**IEQAS**
**Blood Cell Morphology Review 2022**
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**BCM: 139**

**DIAGNOSIS:** Acute Myeloid Leukaemia

**CLINICAL DETAILS:** 38 year old female. WCC = 2.5 x 10 9/L, Hb = 5.0 g/dL, Plt = 47 x 10 9/L

**ADDITIONAL COMMENT:**
Red cells are hypochromic with some tear drops and rare NRBC and basophilic stippling. Thrombocytopenia, but platelets appear normal with rare platelet clump.

Blasts account for 54% of mononuclear cells; most are small/medium with nondescript features. A minority have folded nuclei with slightly more abundant cytoplasm.
Most have 1-2 visible nucleoli. No granulation is seen, and no Auer rods are seen.
54% blasts, 16% neutrophils, 28% lymphocytes, 1% eosinophils, 1% monocytes and 1 NRBC/100 WBC.

Almost all centres correctly identified a correct diagnosis of acute leukaemia with >20% blasts in peripheral blood. One or 2 centres have counted blasts as lymphocytes in the differential even though the immature chromatin was clear. The blasts were non-descript with no granulation or Auer rods and on the film alone, it would have been difficult to call this AML versus ALL. All centres commented on tear drop poikilocytes which are notable and likely related to the bone marrow infiltration with the co-existent NRBCs. However, given the young age of this lady, with the rare basophilic stippling, it is also possible that tear drop poikilocytes may be due to coexisting iron deficiency.

The final diagnosis is AML with normal karyotype. NPM1 and Flt 3 were negative. This would be intermediate risk AML by ELN criteria. Myeloid NGS revealed mutations in DNMT3 and IDH2. DNMT3A mutations are seen in patients with de-novo AML with intermediate risk profile and may be associated with a less favourable outcome. The association of DNMT3A mutations with IDH1/2 mutations have been reported. Given Intermediate risk AML profile with IDH2 mutation, clinical trials offer exposure to novel therapeutic IDH2 inhibitors (Enasidenib) and given young age, consideration should be given to clinical trial entry.

**NOTES:**

**BCM 140:**

**DIAGNOSIS:** Chronic Lymphocytic Leukaemia and Acute Myeloid Leukaemia.

**CLINICAL DETAILS:** 81 year old male. WCC = 12.0 x 10 9/L, Hb = 8.0 g/dL, PLT = 51 x 10 9/L.

**ADDITIONAL COMMENT:**
All laboratories detected the lymphocytosis and smear cells and most mentioned a lymphoproliferative disorder in their differential. Almost all laboratories mentioned monocytes and neutropenia.

1 laboratory did not have monocytic cells in their differential. 1 lab mentioned blasts in their comment but not in differential. Only 4 laboratories detected blasts in their differential and there were varied comments about the implications as to whether this was evidence of disease transformation or immature lymphoid cells.

Severe neutropenia is unusual in CLL but not impossible but may have raised suspicion of disease transformation or co-existing diagnosis. The key to this film is a very careful differential count. It is important that differential counts total 100% and the NRBC count should not be included in the White Cell Differential.

This striking feature on this film is the lymphocytosis with small mature lymphocytes with clumped chromatin accounting for >80% of NCs. These mature lymphocytes predominate. There are a smaller number of larger lymphoid cells with cleaved nuclei, and multiple smear cells. It is critical that a chronic lymphoproliferative disease, most likely chronic lymphocytic leukaemia, is mentioned in the differential diagnosis.

In addition, however there are a smaller number of large blasts which could be missed without a careful differential count. These cells have monocytic features with folded nuclei and indeed the long-standing discussion about whether these are monoblasts or promonocytes is debatable. These cells enumerate 4-6% of NCs. While examining this film there were rare basophilic stippled red cells, rare NRBCs, thrombocytopenia and some large platelets.

The bone marrow aspirate revealed hypercellular marrow with dysplastic megakaryocytes, left shifted myeloid and reduce erythodysplasia with dysplasia. Blasts enumerated 37% with monoblastic features.

