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CASE REPORT

Eccentricity of Acute Myeloid Leukemia with NPM1 and FLT3-ITD Mutation: A Case Report

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ABSTRAK

Leukemia myeloid akut (AML) ialah sejenis leukemia akut yang paling kerap dihidapi oleh golongan dewasa, dengan kepelbagaian landskap sitogenetik. Leukemia myeloid akut dengan mutasi NPM1 telah diletakkan di dalam entiti sementara di dalam edisi 2008 di dalam buku Klasifikasi Tumor Hematopoietik dan Limfoid oleh Badan Kesihatan Dunia. Di dalam edisi semakan keempat yang dikeluarkan pada tahun 2017, AML telah diiktiraf sebagai satu entiti unik dengan ciri sitologi, molekular dan klinikopatologikal yang tersendiri. Contohnya, ia sering dikaitkan dengan leukemia myelomonositik akut dan leukemia monositik akut. Dalam kajian terbaru, AML dengan mutasi NPM1 dan FLT3-ITD telah dikaitkan dengan sel blas dengan bentuk seperti cawan. Kami melaporkan satu kes dengan morfologi ini yang berlaku kepada seorang wanita berumur 68 tahun yang telah didiagnos dengan AML disertai dengan mutasi NPM1 dan FLT3-ITD, dan mempunyai sejarah pendek demam dengan keputusan makmal yang menunjukkan sel darah putih yang sangat tinggi, anemia ringan dan jumlah platelet yang rendah. Filem darah periferi dan sampel aspirasi sumsum tulang menunjukkan kehadiran sebahagian sel leukemia dengan nukleus berbentuk cawan. Sitometri aliran telah menunjukkan ciri-ciri yang dikaitkan dengan AML dengan mutasi NPM1. Tindak balas rantai polimerase (PCR) mengesan mutasi FLT3-ITD dan NPM1. Pesakit ini telah dirawat dengan protokol AML tetapi meninggal dunia kerana sepsis. Kes ini menekankan kepentingan untuk mengenalpasti ciri-ciri klinikopatiologi ini dalam memberi diagnosis yang cepat dan memberi panduan untuk ujian molekular yang sesuai. Modaliti rawatan baru yang tersedia untuk jenis AML ini dan kajian terdahulu juga dibincangkan dalam kajian ini.

Kata kunci: AML, FLT-3, NPM1, nukleus cawan

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ABSTRACT

Acute myeloid leukaemia (AML) is the most prevalent type of acute leukaemia in adults, with a heterogenous cytogenetics landscapes. NPM1 mutated AML was designated as a provisional entity in 2008 World Health Organisation (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues. In 2017, fourth edition was revised and AML was recognised as a distinct entity with distinctive cytological, molecular and clinicopathological features. For example, AML with NPM1 mutation is strongly associated with acute myelomonocytic and acute monocytic leukemia. In recent studies, AML with both NPM1 and FLT3-ITD mutations, had been associated of blasts with cup-like nuclei. We described this characteristical morphology in a 68-year-old female who was diagnosed with AML alongside NPM1 and FLT3-ITD mutation. She presented with a short history of fever and laboratory findings of hyperleukocytosis, mild anemia and thrombocytopenia. A diagnosis of AML was proposed from the cytological and flow cytometry examinations. The full blood picture and bone marrow aspirate showed some of the blasts with cup-like nuclei and the flow cytometry examination showed characteristical feature which was suggestive of AML with NPM1 mutation. Polymerase chain reaction (PCR) detected mutation in FLT3-internal tandem duplication (ITD) and NPM1. This patient was treated with AML protocol but succumbed due to sepsis. This case highlighted the importance of recognising this clinicopathological presentations to provide rapid diagnosis and guide for the appropriate molecular testing. In this study, new treatment modalities available for this type of AML and literature review of previous studies were also discussed.

Keywords: AML, cup-shaped nucleus, FLT-3, NPM1

INTRODUCTION

Genetics studies for classification of myeloid neoplasm has been first introduced in the World Health Organisation (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues (3rd edition) published in 2001 (Swerdlow et al. 2007). Since then, cytogenetics analysis of acute myeloid leukaemia (AML) has taken centre stage in the diagnostic algorithm with more than 160 recurrent structural chromosome abnormalities are observed (Mrózek et al. 2001). In the latest classification by WHO, a new distinct entity of AML, NPM1-mutated AML, is recognised based on its unique molecular, pathological and clinical features (Falini et al. 2021). It is now recognised as the commonest mutation in AML, encompassing more than 30% of the patients with primary AML and concomitant FLT3-ITD mutation is detected in 40% of the NPM1 mutated AML (Falini et al. 2005; Grimwade et al. 2016). The European LeukaemiaNet (ELN) has made a

requirement to determine the status of NPM1 mutation at diagnosis stage as it is a defined category, which carries a prognostic significance as well as a target for minimal residual disease monitoring (Döhner et al. 2017).

