Myelodysplasia in autosomal dominant and sporadic monocytopenia immunodeficiency syndrome: diagnostic features and clinical implications

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ABSTRACT

A novel, genetic immunodeficiency syndrome has been recently described, herein termed "MonoMAC". It is characterized by severe circulating *mono*cytopenia, NK- and B- lymphocytopenia, severe infections with *M. avium* complex (*MAC*), and risk of progression to myelodysplasia/acute myelogenous leukemia. Detailed bone marrow analyses performed on 18 patients further define this disorder. The majority of patients had hypocellular marrows with reticulin fibrosis and multilineage dysplasia affecting the myeloid (72%), erythroid (83%) and megakaryocytic (100%) lineages. Cytogenetic abnormalities were present in 10 of 17 (59%). Despite B-lymphocytopenia, plasma cells were present but were abnormal (e.g. $CD56^+$) in nearly half of cases. Increased T-cell large granular lymphocyte populations were present in 28% of patients. Chromosomal breakage studies, cell cycle checkpoint functions, and sequencing of *TERT* and *K-RAS* genes revealed no abnormalities. MonoMAC appears to be a unique, inherited syndrome of bone marrow failure. We describe distinctive bone marrow features to help in its recognition and diagnosis. *(Clinicaltrials.gov identifiers: NCT00018044, NCT00923364, NCT01212055)*

Key words: myelodysplasia, MDS, monocytopenia, mycobacterium avium complex, MonoMAC, *GATA2* deficiency.

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Introduction

We have previously defined a novel immunodeficiency syndrome with the following distinct clinical features: i) onset, primarily during young adulthood, of infections with disseminated non-tuberculous mycobacteria (NTM), human papillomavirus (HPV), and/or fungi; ii) peripheral blood demonstrating paucity or absence of monocytes, Natural Killer (NK) cells, and B lymphocytes; iii) the propensity to develop myelodysplasia (MDS)/acute myeloid leukemia (AML) in nearly half of patients; and iv) occasional pedigrees with two or more affected generations, suggesting autosomal dominant inheritance.[1] Recently, Bigley *et al.* additionally demonstrated the near absence of circulating dendritic cells which may further contribute to the severe immunodeficiency observed in this disorder.[2] This syndrome is herein referred to as the "MonoMAC" syndrome, designated as such based on its sentinel and salient features of *mono*cytopenia and *Mycobacterium avium complex* (MAC) infection, the predominant non-tuberculous mycobacterial species causing disease. The progressive loss of multiple distinct lineages (monocytes, B cells, NK cells, with eventual involvement of erythrocytes, granulocytes and megakaryocytes) suggests that this syndrome may be the manifestation of a process of bone marrow failure involving hematopoietic stem cells or early progenitors. Here, we comprehensively describe bone marrow findings demonstrating that the MDS associated with this syndrome has features distinct from *de novo* forms of MDS, and further report molecular studies indicating that MonoMAC is distinct from other inherited bone marrow failure syndromes.

Design and Methods

Study design and patient selection

Patients enrolled in protocols approved by the institutional review boards (IRB) and diagnosed with MonoMAC at the National Institutes of Health between 1996 and 2010 were included in this study if they developed additional persistent cytopenia(s) typically associated with MDS (anemia, neutropenia, and/or thrombocytopenia). A total of 18 patients (7 males and 11 females) were included; 13 patients were from the original published report.[1]

Bone marrow aspirate, biopsy, and immunohistochemistry

Core biopsies and aspirates were independently evaluated by 3 hematopathologists. Immunohistochemistry (Factor VIIIvw, hemoglobin, myeloperoxidase, CD34, CD68, CD14, CD3, CD20, CD56, CD138, kappa and lambda light chains; Dako autostainer), special stains (reticulin, acid fast bacilli (AFB) and Grocott's Modified Silver)

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and *in situ* hybridization for kappa and lambda light chains, were performed. Reticulin fibrosis was graded using the system defined by Manoharan *et al.*[3]

Cytogenetic analysis

Cytogenetic studies were performed using standard methods. Clones were defined and karyotypes were designated according to the ISCN (2009).[4]

