INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

2022 March; 28(2): 215-218
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Abnormal Complex Karyotyping in A Patient Suspected of Acute Myeloblastic Leukemia (AML-M5): A Case Study

Purbosari, Usi Sukorini, Rahmat Dani Satria, Tri Ratnaningsih, Setyawati

Department of Clinical Pathology, Faculty of Medicine, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia. E-mail: purbosari84@gmail.com

ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a condition of immune dysregulation characterized by severe organ damage induced by a hyperinflammatory response and uncontrolled T-cell and macrophage activation. Patients with Acute Myeloblastic Leukemia (AML) may be prone to develop HLH. Hemophagocytic lymphohistiocytosis syndrome in AML patients with an abnormal complex karyotyping can worsen the patients' prognosis and outcome. A 47-year-old-female presented with prolonged fever, chills, fatigue, weight loss, productive cough, and anemia (blood transfusion (+)). Laboratory findings: hemoglobin 8.5 g/dL, WBC 151.99x103/µL, and platelet count 28x103/µL, peripheral blood 13% blast like cells, 19% promonocytes, 43% atypical (bizarre) monocytes, 25% neutrophils. Levels of CRP>150 mg/L and procalcitonin 82.67 ng/mL, negative HBsAg, and positive IGRA test. Bone marrow morphology showed hypercellularity, decreased thrombopoiesis and erythropoiesis, increased granulopoiesis, macrophages, and hemophagocytosis. Karyotyping results: abnormal karyotypes: 46: XX (9 cells), 44: X (-18), 45: XX (-4), 45: XX (+7, -2, -16), 46: XX (chtb (3), chtb (4), chtb (5), chtb (9), chtb (12), chtb (22)), 46: XX (chtb (5), chtb (7)), 46: XX (chtb (6), chtb (12)), 46: XX (dic 2), 46: XX (chtb (1) (q12), chtb (3) (p21)), 46: XX (chtb (X) (q25)), 46: XX (der (9), dic (9)), t (9:22)), 46: XX ((+ 21), (-13) chtb (2), p (23), t (9:22)). The conclusion was abnormal complex karyotyping. High concentrations of inflammatory cytokines (interleukin-1, interleukin-6, TNF-alpha, and interferon-gamma) secreted by malignant cells and increased phagocytic function of leukemic cells play an important role in the pathogenesis of HLH. Monocytic components (subtypes AML4 and AML5 of the FAB classification) are predisposing factors in cases of AML-related HLH. Cytogenetic abnormalities involving 8p11 and 16p13 are more common in AML-related HLH. Complex genetic abnormalities exacerbate the prognosis of AML, especially in treatment failure. A concluded that was diagnosed with HLH due to AML-M5 with genetic abnormalities of BCR ABL (+), monosomy, trisomy, and multiple chromatid breakage with high mortality. Karyotyping examination is important to determine the prognosis of the disease.

Keywords: Hemophagocytic lymphohistiocytosis, acute myeloblastic leukemia, karyotyping

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a condition of immune dysregulation that is characterized by severe organ damage caused by a hyper inflammation response and uncontrolled activation of T-cells and macrophages. This disease is a rare and fatal hematologic disorder that mainly affects the mononuclear phagocytic system. Clinical signs of HLH vary but usually consist of prolonged fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis in the bone marrow, liver, spleen, or lymph glands. Hemophagocytic Lymphohistiocytosis is categorized into primary and secondary HLH. Primary HLH consists of several genetic conditions, such as familial-HLH (F-HLH)2-5, type 2 Griscelli syndrome, Chediak-Higashi syndrome, etc. Secondary HLH is usually caused by infection, malignancy, autoimmune disease, metabolic disease, and immune deficiency. Leukemic HLH rarely occurs and is rarely reported. Clinical manifestations are variative causing a high incidence of misdiagnosis and mortality. Late diagnosis may cause a delay in therapy or even early death.[1]

Patients with Acute Myeloblastic Leukemia (AML) are highly susceptible to HLH. HLH syndrome in AML patients with abnormal genetic complex karyotyping may worsen the prognosis and outcome of the patient.

