CASE REPORT

A Case Report of Myelodysplastic and Myeloproliferative Neoplasms (MDS/MPN) With Neutrophilia; An Evidence of Changes in Their Dynamics

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ABSTRACT

Myelodysplastic and myeloproliferative neoplasms (MDS/MPN) with neutrophilia, previously referred to as atypical chronic myeloid leukaemia (aCML), constitute a disease entity of BCR-ABL1 negative MDS/MPN according to the new 5th edition World Health Organization (WHO) classification. It is characterized by an overlap syndrome that combines features of both myelodysplastic and myeloproliferative disorders, with a high propensity for progressing to acute myeloid leukaemia (AML) and an overall unfavourable prognosis. We report the case of a 72-year-old female who was referred to our hospital for further investigation of anaemia, thrombocytopaenia, and leucocytosis and was diagnosed with MDS/MPN with neutrophilia. Bone marrow morphology exhibited hypercellular marrow with dysplastic features in all three lineages. Our case report and literature review offer valuable insights into the dynamics of the morphological features of MDS/MPN with neutrophilia.
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INTRODUCTION

MDS/MPN with neutrophilia predominantly affects elderly patients, with a reported median age at diagnosis ranging from 70 to 74 years and a higher incidence of the disease in males, according to the recent study. An analysis in 2023 of 347 adult patients with aCML, registered in the Netherlands Cancer Registry between 2001 and 2019, unveiled a median age of 72 years (1). Among these patients, 71% were aged over 65 years, and 65% were male. The clinical presentation encompasses leucocytosis, frequent splenomegaly, anaemia and thrombocytopaenia symptoms, and extramedullary disease. Less common are disseminated intravascular coagulation, spontaneous tumour lysis, and acute renal dysfunction (2). The prognosis for aCML is grim, with median survival of 10 to 29 months and leukaemic transformation occurs in 30–40% of patients within 12–18 months (2).

This report aims to highlight the morphological diagnostic intricacies in this dual-natured haematologic disorder, which may not always be straightforward. Even with recent emerging cytogenetic and molecular features as supportive data, they may not always be available, necessitating a comprehensive and prompt accurate diagnosis.

CASE REPORT

A 72-year-old female was referred to our centre in July 2023 for evaluation of anaemia, thrombocytopaenia, and leucocytosis. Her past medical history includes chronic lung disease treated with MDI Ventolin and Seretide. She was previously admitted to Intensive Care Unit (ICU) at another centre for septic shock from community-acquired pneumoniae and, during this period, she required four packed red cell transfusions for anaemia. Later on, she was discharged with follow-up care.

A month later, in June 2023 during follow up at the other centre, she experienced anaemia again and required two additional packed red cell transfusions. Her baseline FBC showed Hb: 5.7 g/dL (12.0–15.0), MCV: 100 fL (83-100), PLT: 360×10^3/uL (150–400), and WBC: 6.9×10^3/uL (4–10). Her peripheral blood smear revealed macrocytic red cells with no significant abnormalities. Biochemical tests, including serum vitamin B12, folate, renal profile,

thyroid, and liver function tests, were normal. Despite being advised to undergo a bone marrow aspiration and biopsy at that time, she declined and defaulted on follow-up.

Table I: Summary of serial Full Blood Count parameters.

FBC Parameters	Baseline	First encounter	On treatment
Hemoglobin, Hb	5.7	6.8	8.1
Mean corpuscular volume, MCV	100	86	91
Platelet count, PLT	360	127	24
White blood cell count, WBC	6.9	54.7	14.8

Note: Full blood count for baseline, during first clinic encounter and on treatment. Reference range: Hb (12.0–15.0 g/dL), MCV (83-100 fL), PLT (150–400×10^3/uL) and WBC (4–10×10^3/uL).

In July 2023, she was referred to us for a second opinion as she presented with recurrent fever, fatigue, and easy bruising, but no infective symptoms or history of traditional medicine use. Abdominal palpation revealed hepatosplenomegaly. Her lab results showed Hb: 6.8 g/dL, MCV: 86 fL, PLT: 127×10^3/uL, and WBC: 54.7×10^3/uL. Due to declining haemoglobin and platelet levels with elevated WBC, she was counselled for bone marrow aspiration and biopsy. Her full blood picture findings revealed leucocytosis with dysplastic myelocytes and neutrophils, mainly in pseudo Pelger-Huet form, along with 2% circulating blasts. [Figure 1(a)]