Flow cytometric analysis

Peripheral blood and heparinized bone marrow aspirate specimens were analyzed by flow cytometry to evaluate hematopoietic lineages, as previously described.[5]

TRG@ gene rearrangement

TRG@ gene rearrangement analysis was performed in a single multiplexed reaction, as previously described.[6]

TERT gene mutation analysis

Epstein-Barr virus (EBV)-transformed lymphoblastoid cell lines (EBV-LCL) were established from patient or healthy donor peripheral blood mononuclear cells (PBMC), as previously described.[1] Genomic DNA was extracted from EBV-LCLs from 9 patients using the PureGene Gentra DNA isolation kit (Qiagen). Primers targeting the human Telomerase Reverse Transcriptase (*TERT*) gene were designed using Primer Select (DNAstar Lasergene). Sequencing was performed on an Applied Biosystems 3100 sequencer and analyzed using Sequencher software (Gene Codes).

K-RAS gene mutation analysis

DNA was extracted from peripheral blood or bone marrow mononuclear cells and subjected to PCR using two sets of primers from the Qiagen PyroMark™KRAS v2.0 test kit. The products were subjected to pyrosequencing on a Qiagen PyroMark Q24 system.

Chromosomal instability

Genomic instability was assessed as previously described[7] using EBV-LCL cells from 5 patients and 5 healthy donors. A total of 50 metaphases *per* subject were scored for chromosome breakage.

Cell cycle checkpoint analysis and mitotic index assay

EBV- LCL cells from 2 patients and 2 healthy donors were treated with 10 Gy of ionizing radiation (IR) and harvested at 24 and 48 h after IR. Cells were fixed with 75% ethanol/PBS and stained with propidium iodide (10 μg/mL). Cell cycle profiles were obtained using FACSCalibur (Becton Dickinson, San Jose, CA, USA). For mitotic index assay, colcemid (0.1 μg/mL) (Invitrogen, Carlsbad, CA) was added 4 h before harvesting cells at 24 h after ionizing radiation (IR). Cells were stained with DAPI (5 ng/mL) and evaluated by fluorescence microscopy.

Results and Discussion

In comparison to *de novo* forms of MDS, we found the clinical and bone marrow features of MDS in MonoMAC were unusual (Table 1). *De novo* MDS is typically diagnosed in the 7th or 8th decade of life.[8] In contrast, the median age of MonoMAC patients at the time of MDS diagnosis was 33.5 years (range 9-63 years). All patients had a history of disseminated opportunistic infections (NTM, fungal, and/or HPV), profound monocytopenia (median monocyte count of 10 cells/μL; normal 300-820 cells/uL), B-cell lymphocytopenia (median count of 2.0/uL; normal 61-321/μL), and NK-cell lymphocytopenia (median count of 3.0/uL; normal 126-729/μL). Hematologic parameters were abnormal: 11 of 18 (61%) patients were thrombocytopenic (median platelet count 47x10^9/L); 14 of 18 patients (78%) were anemic (median hemoglobin 8.9 g/dL); 11 of 18 (61%) were neutropenic (median absolute neutrophil count 0,795 cells/L); 7 of 18 (39%) were pancytopenic.

Hypocellular bone marrow with fibrosis

We found 13 of 18 (72%) of MonoMAC patients had hypocellular marrows (Figure 1A), 3 out of 18 (17%) had normocellular marrows, and only 2 of 18 were hypercellular. These findings are in contrast to *de novo* MDS in which 90-95% of patients present with hypercellular marrows.[9] Most marrows (73%) showed significant reticulin fibrosis (grade 2+ out of 4 or higher), predominantly seen in cellular areas (Figure 1B). In contrast, reticulin fibrosis is typically seen in only 5-10% of *de novo* MDS and is associated with aggressive marrow failure.[10,11]

Surprisingly, despite the absence of monocytes in the peripheral blood, bone marrow histiocytes and macrophages were prominent in all bone marrows, confirmed by immunohistochemistry for CD68 and CD163. Bigley *et al.* reported depletion of the granulocyte macrophage progenitor (GMP) based on flow cytometric analysis of BM cells from 4 of their patients.[2] Together these findings suggest that the bone marrow and tissue macrophages observed may be long-lived subpopulations derived from precursors that seeded these organs prior to the onset of clinically-apparent monocytopenia (i.e. prior to development of bone marrow failure). Alternatively, they may derive from a different, possibly extramedullary progenitor. Scattered hemophagocytic histiocytes were seen in 39% of marrows (Figure 1C). Except for pancytopenia, the patients did not demonstrate clinical nor laboratory features associated with hemophagocytic syndrome.[12] Three of 18 patients showed evidence of granulomatous inflammation within the marrow; one was positive for AFB.

