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Title: Comment: In response to "Megaloblastic Anemia with Ring Sideroblasts is not Always Myelodysplastic Syndrome"

Running Title: Ring sideroblasts

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To the Editor,

I read the article "Megaloblastic Anemia with Ring Sideroblasts is not Always

Myelodysplastic Syndrome" by Narang et al when it was published in Volume: 33 Issue: 4 - 2016. The manuscript is well written with the description of a very informative case of megaloblastic anemia with ring sideroblasts in a young female of 18 years old. Ring sideroblasts is associated with abnormal expression of several genes of heme synthesis or mitochondrial iron processing [1]. After exclusion of non-neoplastic causes of ring sideroblasts such as congenital/hereditary sideroblastic anemia and acquired reversible sideroblastic anemia (drugs, toxins, or nutritional deficiency); Myelodysplastic syndrome (MDS) can be strongly suspected, particularly in elderly patients. The presence of ring sideroblasts alone is not sufficient for a diagnosis MDS; presence of refractory cytopenia(s) is a prerequisite. Refractoriness can only be established after exclusion of secondary causes, most importantly nutritional deficiencies. After that a complete evaluation of the erythroid, myeloid and a megakaryocytic lineage on bone marrow is essential. At least 15% ring sideroblasts are required for the diagnosis of MDS with ring sideroblasts (MDS-RS) in cases lacking mutations in the spliceosome gene *SF3B1*. SF3B1 mutations are found in 60%-80% of patients with refractory anemia with ring sideroblasts (RARS) or RARS with thrombocytosis (RARS-T). *SF3B1* gene mutation is associated with 60%-80% of patients with refractory anemia with ring sideroblasts (RARS) or RARS with thrombocytosis (RARS-T) and is associated with favorable prognosis [2]. In recent WHO 2016

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classification, cases with ring sideroblasts and multilineage dysplasia without excess blasts or isolated del (5q) abnormality is categorized as MDS-RS. Recent studies have shown that the percentage of ring sideroblasts in MDS is not prognostically important. Thus in the revised WHO classification, a diagnosis of MDS-RS may be made even if presence of only 5% of ring sideroblasts in cases with *SF3B1* mutation. MDS-RS cases will be subdivided into cases with single lineage dysplasia (previously classified as refractory anemia with ring sideroblasts) and cases with multilineage dysplasia (previously classified as refractory cytopenia with multilineage dysplasia). Furthermore, refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T), has been accepted as an entity and termed MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in the 2016 classification. Unlike MDS with ring sideroblasts, the number of ring sideroblasts required for a diagnosis of MDS/MPN-RS-T is 15%, irrespective of the presence or absence of a *SF3B1* mutation [3]. As described in the case by Narang et al, in a young female of 18 years without a history of *persistent refractory* cytopenia(s), a diagnosis of MDS can only be establish after exclusion of secondary causes as nutritional deficiencies. An adequate trial with hematinics (vitamin B12, folic acid, and pyridoxine) is needed in such cases. After exclusion of secondary causes, if cytopenia(s) is still persists, a repeat bone marrow examination with cytogenetic and molecular studies can be consider to establish the diagnosis of a clonal hematopoietic disease as MDS or MDS/MPN.

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References

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