

## CASE REPORT

# Coexistence of myelodysplastic syndrome and acute megakaryoblastic leukemia: An aggressive disease

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**Abstract**

Coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia is an aggressive disease which often do not respond to standard chemotherapy due to the various molecular and cytogenetic abnormalities. Understanding of the molecular pathogenesis may lead to better therapeutic modalities as current conventional therapies are largely ineffective.

**KEYWORDS**

cytogenetic abnormalities, megakaryoblastic leukemia, molecular pathogenesis, myelodysplastic syndrome

## 1 | INTRODUCTION

A 59-year-old gentleman with coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia was treated with standard intensive chemotherapy. His poor outcome was attributed to advanced age, aggressive disease biology, underlying myelodysplastic syndrome, poor response to induction chemotherapy, high lactate dehydrogenase, and lack of good cytogenetic and molecular mutations.

Coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia is an aggressive disease which has been rarely reported in the literature. Acute megakaryoblastic leukemia (AMKL) is a subtype of acute myeloid leukemia (French-American-British classification AML-M7) which is defined as 50% or more of total blast cells in a bone marrow sample being attributed to megakaryoblasts.<sup>1</sup> As with other subtypes of acute myeloid leukemia (AML), the total blasts of more than 20% of all nucleated cells in the peripheral blood film and bone marrow also applies to AMKL. AMKL was first described by Von Boros, et al in 1931. AMKL may occur as de novo, or secondary to a myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN). Down syndrome (DS) individuals have a 500-fold increase in contracting AMKL, and they have a better prognosis as

compared to non-DS individuals.<sup>2</sup> There is also an association between mediastinal germ cell tumors (GCT) and AMKL in young male children with many of them being diagnosed with AMKL a few months later.<sup>3</sup> AMKL is known to be associated with extensive myelofibrosis resulting in a frequent dry bone marrow aspiration. This disease demonstrates a poor prognosis with the median survival of less than 6 months from diagnosis.<sup>4</sup> Here, we report an unusual case of coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia in a middle-aged male who followed an aggressive course of illness.

## 2 | CASE PRESENTATION

A 59-year-old gentleman of Malay ethnicity who had no past medical history, presented to the department of hematology with fever, lethargy, headache, skin bruising, anorexia, and loss of weight for the past 3 weeks. He had no significant family history. He was a nonsmoker and a teetotaler. He worked as a construction worker.

Physical examination revealed an alert and medium-built gentleman. His Eastern Cooperative Oncology group (ECOG) performance status was 0 (fully active). He had no

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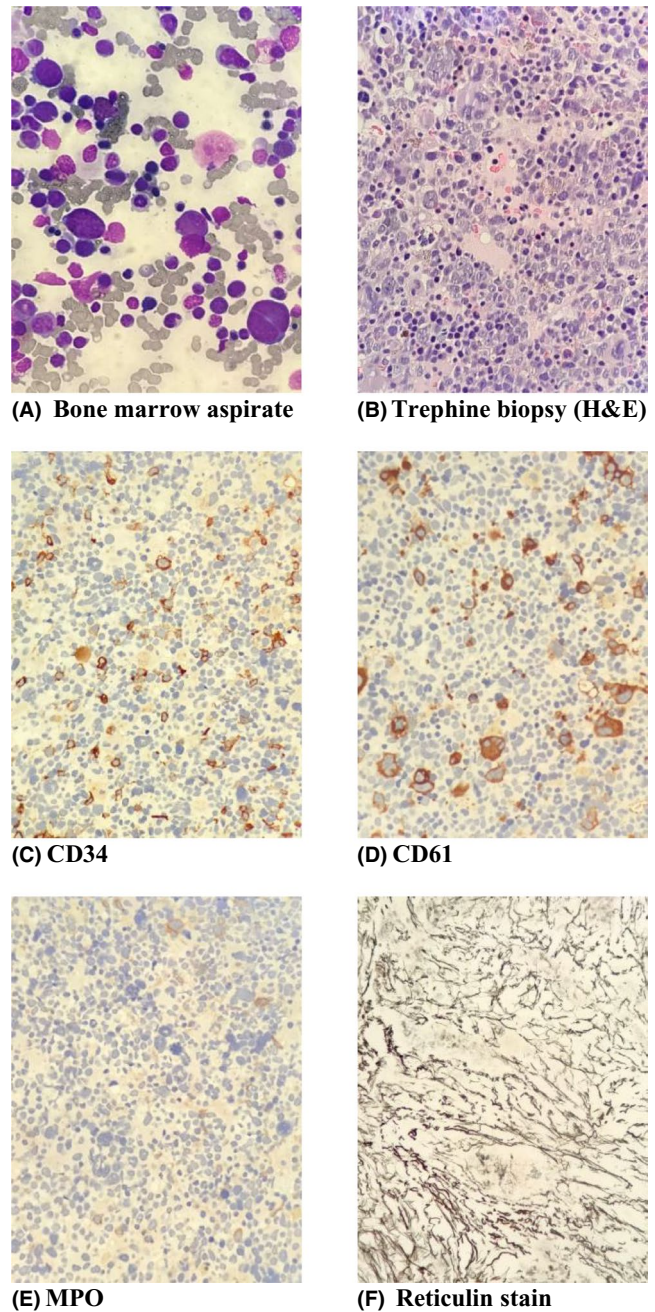
dysmorphism. He was pale with a blood pressure was 110/60 and pulse rate of 96 beats per minute. He had noticeable bruising on the lower limbs. The cardiovascular and respiratory systems were unremarkable on examination. There was no palpable lymphadenopathy or organomegaly.