Marrows display multilineage dysplasia

Megakaryocytic atypia was present in all MonoMAC marrows. Megakaryocytes ranged in size with small mononuclear forms, forms with separation of nuclear lobes, and micromegakaryocytes (Figure 1D-I). Approximately half of the patients had distinctive large megakaryocytes containing multiple separated nuclei resembling osteoclasts (Figure 1F). These abnormal megakaryocytes were positive for the megakaryocytic marker FactorVIIIvw by immunohistochemistry (Figure 1G). Interestingly, there was a discrepancy between the morphological atypia of megakaryocytes and peripheral thrombocytopenia, which was observed in only 61% of patients. Bleeding diathesis was not seen in any patient.

Myeloid precursors displayed evidence of dysplasia in 13 of 18 patients (72%). Dysplastic features included hypogranulation, hyposegmentation (Pelgeroid nuclei), and binucleation of myeloid precursors (Figure 1J-Q). A distinctive finding involved uneven abnormal localization of cytoplasmic granules, with clumping of granules in focal areas of the cytoplasm, and large areas devoid of granules (Figure 1O-Q), seen in neutrophils, basophils and eosinophils.

Dyserythropoiesis was seen in 14 of 18 (78%) marrows (Figure 1R-U) and included nuclear budding, binucleation, nuclear karyorrhexis, and megaloblastic changes in ery-

throid precursors. No cases contained ringed sideroblasts. Red cell aplasia was seen in 2 of 18 patients (11%) without evidence of parvovirus infection.

Characteristic flow cytometry bone marrow profiles

Flow cytometric analysis can be useful in the evaluation of MDS[13] and was performed on bone marrow aspirates of 13 patients. Analyses revealed the following characteristic flow cytometry features (Figure 2): i) marked decrease to absence of monocytes; ii) decreased side scatter of the granulocyte population correlating with hypogranulation; and iii) abnormal immunophenotoypic maturation sequence in myeloid precursors which often included loss of CD10 expression on neutrophils, and/or abnormal

Table 1. Features of MDS associated with MonoMAC in comparison to *de novo* MDS.

	de novo MDS	MDS associated with MonoMac syndrome
Average age of presentation	70-80 yrs	33 yrs (range 9-63 yrs)
Typical peripheral blood findings	Cytopenias	Cytopenias
Monocyte count	Variable	Profound monocytopenia
B cells and NK cells	Normal or mild lymphopenia	Profound NK and B-cell lymphopenia
History of opportunistic infections	Rare	Common (disseminated MAC, fungal, HPV)
Warts	None	Common
Family history of infections	None	Common in first degree relatives
Family history of MDS or leukemia	None	Common in first degree relatives
Bone marrow cellularity	Hypercellular in majority	Hypocellular in majority
Bone marrow fibrosis	Uncommon (10%)	Common (73%)
Micromegakaryocytes	Common	Common
Abnormal plasma cells (CD56+)	Uncommon	Common
Dysplasia	Unilineage, bilineage or multilineage	Frequently multilineage
Presence of hemophagocytic histiocytes	Uncommon	Common
Cytogenetic abnormality	~ 50%	~50-60%

