 mg/dl, Indirect Bilirubin: 0.59 mg/dl, Direct Coombs: Positive. Serological results as TORCH, revealed that: CMV IgM: (-), HBcAb: Reactive, Rubella IgM: (-), Hepatitis A IgM: (-), HSV 1 IgG: Reactive, HSV 2 IgG: Not Reactive, Echocardiogram: LVEF: 65 %. During follow-up it was found that on the tenth day of hospitalization she was evaluated by hematology and rheumatology whose diagnostic impression was active SLE with severe hematologic compromise, suggesting cyclophosphamide pulses and transfusion support. An abdominal ultrasound was performed and showed: hepatosplenomegaly, thickened gastric wall to consider an inflammatory process, signs suggestive of diffuse liver disease. Since there was no clinical improvement, she was reevaluated by hematology on the twenty-fifth day of hospitalization who indicated bone marrow aspirate, bone biopsy and flow cytometry to rule out: myelodysplastic syndrome vs acute leukemia vs active SLE with hematologic involvement (Figure 1). Bone marrow sample was sent for flow cytometry analysis.

The Flow Cytometry Report concluded that the bone marrow immunophenotyping study showed a CD45+, CD56+, CD16+, CD2+, cyCD3neg, sCD3neg, CD7+d, CD8neg/+, CD38+, CD94+/++, CD4neg, CD19neg, CD79aneg, MPOneg, CD34neg, CD117neg, CD64neg, CD13neg, CD11bneg, CD25neg, CD30neg, CD203neg, CD123neg, HLA-DRneg, CD57neg, CyGranzime negative, CyPerforin negative. Findings suggestive of aggressive NK cell leukemia (Figure 2).

The abdominal ultrasound showed that the liver had an ah of 200 mm, regular borders, preserved shape and size, homogeneous parenchyma, preserved

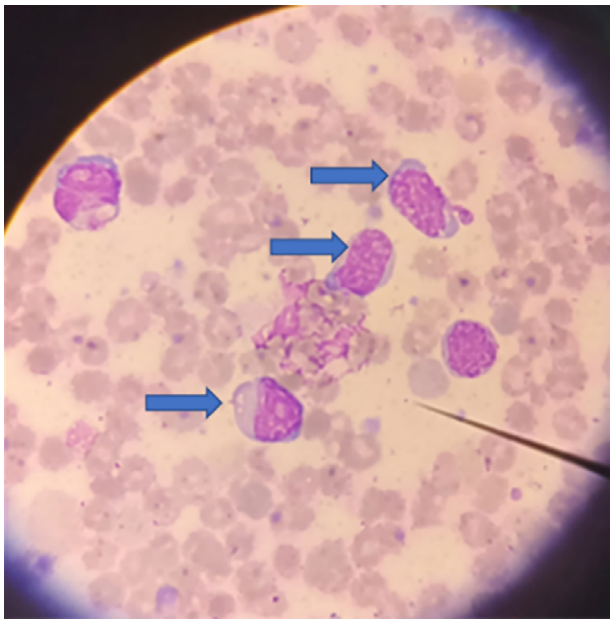

Figure 1. Bone marrow smear shows blast-like cells (blue arrows) 100X.

echogenicity, no focal lesions, biliary tract not dilated. Gallbladder: 82 x 30 mm, wall: 2.8 mm, regular borders, no lithiasic images were visualized inside, common bile duct: 4 mm, portal vein: 10. 1 mm; gastric wall, measured: 2 mm, pancreas: regular edges, shape and size preserved, homogeneous parenchyma, head: 17 mm, body: 15 mm, tail: 11.8 mm; spleen: homogeneous parenchyma, size preserved, measured: 158 x 55 mm, kidneys: regular edges, shape and size preserved. Right kidney: measures: 105 x 54 mm, parenchyma: 16 mm, left kidney: measures: 106 x 52 mm, parenchyma: 15.8 mm, no free fluid in abdominal cavity, retroperitoneum: vessels of preserved caliber, no adenopathies are appreciated. Bladder: repletion, thin walls, no lithiasis. The patient presented a torpid evolution, then progressive hepatic and renal dysfunction was added in addition to sepsis, and she died approximately one month after her admission (Figure 3).