The complete blood count (CBC) which was analyzed by an automated hematologic analyser (Sysmex, XE-5000) showed severe peripheral pancytopenia; hemoglobin of 6.5 g/dL, total white blood cell count of  $1.5 \times 10^9/L$ , and a platelet count of  $21 \times 10^9/L$ . He had an elevated lactate dehydrogenase (LDH) of 550 U/L. His serology screen was negative for viral hepatitis and human immunodeficiency virus (HIV). The peripheral blood film which was stained with Wright-Giemsa revealed red blood cell anisopoikilocytosis, nucleated red blood cells, numerous mononuclear cells, and giant platelets. The chest radiograph did not show any mediastinal widening. The bone marrow aspiration (Figure 1A), bone marrow trephine biopsy (Figure 1B), and immunohistochemistry (Figure 1C-E) were consistent with coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia. Immunophenotyping of the bone marrow sample by 8-color flow cytometer (BD FACSCanto II) showed 55% cluster of blasts expressing CD13, CD33, CD34, CD36, CD41, and CD61 and were negative for cMPO and HLA DR. Silver impregnation stain of the trephine biopsy (Figure 1F) showed increased reticulin fibrosis (World Health Organization 2016 grading system for bone marrow fibrosis: Grade 2). Cytogenetic studies using Giemsa banding technique revealed  $-7q$  and trisomy 8 abnormalities.

He was diagnosed as coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia. He was induced with standard combination chemotherapy consisting of daunorubicin ( $60 \text{ mg/m}^2$ ), an anthracycline for three days, and continuous infusion of cytarabine ( $100 \text{ mg/m}^2$ ), an antimetabolite for seven days. However, he was refractory to induction chemotherapy. He was reinduced with FLAG chemotherapy (fludarabine  $30 \text{ mg/m}^2$  and high dose cytarabine  $2 \text{ g/m}^2$  once daily for 5 days), in which he failed to respond. He succumbed to his illness at 7 months of diagnosis.

### 3 | DISCUSSION

We describe a rare case of coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia in a middle-aged male who did not respond to standard chemotherapy. The diagnosis was concurred as our patient presented with coexistent features of pancytopenia, myelodysplasia, and laboratory evidence of acute megakaryoblastic leukemia. Pancytopenia as seen in this case was consistent with most literature on MDS/AMKL, but in 30% of the cases, patients may present with leucocytosis.<sup>5</sup> Organomegaly in the form of hepatosplenomegaly and lymphadenopathy is commonly



**FIGURE 1** A, The bone marrow aspirate demonstrates hypercellularity for age, trilineage dysplasia with 52% megakaryoblasts. The megakaryoblasts are described as agranular, medium-to-large cells with round nucleus, scanty basophilic cytoplasm with cytoplasmic blebs and pseudopods. Erythropoiesis and granulopoiesis are suppressed. B, H & E stain of trephine biopsy ( $\times 40$  magnification) shows infiltration of marrow by large clusters of megakaryoblasts. C-E, A panel of immunohistochemical staining, Dako, Denmark ( $\times 40$  magnifications) shows positivity for CD34 and CD61 and negativity for MPO. F, Reticulin stain shows Grade 2 marrow fibrosis

seen in AMKL unlike other subtypes of AML. De novo AMKL is more frequently seen in children than in adults with an incidence of 3%-10% whereas, only 1.2% of adult

AML can be attributed to AMKL.<sup>6</sup> It is also interesting to note that coexistent MDS/AMKL is more commonly seen in older adults.