CASE

A-47-years old female patient was referred to Dr. Sardjito Hospital with suspicion of hematological malignancy and a history of repeated anemia (history

of PRC transfusion) prolonged fever, shivering, fatigue, weight loss, and productive cough.

A month before admission, the patient complained of fatigue, dizziness, and heaviness in both legs; and was diagnosed at RSUD Sleman with anemia and was given 5 bags of PRC. On the eighth day of care, the patient complained of increasing fatigue, was transfused with 5 more bags of PRC, and was planned to be referred to Sardjito Hospital for further care.

On admission at Dr. Sardjito Hospital, the patient complained of yet increasing fatigue, blurry vision, productive cough, shortness of breath, and weight loss of as much as 7 kg during the past month. History of hypertension and diabetes mellitus was denied, and there was no family history of the same disease.

SUMMARY OF PHYSICAL EXAMINATION AND CARE

During admission, the patient had a compos mentis mental state, had a recurrent fever, and was pale. Vital signs show sub-febrile temperature (37.9ºC per axilla), normal heart rate (88x/minutes), cough and shortness of breath, anemic conjunctiva, no icteric sclera, isochoric pupils with symmetrical reaction to light. There were no abnormalities in the nose and throat. No palpable lymph nodes or stiff neck. Symmetrical breathing, no chest retraction, decreased vesicular breathing in both lungs and there was faint wheezing in both lungs, no abnormalities in the heart. Soft abdomen, normal peristaltic, tympanic percussion in all regions, no tenderness, liver, and spleen were not palpable. No edema or atrophy in extremities, no skin petechiae.

Laboratory results on admission at Dr. Sardjito Hospital are as follows: Hemoglobin 8,5 g/dL, WBC 151.99x106/µL, and platelets 28x106/µL. Peripheral blood smear showed 13% blast-like cells, 19% promonocytes, 43% atypical/bizarre monocytes, and 25% neutrophils, suggesting an acute hematological malignancy. Prothrombin Time (PPT) value of 18.4 seconds, APTT value of 26.9 seconds, and an INR of 1.39. CRP >150 mg/L dan procalcitonin 82.67 ng/mL, negative HBsAg, and positive IGRA test. Chest X-ray showed pneumonia.

Bone Marrow Aspiration (BMA) was conducted on the fourth day of care, the bone marrow morphology showed hypercellularity, a decrease of thrombopoiesis and erythropoiesis, an increase in granulopoiesis (1% myeloblasts, 5% promyelocytes, 6% myelocytes, 3% metamyelocyte, 28% neutrophils, 10% monoblasts, 9% promonocytes, 34% monocytes (11% atypical/bizarre monocytes, 21% activated monocytes with vacuolation) macrophages, and hemophagocytosis. The conclusion led to HLH with a suspect of Acute Myeloblastic Acute (AML-M5) and was recommended karyotyping and a BMA monitoring if it was possible for the patient.

Karyotyping resulted in an abnormal karyotype, as follows: 46: XX (9 sel), 44: X (-18), 45: XX (-4), 45: XX (+7, -2, -16), 46: XX (chtb (3), chtb (4), chtb (5) , chtb (9), chtb (12), chtb (22)), 46: XX (chtb (5), chtb (7)), 46: XX (chtb (6), chtb(12)), 46: XX (dic 2), 46: XX (chtb (1) (q12), chtb (3) (p21)), 46: XX (chtb (X) (q25), 46: XX (der (9), dic (9)), t (9:22)), 46: XX ((+21), (- 3) chtb (2), p(23), t (9:22)) with the conclusion of abnormal complex karyotyping, and suggestion of quantitative BCR ABL examination.

The hemoglobin and thrombocytes levels decreased during care (hemoglobin 7.2 g/dL) causing the patient to get 2 PRC blood transfusions. The patient got antibiotic therapy (Meropenem and Moxifloxacin injection), anti-tuberculosis medication (OAT); and antifungal therapy (micafungin injection). The patient was admitted for 28 days and was discharged after improving, with the following laboratory results (hemoglobin 10.1 g/dL, WBC 9.35x103/µL, and thrombocytes 6x103/µL. A couple of weeks after the patient went home, the family stated that her condition deteriorated and the patient passed away.

