

Review Article

Myelodysplastic and myeloproliferative neoplasms: Updates on the overlap syndromes

Clinical Pathology

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ABSTRACT

Background: Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are disorders of the hematopoietic stem cell as well as evolved entities which have characters of both myelodysplastic syndrome and myeloproliferative neoplasms resulting in difficulty in diagnosis. Chronic myelomonocytic leukaemia (CMML), juvenile myelomonocytic leukaemia (JMML), atypical chronic myeloid leukaemia (aCML), MDS / MPN-unclassifiable (MDS / MPNU) and MDS / MPN with ring sideroblasts and thrombocytosis (MDS / MPN-RS-T) are encompassed in the 2016 MDS / MPN classification system (WHO). Each type of MDS/MPN has its specific characteristic feature such as increased number of monocyte in CMML, prominent dysplasia in granulocytic lineage in aCML, and increase platelet count in MDS/MPN-RS-T. Multiple molecular techniques are used in diagnosis, follow up, and prognosis of hematological malignancy. These techniques are used for the detection of molecular and cytogenetic abnormalities. They include conventional karyotyping, fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), polymerase chain reaction (PCR), next-generation sequencing (NGS) technology, and nanopore sequencing. Recent techniques as Next generation sequencing (NGS) studies helps in identification of various genetic pathways and somatic mutation. Adding the molecular findings to pathomorphologic characters has raised the accuracy of diagnosis in MDS/MPN.

Objective: to give new trends in diagnosis of myelodysplastic/myeloproliferative neoplasms.

Conclusion: MDS/MPN has overlapping features of both MDS and MPN, which further make it difficult in diagnosis. New molecular techniques such as NGS and nanopore sequencing, detect all types of genetic abnormalities and improve the diagnosis of MDS/MPN.

JRAM 2021; 2 (2): 226-229

Keywords: MDS, MPN, MDS/MPN.

Submission Date: 4 November 2020

Acceptance Date: 15 December 2020

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Please cite this article as: Mansour HS, El Mahdy MM, Badawi DI. Myelodysplastic and myeloproliferative neoplasms: Updates on the overlap syndromes. *JRAM 2021; 2 (2): 226-229.* DOI:10.21608/jram.2020.48353.1098

INTRODUCTION

Myelodysplastic / myeloproliferative (MDS / MPN) overlap syndromes are categories within malignant myeloid clone disorders with (MDS / MPN) characteristics^[1]. MDS features include cytopenia and multiple cell lines dysplasia, and the characteristics of MPN include constitutional signs, increased blood counts and extramedullary infiltration^[2].

PATHOGENESIS OF MDS/MPN

The underlying pathogenesis for MDS / MPN is unclear, as is the point of molecular convergence which defines the MDS / MPN category biologically. The conventional phenotype of the bone marrow (BM) involves accelerated cell death and overlapping myeloid subsets resulting in dysplasia and cytopenia^[3].

Since there was no molecular marker that was entirely specific for MDS / MPN syndrome it has been found that improved molecular characterization and repetitive genetic mutations can help explain these disorders. These analyses clearly showed considerable molecular deficiency heterogeneity and complexity within the MDS / MPN community and explained many pathways likely to include the pathogenesis of diseases^[4].

MDS/MPN CLASSIFICATION in WHO

Regarding WHO MDS / MPN classification, CMML, JMML, aCML, MDS / MPNU and MDS / MPN with ring sideroblast and thrombocytosis (MDS / MPN-RS-T) are included. MDS / MPN – Rs are added to 4th WHO classification of myeloid neoplasms has also enhanced the integration of somatic molecular markers, in particular SF3B1 mutations^[5,6].

The Refractory anemia with ring sideroblasts (RARS-T) threshold has declined from 600x10³ / IL to 450 x10³ /IL and the parameters of BM have been included in this version. RARS-T was also established and renamed a separate organization, MDS / MPN with ring sideroblasts and raised thrombocytes (MDS / MPN-RS-T) are included within fourth edition of WHO which released in 2017^[1,7].