On cytomorphology, megakaryoblasts in AMKL are described as pleomorphic, medium-to-large in size which exhibit scanty cytoplasm, inconspicuous nucleoli, and cytoplasmic pseudopods. Megakaryoblasts show diffuse reaction on Periodic acid Schiff (PAS), nonspecific esterase (NSE), and acid phosphatase cytochemistry.<sup>7</sup> On electron microscopy, megakaryoblasts express platelet peroxidase.<sup>8</sup>

Acute megakaryoblastic leukemia may arise as de novo, or from a pre-existing/coexisting myelodysplastic syndrome (MDS) such as seen in our case, in which, the latter has a worse prognosis. Megakaryoblasts often express Factor VIII, CD13, CD33, CD34, CD36, CD38, CD41 (Gp IIb/IIIa), CD42b (Gp Ib), and CD 61(Gp IIIa) on immunophenotyping analysis.<sup>8</sup> The tumor cells are negative for CD117, HLA DR, and cMPO.

Common molecular abnormalities encountered in AMKL are mutations of the megakaryoblastic leukemia protein-1 (MKL-1) and GATA1 gene.<sup>9</sup> The tumor cells in AMKL are thought to overexpress multidrug resistant-1 gene (MDR-1) and P-glycoprotein (P-gp) which contribute to its poor prognosis.<sup>9</sup> Cytogenetic abnormalities are more frequently encountered in adult MDS/AMKL than in other subtypes of AML. They are trisomy 8, -7q, -5q, and balanced reciprocal chromosomal translocations such as t(1;22), t(1;5), and t(8;17).<sup>9</sup> Cytogenetic abnormality t(1;22) is commonly associated with AMKL in children, more extensive myelofibrosis and cytopenia.<sup>10</sup> The presence of t(9;22) abnormality may indicate the transformation of an underlying chronic myeloid leukemia (CML).

The differential diagnosis for MDS/AMKL is pure erythroid leukemia (PEL) and MDS-erythroleukemia. The World Health Organization (WHO) 2016 has reclassified PEL as the only subtype of de novo acute erythroid leukemia (AEL) and erythroleukemia into the MDS category.<sup>11</sup> PEL is defined as clonal proliferation of erythroid precursors >80% of all nucleated cells, of which at least 30% are proerythroblasts.<sup>11</sup> MDS-erythroleukemia often refers to progression of disease from pre-existing MDS. In both PEL and MDS-erythroleukemia, peripheral pancytopenia is common, with the marrow erythroblasts being medium-to-large in size, agranular and they exhibit deep basophilic cytoplasm. The neoplastic cells show reactivity with acid phosphatase, NSE, and PAS cytochemistry. Erythroblasts usually express CD36 (early erythroid marker), glycophorin A/CD235a (late erythroid marker), and CD71 (transferrin receptor-1) but are negative for CD34 and HLA DR.<sup>12</sup> High frequency of TP53 mutations may indicate the importance of TP53 in the pathogenesis of the disease.<sup>13</sup> Presence of complex karyotype, AXL1, DNMT3a, 5q- and 7q- should prompt the possibility of MDS-erythroleukemia rather than

de novo PEL. Prognosis of PEL and MDS-erythroleukemia is poor with a median survival of less than 6 months from diagnosis.

A combination chemotherapy regimen of daunorubicin, an anthracycline and cytarabine, an antimetabolite, is used commonly as first-line treatment in coexistent MDS and AMKL. This similar regimen is also employed in the treatment of de novo AMKL. However, the complete remission (CR) rate with this standard therapy is at 50%.<sup>14</sup> Those who achieve CR are only able to sustain as such for a brief period. Patients should be given the option of allogeneic stem cell transplantation (Allo-SCT) at first remission but relapse rates post-Allo-SCT are high. As of today, there are no novel agents to treat this aggressive disease.

## 4 | CONCLUSION

In summary, we report a rare case of coexistent myelodysplastic syndrome and acute megakaryoblastic leukemia in a middle-aged gentleman who was refractory to induction and salvage chemotherapy. The risk factors for his poor outcome are advanced age, aggressive disease biology, underlying presence of MDS, poor response to induction chemotherapy, high lactate dehydrogenase, and lack of good cytogenetic and molecular mutations. More intensive research into the molecular pathogenesis of this disease is required to achieve better therapeutic modalities as current conventional therapies are ineffective.

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## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

GK: analyzed the data, designed the paper, and wrote the manuscript. LBS: involved in critical revisions and approved the final manuscript.

## ETHICAL APPROVAL

Ethical approval is not required as this is not a clinical trial.

## INFORMED CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## DATA AVAILABILITY STATEMENT

The data used and analyzed during this study are available from the corresponding author on request.

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