MonoMAC *versus* idiopathic CD4+ lymphocytopenia. *Comment* to Haematologica. 2011;96(8):1221-5

We read with interest a recent article in Haematologica describing a novel defined disorder known as MonoMAC (monocytopenia with *Mycobacterium avium* complex).[1] It is not infrequent for patients with MonoMAC to present with a low CD4 count, leading to a consideration of idiopathic CD4-positive (CD4+) lymphocytopenia (ICL).[2] Here we describe a case of MonoMAC who was initially thought to have ICL and aplastic anemia. However, the combination of pancytopenia, profound monocytopenia, and bone marrow (BM) findings support a diagnosis of MonoMAC.

A 24-year old Hispanic male presented with 2 ulcers on the lower extremities that he had had for two months. These ulcers were 1.0 to 3.5 cm in size at their widest point and had slightly raised erythematous borders with pink-glistening to black eschar bases (Figure 1A). Over the previous months he had developed fatigue, weight loss, fevers and chills, and had had a non-productive cough for three weeks. There were no HIV-associated risk factors. No family members with opportunistic infections or malignancy were reported. Physical findings included a low-grade fever, pallor, and decreased breath sounds and crackles in the lung. Laboratory results are summarized in Table 1. HIV antibody was negative by ELISA and HIV viral load was undetectable (< 400 copies/mL).

The patient was admitted for pancytopenia and constitutional symptoms, and was started on broad-spectrum antibiotics. Workup included a punch biopsy of the left medial thigh ulcer which revealed necrotizing granulomatous dermatitis with acid-fast bacilli detected on Fite stain (Figure 1B-D). He also had a lymph node biopsy in the mediastinum which yielded acid-fast bacilli. Sputum cultures grew *Mycobacterium avium-intracellulare* complex (MAC) and were negative for *M. tuberculosis*. He was started on an anti-tuberculosis multi-drug therapy and was discharged on long-term therapy with clarithromycin, ethambutol, and rifampin. His skin lesions resolved within a month of starting therapy. The cause of pancytopenia was initially thought to be due to BM suppression associated with disseminated MAC infection. However, pancytopenia did not resolve and a BM biopsy was performed. This showed a markedly hypocellular

Table 1. Summary of patient's laboratory findings.

	Patient	Reference range
WBC	1.2×10^9/L	$4.1\text{-}10.9\times10^9$/L
Absolute neutrophil count	876 cells/μL	1400-6500 cells/μL
Absolute lymphocyte count	144 cells/μL	1200-3400 cells/μL
Absolute monocyte count	12 cells/μL	300-820 cells/μL
Hemoglobin	5.2 g/dL	14.0-18.0 g/dL
Hematocrit	16.2%	40-54%
MCV	90 fL	82-92 fL
Platelets	44×10^9/L	$150\text{-}400\times10^9$/L
CD4 T-cell count	65 cells/μL	431-1623 cells/μL
CD8 T-cell count	60 cells/μL	170-1078 cells/μL

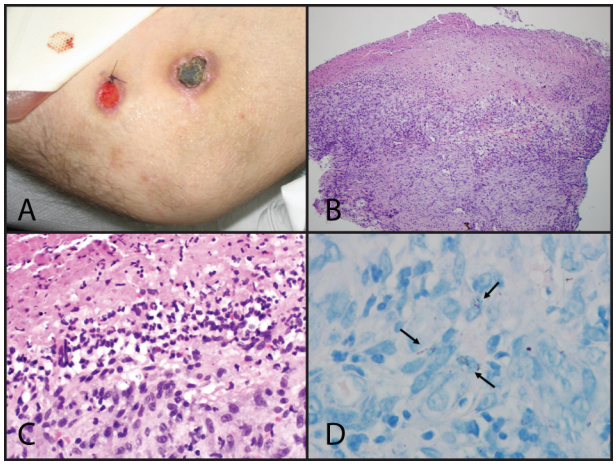

Figure 1. Skin findings. (A) Necrotic ulcers on the lower extremity with erythematous and eschar centers and raised peripheral borders; (B) epidermal and dermal necrosis and granulomatous inflammation throughout the dermis (H&E, magnification x20); (C) dermal necrosis with collection of epithelioid histiocytes (H&E, magnification x200); (D) acidfast positive bacilli (arrows) (Fite stain, magnification x400).

