## MonoMAC and GATA2 deficiency: overlapping clinical and pathological features with aplastic anemia and idiopathic CD4+ lymphocytopenia. *Reply* to Haematologica 2012;97(4):058669

Multiple heterozygous germline mutations have been identified in GATA2 that are associated with a range of phenotypic presentations including MonoMAC[1-3]/ dendritic cell, monocyte, B- and NK-lymphoid deficiency (DCML deficiency),[4-5] familial myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML),[6] and lymphedema/Emberger syndrome.[7-9] The clinical presentation of the patient in the case report by Chu *et al.*,[10] who had a history of *M. avium* complex (MAC) infection with cytopenias and was diagnosed with aplastic anemia and idiopathic CD4-positive ($CD4^+$) lymphocytopenia (ICL), is not uncommon for MonoMAC patients.[1-2] MonoMAC is associated with a peripheral blood flow cytometric profile of profound monocytopenia, and NK and B lymphopenia, which underlie immunodeficiency and susceptibility to infections with MAC, human papillomavirus, and other opportunistic fungal pathogens. Several MonoMAC patients have displayed $CD4^+$ lymphocytopenia,[1] while others have evidence of increased $CD3^+/CD8^+$ large granular lymphocyte populations with clonal T-cell gene rearrangements.[2] Over half of MonoMAC patients at our institution present with, or ultimately develop, additional cytopenias (anemia, neutropenia and thrombocytopenia) associated with MDS/AML. Similar to the patient reported by Chu *et al.*, the marrows of the majority of MonoMAC patients with MDS/AML in our study[2] were hypocellular with trilineage hypoplasia with morphological features often resembling aplastic anemia, in contrast to *de novo* MDS, which typically presents with hypercellular marrows.

GATA2 is a zinc finger transcription factor that is critical in hematopoiesis. To date, mutations identified include missense mutations, frameshift mutations, splice site mutations, and large intragenic deletions.[3,5,6,8,9] Several of these GATA2 mutants result in haploinsufficiency,[3,9] and presumably impair self-renewal of hematopoietic progenitors.[11] Over time, haploinsufficiency of *GATA2* may contribute to progressive cytopenias that develop in adolescence or adulthood, manifesting as the MonoMAC phenotype and predisposing to MDS/AML. Some mutants have been reported to have dominant negative function impairing the activity of wild-type *GATA2* expressed from the non-mutated allele.[6] Inheritance is consistent with autosomal dominance with variable expression. Phenotypic variation suggests that other genetic or environmental factors may impact the evolution of MDS/AML, cytopenias and immunodeficiency.

The diagnosis of hypocellular MDS in unrecognized *GATA2* deficiency can be challenging since cytopenias in the presence of a hypocellular marrow can have overlapping features with aplastic anemia. In our study, several MonoMAC patients carried prior diagnoses of aplastic anemia or had family members who were diagnosed with aplastic anemia based on hypocellularity of bone marrow biopsies. However, severe immunodeficiency and opportunistic infections with MAC are not typically seen in aplastic anemia and, if present, should warrant further investigation for the possibility of MonoMAC with *GATA2* mutational analysis.

For the hematologist or hematopathologist, the recognition of dysplasia in hypocellular MDS is frequently complicated by paucicellular aspirates with insufficient material for adequate morphological evaluation of erythroid and myeloid dysplasia on smears, and suboptimal material for flow cytometry and cytogenetic analyses. The large majority of MonoMAC marrows we studied have shown evidence of megakaryocytic atypia, which can help differentiate hypocellular MDS from aplastic anemia. Large osteoclast-like megakaryocytes with separated nuclear lobes are also present in many monoMAC marrows (similar to Figures I-K in Chu *et al.*[10]), in addition to hypolobulated, mononuclear and/or micromegakaryocytes (best appreciated by immunohistochemical stains for Factor VIIIvw or CD61). In cases with adequate aspirate smears, the level of dysplastic changes in MonoMAC can be subtle (e.g. 10-20% of hematopoietic precursors in a given lineage). Immunohistochemistry for CD34 on core biopsies is critical in the identification of increased blasts. When adequate material is obtained for cytogenetic analysis, the presence of a cytogenetic abnormality is useful in establishing or confirming the diagnosis of hypocellular MDS; albeit up to 40% of monoMAC patients with MDS/AML do not have detectable cytogenetic abnormalities. When present, the cytogenetic abnormalities in MonoMAC and other *GATA2* deficiency phenotypes are heterogeneous and have included monosomy 7, trisomy 8, trisomy 1q, and monosomy 6.

Patients with cytopenias and hypoplastic or aplastic bone marrows who have a history of MAC infections, HPV infections, familial MDS/AML and/or lymphedema warrant further investigation for germline *GATA2* mutations. MonoMAC has high morbidity and mortality, and bone marrow transplantation is a viable option for many MonoMAC/*GATA2* deficient patients.[12] We agree with Chu *et al.* that the history and bone marrow findings in their patient are compatible with MonoMAC. A positive family history for MAC or MDS/AML, along with cytogenetic abnormalities in the hypoplastic bone marrow, would support the diagnosis of MonoMAC. Mutational analysis for *GATA2* is critical in confirming the diagnosis, facilitating the screening of family members, and identifying matched related donors for allogeneic hematopoietic stem cell transplantation.

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