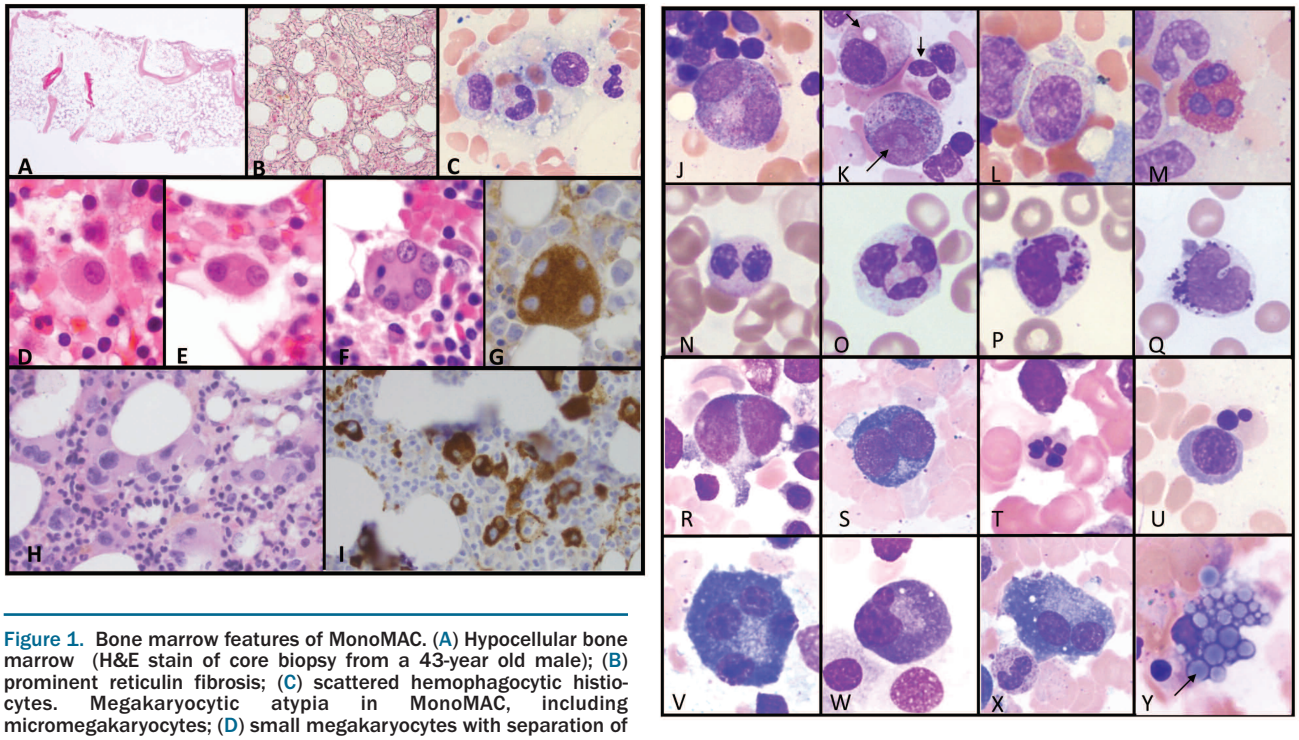

Figure 1. Bone marrow features of MonoMAC. (A) Hypocellular bone marrow (H&E stain of core biopsy from a 43-year old male); (B) prominent reticulin fibrosis; (C) scattered hemophagocytic histiocytes. Megakaryocytic atypia in MonoMAC, including micromegakaryocytes; (D) small megakaryocytes with separation of nuclear lobes; (E) large osteoclast-like megakaryocytes with multiple separated nuclear lobes; (F) which were positive for the megakaryocytic marker Factor VIIIvw by immunohistochemistry. (G) Dysplastic megakaryocytic hyperplasia with mononuclear megakaryocytes in the marrow of a MonoMAC patient; (H) (H&E) and (I) immunohistochemistry for Factor VIIIvw. (J) Myeloid dysplasia: binucleated or mitotic promyelocyte; (K) cytoplasmic vacuoles, hyposegmentation, abnormal maturation; (L) ring nucleus; (M) binucleated or hypersegmented eosinophil; (N) hyposegmented neutrophil; (O, P, Q) hypogranulated granulocytes; (R, S) erythroid dysplasia: binucleation; (T, U) nuclear budding; (U) megaloblastic changes. (V, X) Abnormal plasma cells: multinucleated plasma cells; (W) plasma cells with nuclear budding; and (Y) Mott cells with numerous Russell bodies (arrow) representing stored immunoglobulin.