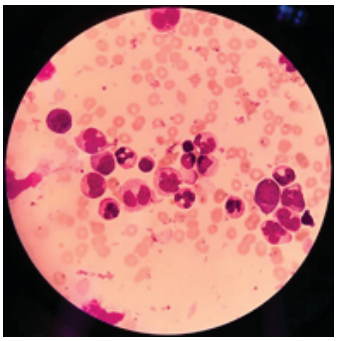

Figure 1a

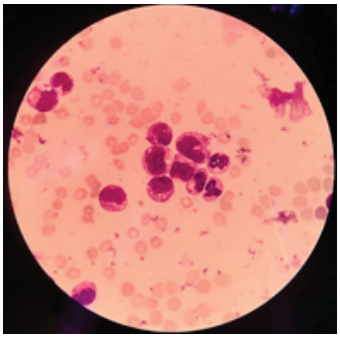

Figure 1b

Figures 1a and 1b. Peripheral blood smear showed blasts like cells, promonocytes, and atypical/bizarre monocytes

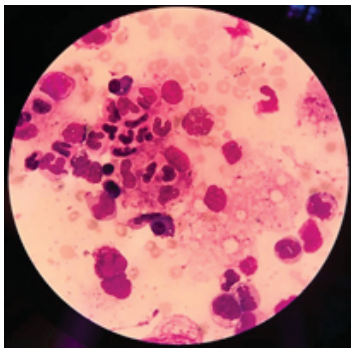

Figure 2a

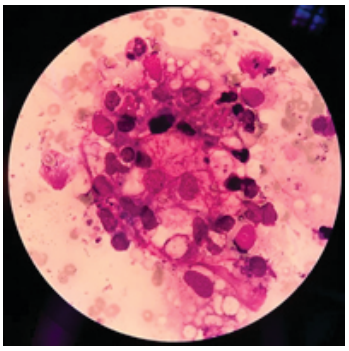

Figure 2b

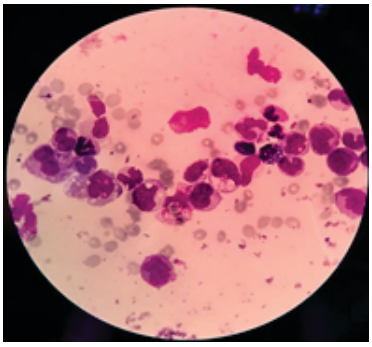

Figure 2c

Figures 2a and 2b. Hemophagocytosis in a BMA smear

Figure 2c. Mononuclear cell domination in the BMA smear (monoblast, promonocytes, monocytes with vacuolation)

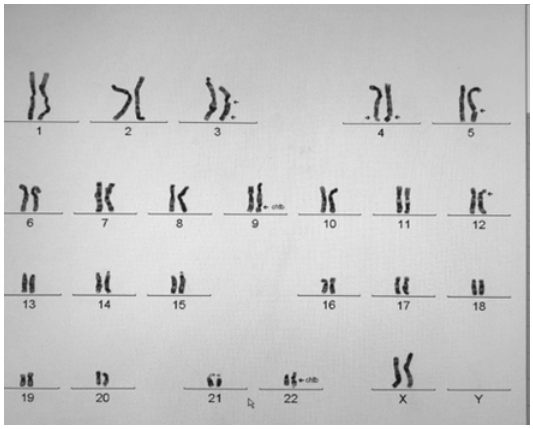

Figure 3a. Chromosome breakage (in chromosomes 3, 4, 5, 9, 22)