Immunophenotypic analysis of the peripheral blood is key to identifying the dual populations. 30% NEC were B-CLL (CLL score 5/6) and 70% NEC were consistent with acute myelomonocytic leukaemia. The known history of chronic lymphocytosis or indeed CLL in the referring laboratory may have assisted the team in making the diagnosis.

The coexistence of acute myeloid leukaemia (AML) and CLL in the same patient has been occasionally reported. Most cases have been reported to occur after treatment of CLL with cytotoxic drugs suggesting that AML may be a secondary leukaemia. Cases in the absence of prior treatment are rare. Only a minority of reports represent de novo AML following untreated CLL or concomitant AML and CLL appearing as two distinct and unrelated malignancies.

The AML has a normal karyotype and by NGS has mutations in IDH1, NPM1 and SRSf2. Somatic mutations in exon 12 of the NPM gene (NPM1) are the most frequent genetic abnormality in adult AML, found in approximately 35% of all cases and up to 60% of

patients with normal karyotype AML. Co-mutation with IDH1 is seen in about 50% of NPM1 positive cases with a monocytic phenotype.

The presence of the IDH1 co-mutation with NPM1 is associated with a lower overall survival. Of course, in this case whether or not the leukaemia is therapy related is not known and would have prognostic implications.

**NOTES:**

**BCM 141:**

**DIAGNOSIS**: Diagnosis by WHO 2016 classification: AML with myelodysplasia related changes.

**CLINICAL DETAILS**: 71 year old male. WCC = 10.2 x 10 9/L, Hb = 7.2 g/dL, PLT 19 x 10 9/L.

**ADDITIONAL COMMENT:**

This film was a good example of the continued debate about the differences in the strict definitions of MDS EB2 and AML where the blast percentages matter but the clinical outcomes are similar. Inevitably we do not know if this case arose de novo or had a history of cytopenia or indeed sequential marrow examinations which would further assist in the diagnosis. The other notable finding in this film is the dysplastic changes in the myeloid and erythroid precursors and the abundance of NRBCs.
This film was leucoerythroblastic with an obvious leucocytosis and multiple NRBCs. It is important to remind all labs that the NRBCs should not be counted within the 100 white cell differential but NRBCs should be counted separately and reported as the number of NRBCs per 100 white cells.

There was marked thrombocytopenia with obvious large blasts and dysplastic myeloid cells including precursors. There was also a background of marked red cell anisocytosis with macrocytes and tear drops. My blast percentage was 21% and the variation in blast percentage is noted throughout the labs participating with 14-30% blasts counted in the differentials. WHO 2016 defines AML by > or equal to 20% blasts while MDS EB2 has blasts between 10-20%. International debate is ongoing about the correct blast percentage to define AML and there is likely to be a change in the next update of the WHO classification to a lower blast percentage defining AML. This reduction in blast count in the definition is due to the similar clinical behaviour of these 2 subgroups of myeloid diseases and is better reflected in their genetic and molecular signature. In addition, this modification will allow patients with MDS-EB2 to have access to new drugs and access to clinical trials currently confined to AML.

Among the laboratories participating, almost 70 % of labs noted hypogranular or dysplastic neutrophils, which I think is a key observation in making the diagnosis on the blood film. While not specific the irregular nuclear outlines within the myeloid cells and hypogranular precursors in the PB are more specific than the red cell changes for a preceding myelodysplastic syndrome. Hypogranular neutrophils and precursors have less granules than normal and are highly suggestive of myelodysplastic syndrome. This film has many red cell changes which also prompt consideration of preceding MDS including anisocytosis, poikilocytosis, presence of nucleated erythroid precursors, tear drop cells, and occasional fragments. The red cell changes tend to be less specific. The possibility of preceding MDS is important early on due to the prognostic significance and it may prompt different treatment (i.e. inclusion of Vyxeos during induction).

The karyotype was an abnormal complex karyotype with multiple structural and numerical abnormalities including deletion of the long arm of chromosome 5 and abnormality of the short arm of chromosome 17. This would fit with classification in the AML group with MDS related change specifically the deletion of chromosome 5. Additional information available demonstrates that this case is FLT3 negative, NPM1 negative with a low level VAF in KITpD816 gene, none of these are diagnostic or prognostic in themselves.