MDS/MPN SUBTYPES

1. Chronic myelomonocytic leukemia (CMML):

Chronic myelomonocytic leukemia is known to be clonal hematopoiesis stem cell disorder and known with a prolonged (more than three months) incidence of peripheral blood monocytes (>1x10⁹ / L) with BM dysplastic characteristics, with a monocyte of around 10 per cent white blood cell (WBCs) count. CMML is divided into proliferative and dysplastic (MDS-CMML) subspecies in 2016 WHO classification based on WBCs of $\geq 13 \times 10^9$ / L for MPN-CMML Classification CMML^[8,9]. The CMML is characterized by absence of both BCR-ABL1 fusion gene and PDGFR and FGFR 1 which may occur secondary in MDS^[10]. Peripheral monocytes in CMML are typically irregular in morphology with bizarre- shaped nuclei and cytoplasmic granules. WBCs display leukocytosis, but with variable neutropenia, WBCs may be normal or slightly decreased^[11].

2. Juvenile myelomonocytic leukemia (JMML)

The uncommon, but severe leukemia occurring mainly among children is juvenile myelomonocytic leukemia (JMML). This proliferation is characterized mainly by the granulocytic and monocytic lines with abnormalities in erythroid and megakaryocytic lines. The blasts and promonocytes of peripheral blood and BM are less than 20% of the WBCs. Mutations with RAS genes are typical of JMML while BCR-ABL1 fusion is incomplete^[12]. At diagnosis peripheral blood include leucocytosis and thrombocytopenia, with or without anemia. The BM aspirate and biopsy are hypercellular with proliferation of granulocytic lineage, although in some patient's erythroid precursors may predominate. The monocytes of BM are 5-10% less prominent than those in the peripheral blood^[13,14].

3. Atypical chronic myeloid leukemia (aCML)

It was considered seldom MDS / MPN subtype characterized by hypercellular BM and neutrophil lineage involvement, leucocytosis as well as morphologically increasing dysplastic neutrophils and their precursors. Ph chromosome and BCR ABL fusion gene are absent in aCML^[15].

4. MDS/MPN with ring sideroblasts and thrombocytosis:

It is also seldom myelodysplastic/ myeloproliferative subtype, which has over 450x10⁹/L thrombocytosis, more than 15% BM erythroblast is ring sideroblast, and less than 5% erythroid and granuloid precursor dysplastic characteristics with

blasts^[16,17]. MDS / MPN-RS-T has been a subcategory of MDS / MPN by the commonly documented gene mutations (JAK2, v617F and MPL) and in vitro MDS-like suggested low colony forming capability^[18].

5. MDS / MPN, unclassifiable

Un-classification of MDS / MPN (MDS / MPN-U) among different MDS-MPN subtypes is still the least characterized. At presentation, its clinical, laboratory and morphological characteristics correlate with the MDS and the MPN. CMML, JMML, MDS / MPN-RS-T and aCML do not follow the requirements for MDS / MPN-U^[17,19].

MDS / MPN DIAGNOSIS TECHNIQUES

In diagnosis of MDS / MPN overlap syndromes, several molecular methods are employed to detect cytogenetic and molecular abnormality. They embrace conventional karyotype, hybridization of FISH fluorescence in situ, CGH, polymerase chain reaction (PCR), Next Generation Nanopore Sequencing, and Nanopore Sequencing (NS)^[20]. Conventional karyotyping is the study of chromosomes and consider the gold standard for detecting genetic alterations that is more than 10 MB in size. FISH is a molecular cytogenetic method, in which commercially single stranded DNA with fluorochrome is sampled and the fluorescence microscope visualizes hybridization^[21, 22].

The CGH is based on quantitative double-color FISH along each chromosome. CGH can be used to detect genetic imbalances in genomes, and to determine the chromosomal abnormality as gain or loss of entire chromosomes^[23]. PCR is the most widely used molecular assay in the diagnosis of malignancies. The basic techniques of most PCRs include the enhanced application of primers, nucleotides, and enzymes - as DNA polymerases and reverse transcriptase - to a desired segment of DNA^[24]. NGS tests can primarily identify all forms of genetic anomalies that many laboratories take cheaper, quicker, and easily. The fundamental concept is to have many simultaneous sequencing reactions in a very small area^[25].