Discussion

NK cells normally, do not express CD3 on their surface, nor T cell receptor (TCR), are CD56

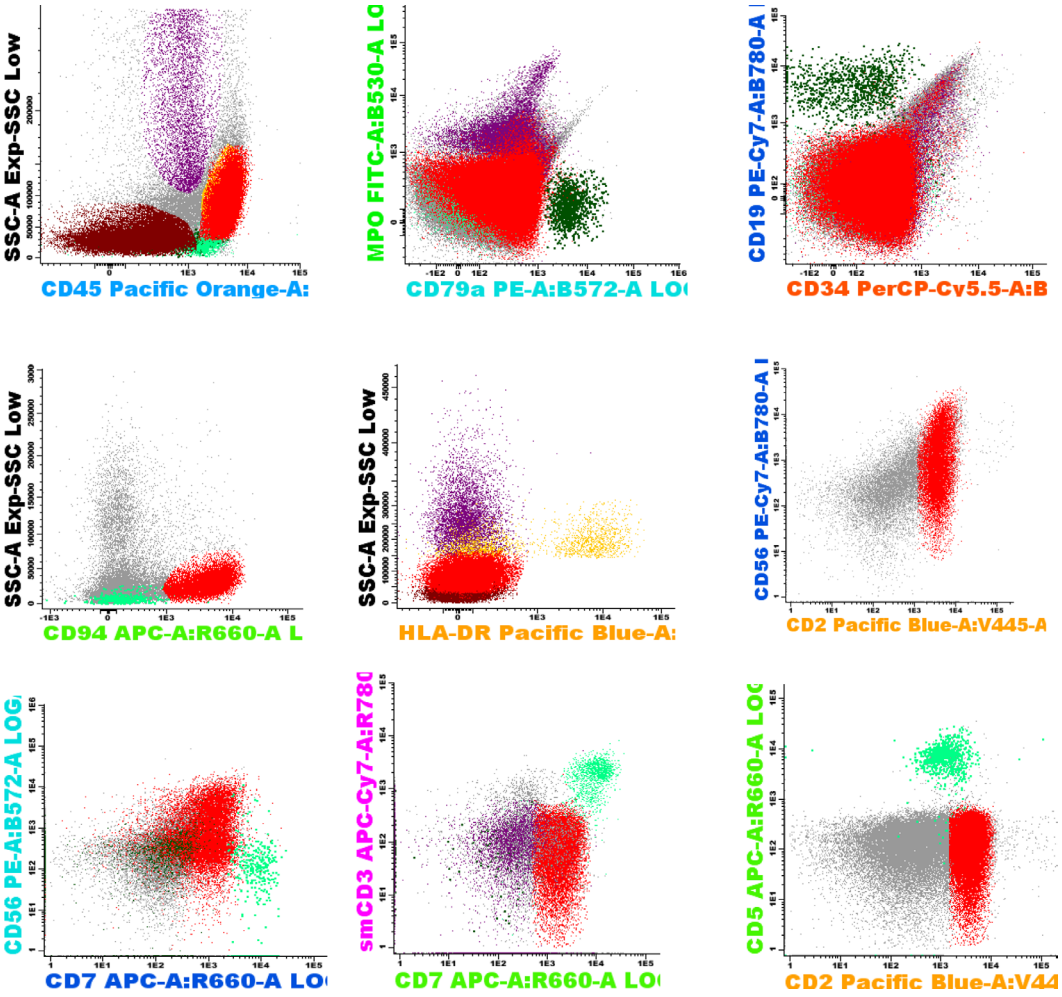

Figure 2. Immunophenotype of peripheral blood, studied by flow cytometry, Novocyte equipment, Exbio reagents, Czech origin. Pathological NK cells (red population). Expression of CD56, CD45, CD2, and CD94.