Blasts were CD34+, HLADR + and CD117 pos which is also relatively non-specific and consistent with no mutation in NPM1.

**NOTES:**

**BCM 142:**

**DIAGNOSIS:** Microangiopathic Haemolytic Anaemia

**CLINICAL DETAILS**: 39 year old male. WCC = 14.1 x 10 9/L, Hb = 8.2 g/dL, Plt 66 x 10 9/L.

**ADDITIONAL COMMENT:**
The clinical scenario is of a young man with a new diagnosis of metastatic oesophageal CA stage IV, with current active infection, on multiple antibiotics associated with a gangrenous rib and recent haemothorax. Multifactorial anaemia due to ongoing infection, diffuse bony metastases, recent GI bleeding and ongoing coagulopathy. Insufficient evidence to diagnose HUS/TTP. Haematology were asked to urgently review on a weekend due to blood film findings.

The film is abnormal with leucoerythroblastic features, obvious leucocytosis and left shift with metamyelocytes, band forms and myelocytes, many of which had toxic granulation. A rare promyelocyte and blast were present. Red cells were pleomorphic, RDW - 18 (Ref range 11-15) with macrocytes and spherocytes, and 3-4 schistocytes per HPF. Rare NRBCs were seen and there were also rare target cells and tear drop poikilocytes. Platelets were reduced and large platelets were seen.
Additional laboratory results included:
Normocytic anaemia, with elevated reticulocytes - 10%, absolute 226 (Ref. range 14-99), low haptoglobins, raised bilirubin - 26 (Ref. range 0-21) and elevated LDH - 1300 (Ref. range 135-250).
B12 and folate levels were normal with elevated ferritin - 10000 (Ref. range 23-393).
In addition, the CRP was very high - 282 (Ref. range <5).
In the coagulation tests, the PT was prolonged - 20 (Ref range 9.5-12.5), APTT was normal and Fibrinogen was elevated - 4.9 (Ref. range 1.9-3.5)

In this oncology patient, extensive bone marrow involvement is the likely cause of the microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. The leucoerythroblastic features are contributed by the bony metastases and co-existent infection. This film is a reminder of the importance of clinical correlation in making a diagnosis on the film. There are many circumstances which can lead to anaemia with a leucoerythroblastic film and schistocytes (fragmented red blood cells).

Among the laboratories participating, a reactive infective/septic picture with DIC is a very reasonable conclusion. Equally those laboratories who included a leucoerythroblastic film, G-CSF treatment in their differential with red cell changes and probable haemolysis/MAHA were correct.
The toxic granulation of the myeloid precursors is prominent and the red cells changes including schistocytes with thrombocytopenia were worthy of note. The presence of schistocytes on the peripheral blood smear suggests red blood cell injury from damaged endothelium and is a characteristic feature of MAHA.
The presence of schistocytes on a peripheral blood film is often considered a haematological emergency that requires prompt review and investigation for MAHA. However, schistocytes, are not specific to MAHA and can be seen with haemoglobinopathies, mechanic heart valves, renal failure, sepsis, malignancy, pre-eclampsia and in preterm neonates.

The diagnosis of a cancer associated MAHA is to remove the driver of the condition (either the cancer or the drug) and avoid unwarranted therapies such as plasma exchange which have a risk of potential complications.

Chronic myeloid leukaemia is unlikely due to the relative predominance of mature neutrophils compared with immature myeloid cells but in a well person with minimal symptoms, it's not unreasonable to consider a BCR-ABL test, even to consider the possibility of atypical CML in the differential. Acute leukaemia or APML are not reasonable conclusions due to the low number of blasts and promyelocytes respectively.

**NOTES:**

**BCM 143:**

**DIAGNOSIS:**

**CLINICAL DETAILS**: 74 year old female. WCC = 11.5 x 10 9/L, Hb = 10.9 g/dL, Plt = 78 x 10 9/L.

**NOTES:**