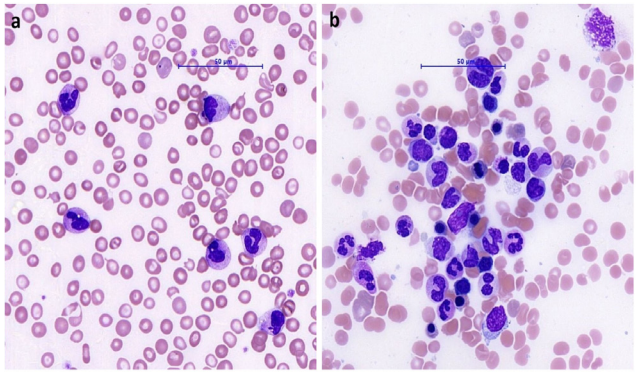

Figure 1: Images showed dysplastic neutrophils under high power field, 40X (a) Full blood picture. (b) Bone marrow aspiration.

Bone marrow aspirate showed hypercellular marrow fragments with relatively adequate granulopoiesis primarily composed of myelocytes and neutrophils, displaying dysplastic alterations such as hypolobation, hypogranulation, and giant metamyelocytes but no increase in blasts. [Figure 1(b)] Erythropoiesis was increased, mainly in proerythroblasts with dysplastic changes, including binuclearity and asynchronous maturation, were observed. Megakaryopoiesis was reduced with dysplastic changes like monolobation and fragmented lobation patterns.

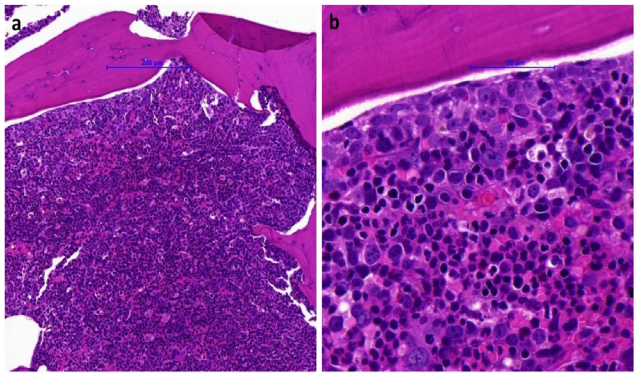

Figure 2: Trephine biopsy images showing hypercellular marrow with dysplastic neutrophils and erythroid hyperplasia. (a) Hematoxylin and Eosin stain under low power field, 10X. (b) Hematoxylin and Eosin stain under high power field, 40X.

Trephine biopsy and immunohistochemical stain (IHC) showed hypercellular marrow [Figure 2] with interestingly marked increased in erythropoiesis, predominantly proerythroblasts at 20% in the intertrabecular region as revealed by E-cadherin staining. Weak p53 staining was seen in proerythroblasts. Granulopoiesis was adequate with neutrophil predominance and no increased blasts by CD34 staining. Megakaryopoiesis was reduced with dysmegakaryopoiesis showing hypolobation/monolobation and occasional micromegakaryocytes by CD61 staining. [Figure 3] Immunophenotyping showed 1% myeloblasts. Molecular and cytogenetic analysis found no JAK2 V617F mutation or BCR-ABL fusion transcripts of the e13a2 or e14a2 type. MPL and CALR tests were not conducted due to patient's financial constraints. With these findings align most closely with MDS/MPN with neutrophilia and erythroid hyperplasia.

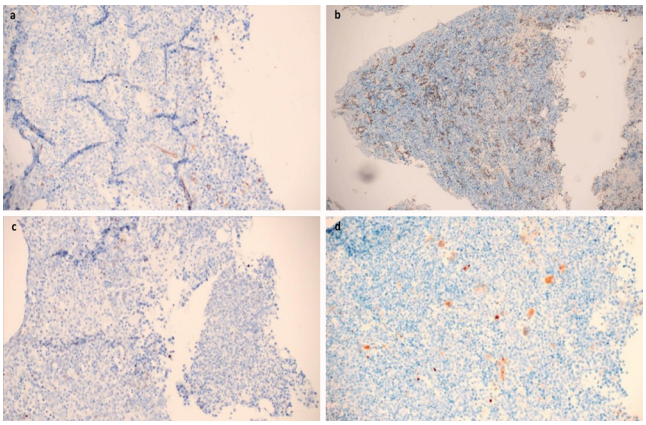

Figure 3: Immunohistochemistry stain under high power field, 40X showed : (a) No increase in blast by CD34 staining. (b) Markedly increased with predominance of proerythroblasts by E-cadherin staining. (c) Scattered weak positive of proerythroblasts by p53 staining. (d) Occasional micromegakaryocytes by CD 61 staining.