positive and express variable amounts of CD16; they are CD2+ (a few are CD2-), CD7+bright, CD5- , CD4- and CD8-/+dim. In the present case, the NK cells observed were aberrant CD56+, CD16+, CD57neg, CD94+/++, with non-activated or late-activated phenotype (HLA DR neg, CD7+d), as occurs in chronically activated NK cells, in which their expression is weak and heterogeneous and non-cytotoxic (CyGranzime neg). The origin of these activated cells is presumed to be a CD56+bright NK cell, and this could partly justify the hepatosplenomegaly, liver failure and invasion of other organs reported in ANKL, since this pattern allows the cells to migrate to peripheral tissues under conditions of chronic inflammation, as occurred in the present case (6). Due to the very aggressive course of leukemized NK lymphomas and the accelerated systemic involvement, as occurred in this patient, it often avoids the initiation of aggressive chemotherapy. Case reports report that less than 5% of leukemized NK lymphomas are diagnosed in early stages, resulting in a lethality of practically 100% (7). It is concluded that aggressive leukemia of natural cytotoxic cells is very rare and of aggressive clinical course, and the cellular origin of its normal counterpart is still not precisely known. Although it was not possible to demonstrate

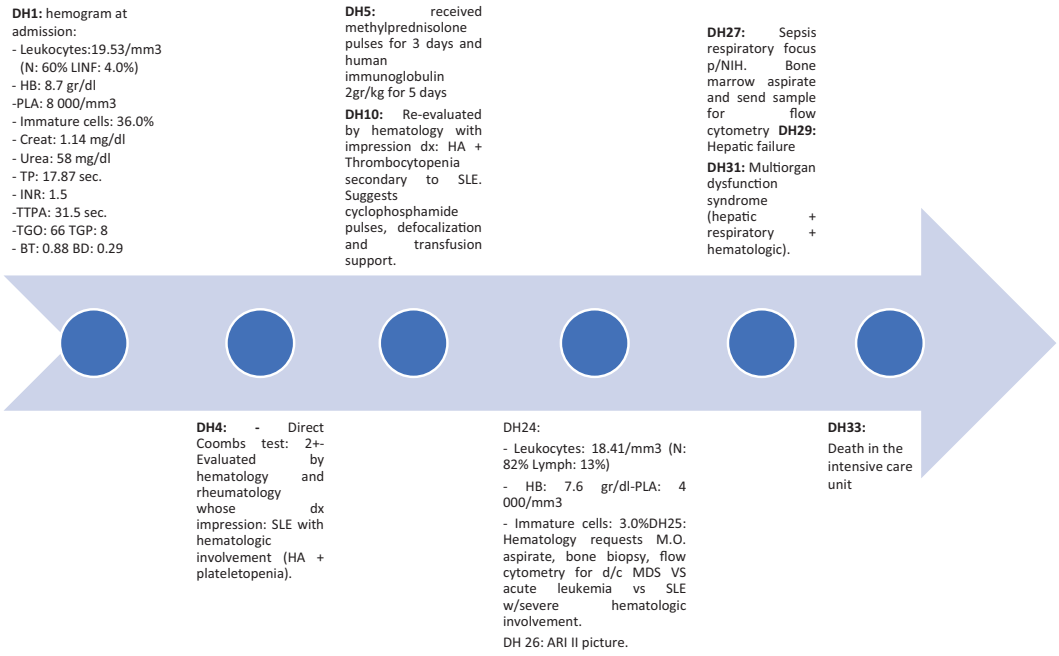

Figure 3. Timeline of important events during the patient's hospitalization.
Abbreviation: **DH:** Day of hospitalization.

clonality of NK cells by multiparametric flow cytometry, the usefulness of this technique is highlighted, as it makes it possible to identify, characterize and quantify NK cells with aberrant expression of antigens which, in the present clinical case, helped to establish the diagnosis.

Ethical Approval: This case was reviewed and approved by the institutional research ethics committee of the Lambayeque-ESSALUD-Peru service network, with resolution number N°047-2024 GRPL-ESSALUD.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: STV: Conception, design and conduct of the study, drafting of manuscript, review and approval of manuscript. WCCV: Conduct of the study, drafting of the manuscript, review of the manuscript. JCHS: Analysis of the results, drafting of the manuscript and revision of the manuscript. LKBG: design of the study, drafting of the manuscript, review and revision of the manuscript.

Declaration on the use of AI: None.

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