However, cytogenetics and molecular results may not be always available immediately, and in certain part of the world, they are not routinely done. Therefore, there is a role for morphology and immunophenotyping as an attempt to rapidly provide a diagnosis and at the same time provide indication for the cytogenetics abnormalities (Bain & Béné 2019). For example, unique morphological recognition of the blasts were seen in acute promyelocytic leukaemia (APML), along with other haematological and clinical findings might provide rapid diagnosis and guide patient management (Fe Joibi et al. 2019). NPM1 mutated AML has been associated with cup-like nuclei in many different studies and case reports (Bain et al. 2015; Chen et al. 2009; Kroschinsky et al. 2008; Park et al. 2013). Kroschinky et al. (2008) had described that these AML exhibited cup-like nuclear invagination extending with at least one fourth of the nuclear diameter of the blasts. This distinct nuclear invagination should involve at least 10% of the blast cells (Chen et al. 2009; Kroschinsky et al. 2008). This case report reviewed the clinical and molecular features associated with NPM1 and FLT3-ITD mutation and the data that had been reported previously.

CASE REPORT

A 68-year-old female with underlying diabetes mellitus, hypertension and dyslipidaemia was referred to our center with a white blood cell count of $110x10^9$/L, hemoglobin of 11.6g/dL and platelet count of $72x10^9$/L. She presented with high grade fever and diarrhoea for 5 days. Otherwise, she had no bleeding tendency or the constitutional symptoms of weight loss or loss of appetite. Physical examination was unremarkable. There were no bruises, hepatosplenomegaly or lymphadenopathy. An urgent peripheral blood film was requested, showing moderate anemia, thrombocytopenia and hyperleukocytosis with 97% blasts.

As illustrated in Figure 1, the blasts were medium sized and exhibited scanty, weakly basophilic cytoplasm with few fine azurophilic granules. The nuclei had irregular nuclear outline, open chromatin pattern with prominent nucleoli with 13% of the blasts displaying prominent nuclear invagination (cup-like blasts). Bone marrow aspirate showed markedly hypercellular marrow fragments and cell trails with presence of more than 90% blasts, characterised by medium to large sized cells with high nuclear to cytoplasmic ratio, minimal weakly basophilic cytoplasm, few with granules, irregular nuclear outline with open chromatin pattern and prominent nucleoli. Eight percent of the blasts displayed prominent nuclear invaginations (cup-like blasts). The residual granulocytes, erythroid precursors, lymphoid and

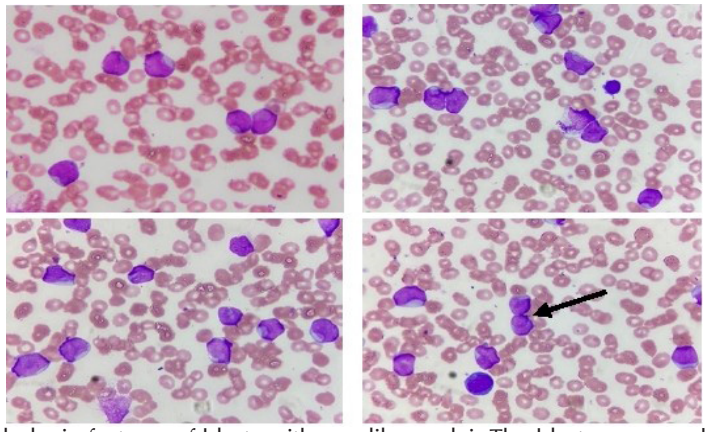

Figure 1: Morphologic features of blasts with cup-like nuclei. The blasts were medium sized with prominent nuclear invagination scanty pale basophilic cytoplasm with occasional azurophilic granules. Some of the blasts exhibited cleaved or bilobed nuclei similar to the hypogranular acute promyelocytic leukaemia, as was shown with arrow (Peripheral blood was stained with Wright stain, original magnification x 400 using Olympus BX-43 microscope)

megakaryocytes were significantly reduced.