The patient was started on oral hydroxyurea, and post therapy FBC parameters showed Hb: 8.3 g/dL, MCV: 91 fL, PLT: 24×10^3/ uL and WBC: 14.8×10^3 /uL. However, this was only a transient response before the disease progressed, where the patient had multiple admissions for symptomatic anaemia complicated by heart failure secondary to hyper viscosity syndrome and septic shock from hospital-acquired pneumoniae. Subsequently, managing her condition became more complex when she developed an Anti-E alloantibody as a result of multiple blood transfusions. Afterwards, ruxolitinib was introduced as part of her treatment plan, alongside hydroxyurea, in a palliative setting.

DISCUSSION

MDS/MPN with neutrophilia has features of both MDS and MPN, this dual nature presents an initial diagnostic challenge when determining the appropriate classification. The crucial step is excluding chronic myeloid leukaemia (CML) by confirming the absence of the BCR-ABL rearrangement, a distinction underscored in the updated WHO 2022 classification. In this case report, the full blood picture findings bore a striking resemblance to CML, which posed the initial diagnostic challenge. However, CML is consistently linked to a BCR-ABL1 rearrangement, which is not present in this case. While in MDS/MPN with neutrophilia, the disease hallmark features a dysplastic neutrophilia characterized by an elevated white blood cell count ($\geq13\times10^3$/uL) with immature myeloid cells comprising ≥10% of white blood cells, but with low blasts (<20%) and monocytes (<10%). In this instance, the early identification of granulocytic dysplasia served as a pivotal hint.

Although the absence of the BCR-ABL fusion gene is essential for diagnosing MDS/MPN with neutrophilia, there exist a variant of CML known as chronic neutrophilic leukaemia (CNL). This form is characterized by persistent chronic peripheral blood leucocytosis $\geq25\times10^3$ /uL with preponderance of mature granulocytes (≥80%) at the segmented and band stage. Otherwise, in our specific case, it is the presence of immature granulocytes (promyelocytes, myelocytes, and metamyelocytes) comprising ≥10% of white blood cells emerged as a crucial diagnostic hallmark for MDS/MPN with neutrophilia. Thus, it becomes paramount to highlight the significance of differential counts, especially in detecting the increase in immature granulocytes in our case.

The JAK2, CALR, and MPL genes, typically associated with myeloproliferative neoplasms (MPNs) such as polycythaemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), must be absent in MDS/MPN with neutrophilia. In this case report, out of respect for the patient's financial constraints, only the JAK2 test was conducted, and the result was negative. However, diagnosing MDS/MPN with neutrophilia is exceptionally challenging and primarily relies on morphologic criteria. To our surprise, in this particular case, erythroid hyperplasia stands out as an especially intriguing phenomenon which also complicates the accurate diagnosis, as it becomes necessary to differentiate between acute erythroid leukaemia (AEL) previously known as pure erythroid leukaemia with reactive erythroid hyperplasia.

AEL, is a distinct subtype of AML according to the 2022 WHO classification of myeloid neoplasms and acute leukaemia. It is a rare, aggressive subtype, and the diagnostic criteria for AEL stipulate that more than 80% of bone marrow cells must belong to the erythroid lineage, with at least 30% being proerythroblasts. According to Alexandres et al. (2021), the study discovered that positive p53 IHC staining is a distinctive feature of AEL (3). In this case, the weak p53 staining in the trephine biopsy allows us to confidently conclude that our case leans more toward erythroid hyperplasia.

Based on next-generation sequencing (NGS) analysis, the 5th edition of the WHO criteria highlights specific somatic mutations, including SETBP1 and ETNK1, as supportive evidence for diagnosis (4). Yet, it is important to acknowledge that not all laboratories have the capacity to provide extensive molecular genetic panels due to limitation in funding, resources and also patient-related factors. Despite the comprehensive molecular analysis, the management still lacks a standardised approach. Hydroxyurea is the most frequently used agent, although documented haematologic remissions are often partial and not sustained (5), as happened in this case. Allogeneic haematopoietic stem cell transplantation (HSCT) therapy may have improved outcomes (5).

CONCLUSION

MDS/MPN with neutrophilia is a disease with poor prognosis. Assigning the appropriate classification based on morphologic, clinical, and molecular aspects can be intricate. Although the presence of dysgranulopoiesis in peripheral blood, bone marrow and trephine biopsy serves as the key criteria for establishing diagnosis of MDS/MPN with neutrophilia, haematologists may face challenges in interpreting morphology and quantifying dysplasia, which can result in discordant diagnoses due to variability in assessing disease features. Advances in molecular profiling have revealed specific mutations associated with these neoplasms, providing an understanding of the essential underlying genetic abnormalities. With our case report, there is optimism that these uncommon conditions will progressively become part of collaborative prospective clinical trials, aiming to address lingering uncertainties and pave the way for significant therapeutic advancements.

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