Recently, NS is the most common application in the fields of medication in which single stranded DNA or RNA molecules - through electrophoresis or other linear mechanisms - can be forced through biological pore to determine their base composition at a certain location when an ionic current shift takes place during the molecule's transformation into the pore^[26].

CONCLUSION

MDS/MPN has overlapping features of both MDS and MPN, which further make it difficult in diagnosis. New molecular techniques such as NGS and nanopore sequencing detect all types of genetic abnormalities and improve the diagnosis of MDS/MPN.

Conflict of interest: No direct or indirect conflict of interest

Financial support: This work not funded from any governmental or non-governmental agencies.

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الملخص العربي

خلل التنسج النقوي والأورام النقوية: تحديثات على متلازمات التداخل

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ملخص البحث

الخلفية: متلازمة خلل التنسج النخاعي/ وأورام التكاثر النخاعي (خلل التنسج النقوي والأورام النقوية) هو اضطراب في الخلايا الجذعية المكونة للدم بالإضافة إلى الكيانات المتطورة التي لها سمات كل من متلازمة خلل التنسج النخاعي والأورام التكاثرية النخاعية؛ مما يؤدي إلى صعوبة في التشخيص. وقد تم تضمين ابيضاض الدم النخاعي المزمن أو اللوكيميا ولوكيميا ابيضاض الدم النخاعي اليفعي و ابيضاض الدم النخاعي المزمن غير النمطي التنسج النقوي والأورام النقوية - غير القابل للتصنيف و خلل التنسج النقوي والأورام النقوية مع فقر الدم الحديدي (الأرومات) وكثرة الصفائح في نظام تصنيف التنسج النقوي والأورام النقوية لعام 2016 - منظمة الصحة العالمية. ولكل نوع من خاصية مميزة خاصة به؛ مثل زيادة عدد الخلايا الوحيدة في ابيضاض الدم النخاعي المزمن ، و خلل التنسج البارز في النسب الحبيبية في ابيضاض الدم النخاعي الحاد، وزيادة عدد الصفائح الدموية في خلل التنسج النقوي والأورام النقوية مع فقر الدم الحديدي (الأرومات) وكثرة الصفائح

وتستخدم تقنيات جزيئية متعددة في التشخيص والمتابعة والتنبؤ بأورام الدم الخبيثة. وتستخدم هذه التقنية للكشف عن التشوهات الجزيئية والخلوية؛ وهي تشتمل على التنميط النووي التقليدي والتهجين في الموقع الفلوري والتهجين الجيني المقارن وتفاعل البوليميراز المتسلسل وتكنولوجيا تسلسل الجيل التالي وتسلسل النانو. وتساعد التقنيات الحديثة؛ مثل دراسات تسلسل الجيل التالي في تحديد المسارات الجينية المختلفة والطفرات الجسدية. وقد أدت إضافة النتائج الجزيئية إلى الخصائص الشكلية المورفولوجيا المرضية إلى تحسن دقة التشخيص في خلل التنسج النقوي والأورام النقوية.

الهدف: إعطاء اتجاهات جديدة في تشخيص خلل التنسج النخاعي/ الأورام التكاثرية النخاعية.

الاستنتاجات: يحتوي خلل التنسج النقوي والأورام النقوية على ميزات متداخلة لكل من خلل التنسج النقوي و خلل الأورام النقوية ، مما يجعل التشخيص أكثر صعوبة. تكتشف التقنيات الجزيئية الجديدة وتسلسل الثقوب النانوية جميع أنواع التشوهات الجينية وتحسن تشخيص خلل التنسج النقوي والأورام النقوية.

الكلمات المفتاحية: خلل التنسج النخاعي/ الأورام التكاثرية النخاعية.

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