Flow cytometry immunophenotyping (Figure 2) performed on the bone marrow aspirate showed approximately 96% abnormal myeloid blast population, gated at CD45 versus side scatter plot. The blasts were CD45 dim, low to moderate side scatter, expressing MPO (bright), CD117 (heterogenous), CD33 (dim), CD13 (dim), CD38 (dim), CD9 and CD123. They were negative for CD34, HLA-DR, CD16, CD14, CD64, CD25, GlyA, CD36, CD105, cyCD61, CD41a, CD3, cyCD79a and CD19. Trephine biopsy showed marrow spaces were interstitially infiltrated by blast cells. The blast cells had variable amount of eosinophilic cytoplasm, vesicular

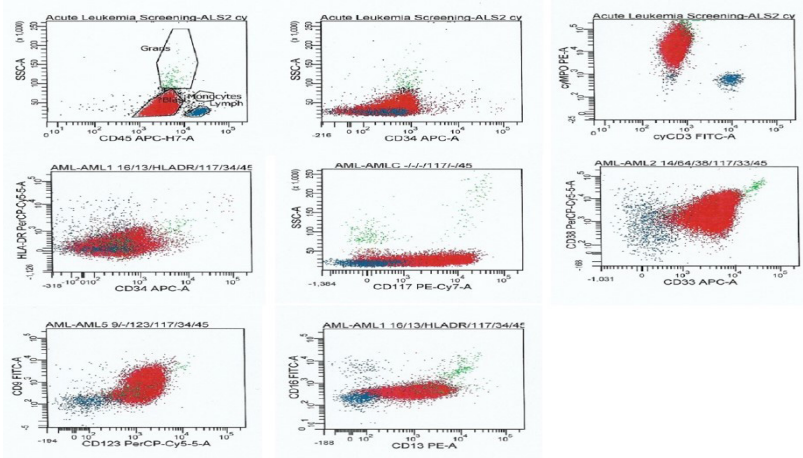

Figure 2: Flow cytometric immunophenotyping showed positivite for MPO, CD117 (heterogenous), CD33 (dim), CD13 (dim), CD38 (dim), CD123 and CD9. They were negative for CD34, HLA-DR and CD16

chromatin pattern and inconspicuous nucleoli. The blast cells were positive for CD117 and MPO. They stained negatively for glycophorin C, CD68 and CD61. Cytogenetics showed a normal 46, XX karyotype, with no evidence of PML-RARA rearrangement, CBFB rearrangement, RUNX1-RUNX1T1 rearrangement or MLL rearrangement via fluorescence in situ hybridisation (FISH). ONCODEduce AML qualitative assays via polymerase chain reaction (PCR) detected mutation in FLT3-internal tandem duplication (ITD) and NPM1.

She underwent induction with 3+7 AML protocol with Cytarabine and Daunorubicin, which was complicated with neutropenic sepsis, viral exanthem and pharyngotonsillitis with supraglottitis. The protocol was truncated to six days due to high grade fever secondary to line-related sepsis with *Pseudomonas* spp. At day-19 after induction, she developed haemoptysis and pulmonary haemorrhage, requiring multiple packed cells and platelets transfusions. This episode was complicated with unstable atrial fibrillation and respiratory failure, subsequently requiring non-invasive ventilation and intubation. Unfortunately, she passed away at day-20 post-induction chemotherapy due to overwhelming sepsis with multiorgan failure.

DISCUSSION

WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues (revised fourth edition) 2017 defined AML with mutated NPM1 as AML which carried NPM1 mutation that usually involved exon 12, with aberrant cytoplasmic expression of NPM1 as a surrogate marker of the mutation (Swerdlow et al. 2017). The category of AML with NPM1 mutation was placed under AML with recurrent genetic abnormalities in the WHO fourth edition. However, in the latest upcoming WHO fifth edition, it is now placed under AML with defining genetic abnormalities (Joseph et al. 2022).

The role of NPM1 mutation in leukemogenesis is likely attributed by aberrant cytoplasmic dislocation of all NPM1 mutants. However, the exact mechanisms in driving leukemogenesis have yet to be elucidated (Heath et al. 2017). Falini et al. (2005) reported the occurrence of FLT3 mutation is twice as likely to be associated with NPM1 mutation. In this patient, both NPM1 and FLT-3 mutation were detected via PCR. Another molecular assay available for detection of NPM1 is by gene sequencing. Another method for detection of the abnormal localisation of the NPM1 protein in the cytoplasm is by immunohistochemistry (Grody et al. 2009). Cytogenetic analysis of the patient revealed a normal karyotype (46xx) with de novo mutation, which concured with previous studies (Becker et al. 2010; Brown et al. 2007; Thiede et al. 2006).