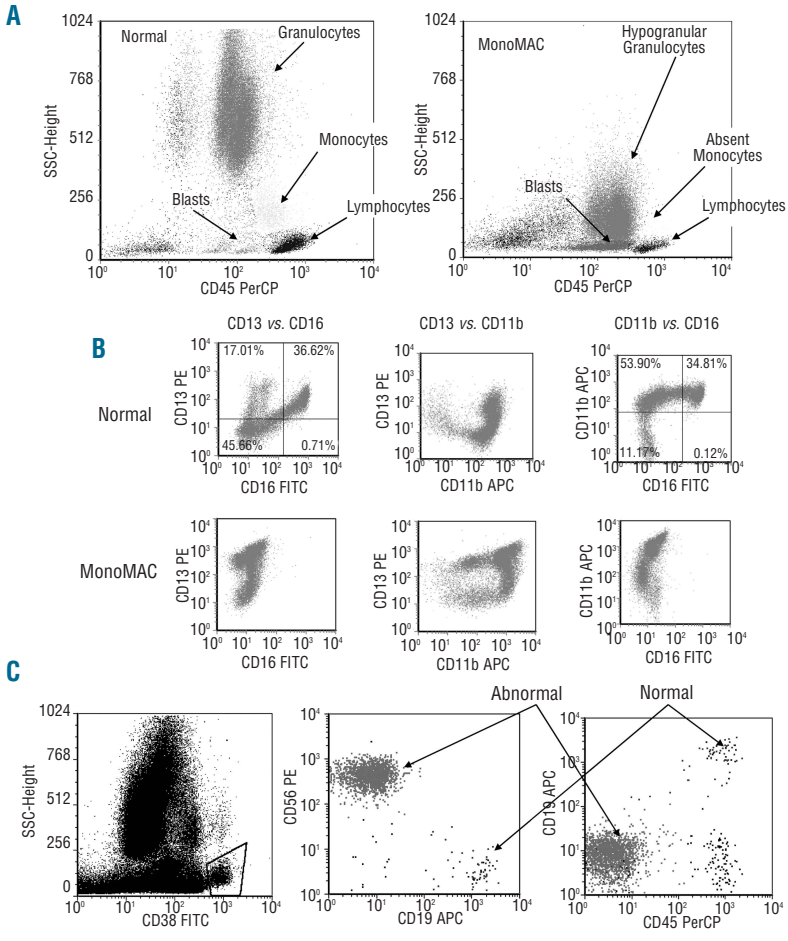

Figure 2. Flow cytometric analysis of bone marrow in MonoMAC. (A) Side scatter [SSC] *versus* CD45. Bone marrow from monoMAC patient shows characteristic pattern of decreased SSC of granulocytes (hypogranular), markedly decreased to absent monocytes, decreased lymphocytes, and increased blasts. (B) Flow cytometric analysis of CD13, CD16 and CD11b expression during myeloid maturation of normal bone marrow and bone marrow from MonoMAC patient. MonoMAC bone marrow shows abnormal dyssynchronous expression patterns of CD13, CD16 and CD11b during myeloid maturation. (C) Flow cytometric analysis of gated plasma cell population in monoMAC patient shows immunophenotypically abnormal plasma cell population ($CD56^+$ and $CD19^-$).

expression patterns of CD11b, CD13 and CD16 during myeloid maturation correlating with maturation asynchrony or dysplasia.