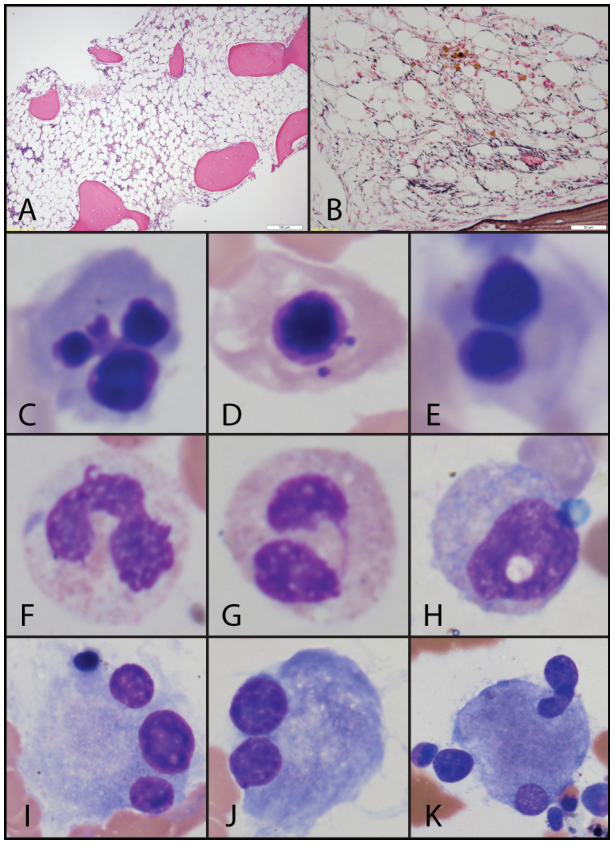

Figure 2. Bone marrow findings. (A) Markedly hypocellular marrow (H&E, magnification x40); (B) moderate reticulin fibrosis (reticulin stain, magnification x200). (C) Erythroid dysplasia: nuclear budding; (D) nuclear cytoplasmic *dyssynchrony*; (E) binucleation. (F) Myeloid dysplasia: hypogranulated granulocyte with uneven distribution of cytoplasmic granules; (G) pelgeroid nuclei; (H) ring nucleus. (I, J, K) Megakaryocytic dysplasia: megakaryocytes with multiple separated nuclear lobes; (K) widely separated nuclei.

Table 2. Features of MonoMAC in comparison to ICL.

	MonoMAC	ICL
Average age of presentation	33 years (range 9-63 years)	43 years (range 17-78)
History of opportunistic infection	Common (disseminated MAC, fungal, HPV)	Common (disseminated NTM, fungal, HPV)
Warts	Common	Relatively common
Family history of infections	Common in first degree relatives	None
Family history of MDS or leukemia	Common in first degree relatives	None
Autoimmune phenomena	Frequent	Frequent
Peripheral blood findings	Cytopenias	Findings associated with opportunistic infection, which can be anemic, occasionally pancytopenic; either leukocytosis or leukopenia
T cells	Frequently show CD4+ T-cell lymphocytopenia, as well as CD8+ T-cell lymphocytopenia	All decreased CD4+ T-cell count, majority reversed CD4:CD8 ratio
B cells and NK cells	Profound NK- and B-cell lymphocytopenia	Frequently decreased
Monocyte count	Profound monocytopenia	Not investigated
Bone marrow findings	Hypocellular marrow, fibrosis, frequently multilineage dysplasia with presence of micromegakaryocytes and hemophagocytic histiocytes	May be hypocellular due to infection-associated bone marrow suppression
GATA2 mutation	Commonly associated	Not implicated

marrow with moderate reticulin fibrosis, and mild erythroid dysplasia (Figure 2A-E). A diagnosis of aplastic anemia was made, and he was treated with antithymocyte globulin and methylprednisolone regimen. Megakaryocytic and myeloid dysplasia was identified retrospectively (Figure 2F-K). His disease course was complicated by several hospital admissions for neutropenic fever, respiratory distress, pleural and cardiac effusions, and persistently positive MAC cultures in the bone marrow, blood, and pleural fluid. Three years after the initial presentation, he succumbed to fulminant disseminated aspergillosis and sepsis.

MAC is one of the non-tuberculous mycobacteria (NTM), and is the most common cause of disseminated infection by NTM in AIDS patients. In HIV-negative patients, ICL is one of the known underlying immunological causes of non-tuberculous mycobacterial infections, which is the major presenting opportunistic infection in this disorder.[3,4] Our patient was found to have persistently low CD4 T-cell counts for more than 18 months, ranging from 18 to150 cells/μL. A provisional diagnosis of ICL was, therefore, made. ICL is a rare heterogeneous syndrome defined by CD4 T-cell counts of less than 300 cells/μL on two occasions, negative HIV testing, and no defined immunodeficiency or therapy associated with decreased $CD4^+$ T-cell count.[4,5]

MonoMAC is a newly defined immunodeficiency syndrome with bone marrow failure in young adulthood, disseminated NTM and fungal infections, monocytopenia, and the propensity to develop myelodysplasia or acute myeloid leukemia. There are familial and sporadic forms of MonoMac.[1,2,6] Mutations in the *GATA2* gene, a regulator of hematopoietic stem cell integrity, in both familial and sporadic forms were recently identified to play a pivotal role in this disease.[6-9]

ICL and MonoMAC share many overlapping clinical features and laboratory findings (Table 2).[1-4,7,8] Both present in the young adult age group, although the mean age at diagnosis of patients with ICL is slightly higher. The majority of patients of both entities present with NTM (including MAC), HPV and fungal infection. Warts and autoimmune phenomena are also shared features. Pancytopenia can occur in ICL due to infection-associated bone marrow suppression. Moreover, lymphocyte subset testing will frequently identify $CD4^+$ lymphocytopenia, $CD8^+$ lymphocytopenia, as well as NK and B-cell lymphocytopenia in both entities. The differential features then rely on an awareness of MonoMAC and multidisciplinary correlation including family history and peripheral blood findings, especially the presence or absence of cytopenia and profound monocytopenia. Finally, bone marrow examination may be indicated to help differentiate between these two entities. *GATA2* mutation analysis may also be helpful.

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