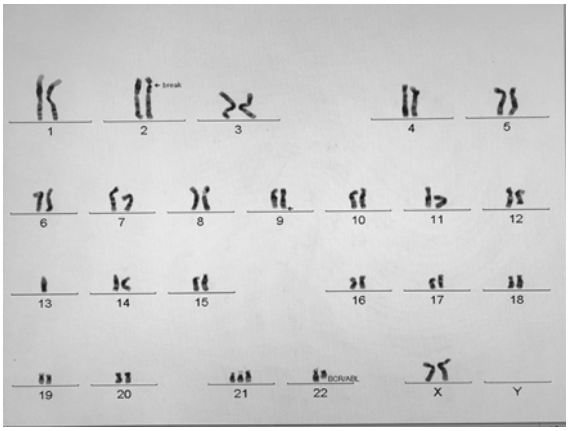

Figure 3b. BCR ABL in chromosome 22

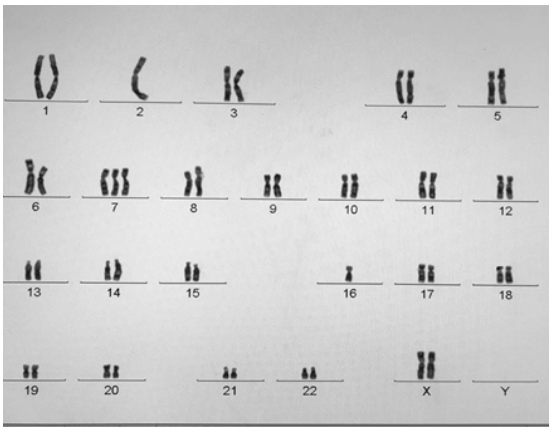

Figure 3c. Monosomy (chromosome 2 and 16) and trisomy (chromosome 7)

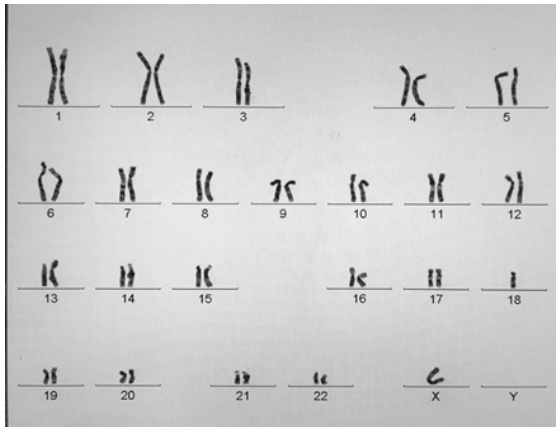

Figure 3d. Monosomy (chromosome X)

DISCUSSIONS

Delavigne *et al*. reported that HLH may be detected in up to 10% of patients during induction therapy, but in almost all cases HLH was due to therapy-related infections.[2] HLH cases are rarely reported in malignancies such as AML, this differs from other malignancies such as non-Hodgkin lymphoma.[3] Even though HLH accompanied by AML cases is rare, the presence of the monocytic component (AML-M4 and AML-M5 subtype from FAB classification) is a predisposing factor in cases of HLH related to AML. High inflammatory cytokine concentrations (interleukin-1, interleukin-6, TNF alpha, and

interferon-gamma) secreted by the malignant cells and the increase of leukemic cell phagocytic functions play an important part in the pathogenesis of HLH.

Although the difference between primary and secondary HLH is clear, a few genetical abnormalities found in adults support the hypothesis that a lot of secondary HLH has a genetical predisposition that must be further analyzed to see if there are genetic abnormalities in every case of suspicious HLH and to learn of more genes that are related with cytotoxic functions that can be identified in the future. Yoon *et al*. hypothesized that all patients participating in this study without genetic study data are secondary HLH cases unless they fulfill the 2004 HLH criteria.[4] Several cytogenetic abnormalities involving 8p11 and 16p13 are seen more frequently in AML-associated HLH.[3]