Abnormalities in lymphoid and plasma cells

B cells were markedly decreased to absent in the bone marrow of MonoMAC patients by immunohistochemistry and flow cytometry for CD20 and CD79a/b. Despite B-cell lymphocytopenia, nearly all patients had detectable plasma cells in the bone marrow. Eight of 18 patients (44%) had increased plasma cell populations amounting to 5% or more in the marrow; 3 of these had plasma cell populations of 10% or more. Morphological atypia in plasma cells was noted in several patients and included binucleation (Figure 1X), multinucleation (Figure 1V), nuclear budding (Figure 1W), and so-called Mott cells with cytoplasmic immunoglobulin (Russell bodies) (Figure 1Y). Of the 13 patients with flow cytometric analysis, 6 (46%) demonstrated atypical plasma cell populations with aberrant expression of CD56 and negativity for CD19. CD56 expression on plasma cells has been proposed as a surrogate marker for abnormal clonal plasma cell populations[14,15] and is negative in reactive plasmacytoses.[16] The clinical significance of $CD56^+$ plasma cells in MonoMAC is unclear. Only one patient showed clear evidence of light chain restriction (lambda) (Figure 2C) with over 10% plasma cells in the marrow consistent with smoldering myeloma; this patient had abnormal serum free light chains with normal SPEP studies.

In the majority of patients, T cells were only mildly decreased, with a median $CD3^+$ count of 577/μL (normal 650-2,108). However, increased atypical populations of $CD56^+/CD8^+$ large granular T-lymphocyte cells were detected by flow cytometry in 6 out of 13 patients analyzed. Abnormal patterns of T-cell gene rearrangement were seen in 5 of these 6 cases by TRG@ PCR; 2 cases showed a clonal pattern, 3 cases showed a restricted pattern, and one was polyclonal. Whether abnormal T-LGL populations play a role in exacerbating cytopenias in MonoMAC patients is unclear.

Cytogenetics

Clonal cytogenetic abnormalities were documented in 10 (59%) of 17 patients. All of the clones were simple, with 3 or less than 3 abnormalities. There were 2 patients with monosomy 7 only, one patient with monosomy 7 and trisomy 21, one patient with a stemline with trisomy 1q and deletion of 7q, and a sideline with these abnormalities and also trisomy 8, 3 patients had trisomy 8 only and one had trisomy 1q only. The remaining 2 patients had -Y only and -6, +ring respectively. Despite the fact that the abnormal clones were simple, according to the IPSS,[17] only one patient had a clone with a favorable prognosis (-Y).

MDS with risk of progression to AML

The majority of cases (13 of 18) were classified as

"Myelodysplastic syndrome, Refractory cytopenia with multilineage dysplasia".[18] There were 3 cases of refractory anemia with excess blasts (RAEB). Only 2 of 18 marrows (1.II.1 and 3.I.1 according to Vinh *et al.*[1]) were hypercellular for age and these marrows had features of MDS/MPN (chronic myelomonocytic leukemia [CMML] and atypical chronic myelogenous leukemia). Both patients developed increasing monocyte counts as a pre-terminal event, emerging after many years of monocytopenia.

The International Prognostic Scoring System (IPSS)[17] for MDS was used to calculate scores for each patient (excluding the 2 patients diagnosed with MDS/MPN and one patient without documented cytogenetics). There were 3 low risk, 8 intermediate risk-1, 4 intermediate risk-2, and one high risk. Five out of 18 patients in the current study died between 1996-2010 (1.II.1, 2.II.3, 3.I.1, 7.I.1 and 13.II.1 according to Vinh *et al.*[1]) of infectious complications or leukemic transformation; 5 patients have undergone bone marrow transplantation.

Molecular and functional studies

Half of the patients in this study had family members with a history of opportunistic infections and/or MDS/AML. The similarities between MonoMAC and inherited bone marrow failure syndromes characterized by chromosomal instability and radiosensitivity (e.g. Fanconi anemia), or by telomerase dysfunction (e.g. dyskeratosis congenita) prompted us to analyze patient EBV-LCL cells for these defects. There was no evidence of abnormal spontaneous or induced chromosome abnormalities. Cell cycle checkpoint was intact and there was no increase in the mitotic index in response to ionizing radiation. No germline mutation in *TERT* was identified. Oncogenic Kras mutations can induce myeloproliferative disease in murine models and are implicated in MDS/MPD.[19,20] No germline mutation in *Kras* was identified.

These findings suggest MonoMAC is associated with an underlying form of bone marrow failure that is nosologically distinct from other inherited bone marrow failure syndromes. The genetic basis of the disease remains to be clarified.

ADDENDUM: While this manuscript was in press the genetic basis of the MonoMAC syndrome was clarified and attributed to mutations in GATA2.[21]

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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