Falini et al. (2005) first identified the expression of cytoplasmic NPM1 in AML patients. More than a third of the patients with primary AML were described to have this mutation, therefore making it as the commonest recurrent genetic abnormality in AML

(Falini et al. 2005). In the study, the cytoplasmic nucleoplasmin was found in all of the leukaemic cells, except in the case of FAB M5b (monocytic leukaemia), where only 30-60% were found to harbour the cytoplasmic nucleoplasmin. The NPMc+ pattern was found in all FAB subtypes except M3, M4eo and M7. The commonest FAB subtype associated with NPMc+ is M5b subtype (87.5%).

In this patient, the significant morphological findings were blasts with nuclear invagination (cup-like nuclei). Cup-like nuclei had been recently associated with NPM1 and FLT3-ITD mutation (Carluccio et al. 2014; Chen et al. 2009; Jost et al. 2015; Kamoda et al. 2017; Park et al. 2013). Park et al. (2013) described the presence of cup-like nuclei in 21.2% of AML with mutation of both NPM1 and FLT3-ITD. This study also found that cup-like nuclei AML was associated with negative CD34 and high blasts count (Park et al. 2013). This was similar to a study by Dohner et al. (2005), which described NPM1 mutation with higher white blood cell (WBC) count, higher bone marrow (BM) blast count and lower CD34 antigen expression. This study also described significant association of mutant NPM1 with myelomonocytic or monocytic morphology, extramedullary involvement, female, higher WBC counts, higher platelet counts, higher lactate dehydrogenase (LDH) as compared to NPM1 negative AML.

Images by transmission electron microscopy of the cup-like nuclei blasts showed assembly of mitochondria within the invagination and pressing on the chromatin (Jost et al. 2015). Although some of the blasts showed distinctive cup-like nuclei, a case report by Pepper and Tan (2020) described an AML with NPM1 and FLT3-ITD which mimicked hypogranular variant of APML due to the presence of morphology with cleaved nuclei, with loss of CD34 and HLA-DR in the flow-cytometry, which were similar to the present case. Therefore, this highlighted the importance for confirmation with molecular study for PML-RARA, along with NPM1 and FLT3-ITD diagnosis. The PML-RARA via FISH was negative in this patient.

The NPM1 gene is located on chromosome 5q35. It encodes NPM1 protein that is composed of 294 amino acids. This protein travels between the nucleus and the cytoplasm and is pertinent is many cellular processes, such as DNA repair and genome stability (Grody et al. 2009). The presence of NPM1 mutation alone confers good prognosis with excellent respond to chemotherapy (Boissel et al. 2005; Brown et al. 2007; Camus et al. 2015; Döhner et al. 2005; Heath et al. 2017; Schnittger et al. 2005; Wilson et al. 2006). However, with the addition of FLT3-ITD mutation, the prognosis is intermediate (Döhner et al. 2017). FLT3-ITD mutation, especially in adults is linked with a poorer prognosis, higher risk of relapse, worse disease-free survival and reduced overall survival (Fe Joibi et al. 2019). Nevertheless, in younger adult, co-existence of FLT3-ITD and NPM1 mutations confer better prognosis than patient with AML with FLT3-ITD and wildtype NPM1

(Swerdlow et al. 2017).

In 2017 ELN Recommendation for Diagnosis and Management of AML in Adults recommended molecular detection of NPM1, FLT3 and CEBPA mutational screening as a routine practice at diagnosis (Döhner et al. 2017). The detection of mutation status of NPM1 not only defines the disease category in AML but also confers prognostic impact and minimal residual disease (MRD) monitoring, which is a predictor of relapse (Döhner et al. 2017). Notably, molecular MRD assessment would also help for transplant decisions in first remission.

The emergence of targeted therapy towards FLT3, such as Midostaurin and Sunitinib, should confer better outcome in the future (Kindler et al. 2010). It is recommended for patients with NPM1 mutation and high FLT3-ITD (ratio 0.5) should be treated with regular chemotherapy and a FLT3 inhibitor following with allo-HSCT (Falini et al. 2021). However, these targeted therapies are not available in our centre.

CONCLUSION

This case report highlighted the importance of morphology, cytogenetic and molecular testing in diagnosing AML. It is important to note that, with prognostic implication and emerging treatment, these cellular characteristic and morphology studies should be used hand in hand as this case illustrated the uniqueness of AML with NPM1 and FLT3-ITD mutation.

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