This patient had a genetic abnormality, which was complex karyotyping. Many cytogenetic disorders happen in leukemia, lymphoma, and many other unique clonal abnormalities in specific patients. Abnormalities in hematological malignancies are deemed clonal when structural rearrangements or addition of chromosomes present in two or more cells, the absence of chromosomes in three or more cells, and the abnormalities may happen in any form or combination. Numerical abnormalities are either addition or deletion. Structural rearrangements can happen balanced or unbalanced. Balanced rearrangements consist of translocation, inversion, and insertion. Unbalanced rearrangements are hereditary chromosomes, isochromosomes, deletion, duplication, etc.[5]

Cytogenetic abnormalities often happen in AML. Many AML subtypes have reoccurring cytogenetic abnormalities, and some are determined by cytogenetic/genetic defects. This patient had several cytogenetic abnormalities. Acute myeloblastic leukemia cases with t (8;21) (q22;q22) and AML with inv (16) (p13.1q22)/t (16;16) (p13.1;q22) are classified as "core binding factor" leukemia (note: Acute lymphoblastic leukemia (ALL) with t (12;21) is also a "core-binding factor" leukemia). Leukemia with core-binding factors has a relatively good prognosis. Acute promyelocytic leukemia (APL) with t (15;17) (q24;q21), also has a good prognosis. Bad prognostic cytogenetic indicators are monosomy 5 and 7, deletion 5q, t (3;3) (q21;q26)/inv (3) (q21q26), t (6;9) (p23;34), 11q23 abnormality (abnormality in AML), abnormal 17p, complex (≥ 3 or ≥ 4 abnormalities that are not related), and monosomy karyotype (1,5-11). The incidence of de novo AML with monosomy 5 or monosomy 7 increases with age, but AML with balanced translocation doesn't. [5]

Acute myeloblastic acute cases with positive Philadelphia chromosome (Ph)/BCR ABL only happen in about 1% of AML. This is typical t (9;22) (q34;q11.2), where der (22) is called the Philadelphia chromosome. Ph-AML cells are immature with little differentiation. These patients have a bad prognosis. Nowadays, Ph-AML patients can be cured with imatinib mesylate (Gleevec®;Novartis), or second-generation Tyrosine Kinase Inhibitor (TKI) has shown to be a successful therapy. In this patient the Philadelphia chromosome has been found in more than one cell, making the patient's prognosis worse.[5]

Complex genetic abnormalities (there are ≥ 3 or ≥4 abnormalities that are not related) as found in this patient, there were BCR ABL (+), monosomy, trisomy, multiple chromatid breakage, and monosomy in chromosome 23 (sex chromosome) that worsen the prognosis, especially in therapy failure and mortality rate.

CONCLUSIONS

A 47-year-old female was diagnosed with HLH due to AML-M5 with genetic abnormalities of BCR ABL (+), monosomy, trisomy, and multiple chromatid breakage that are complex genetic abnormalities that can be a bad prognosis indicator with high mortality. Karyotyping examination is important to determine the prognosis of the disease and the appropriate interventional therapy.

REFERENCES

1. Wang H, Xiong L, Tang W, Zhou Y, Li F. A systematic review of malignancy-associated hemophagocytic lymphohistiocytosis that needs more attention. Oncotarget, 2017; 8(35): 59977-85.
2. Belhadj M, Burroni B, Suarez F. Hemophagocytic lymphohistiocytosis due to acute myeloid leukemia relapse: A very unusual association. J Leuk, 2015; 03(04): 3-5.
3. Hatano K, Nagai T, Matsuyama T, Sakaguchi Y, Fujiwara SI, *et al*. Leukemia cells directly phagocytose blood cells in AML-associated hemophagocytic lymphohistiocytosis: A case report and review of the literature. Acta Haematol, 2015; 133(1): 98-100.
4. Yoon JH, Park SS, Jeon YW, Lee SE, Cho BS, *et al*. Treatment outcomes and prognostic factors in adult patients with secondary hemophagocytic lymphohistiocytosis not associated with malignancy. Haematologica, 2019; 104(2): 269-76.
5. Arsham MS, Barch MJ, Lawce HJ, The AGT Cytogenetics laboratory manual. Fourth Ed., New Jersey, Wiley Blackwell 2016; 4(11): 523-533.