

MonoMAC Syndrome in a Patient With a *GATA2* Mutation: Case Report and Review of the Literature

Jose F. Camargo,¹ Stephen A. Lobo,¹ Amy P. Hsu,² Christa S. Zerbe,² Gary P. Wormser,¹ and Steven M. Holland²

¹Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla; and ²Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

We report a case of MonoMAC syndrome in a patient with a *GATA2* mutation and discuss the manifestations, diagnosis, and treatment of this novel immunodeficiency disorder.

Keywords. *GATA2*; MonoMAC; monocytopenia; mycobacterial infection; immunodeficiency.

Monocytopenia and mycobacterial infection (MonoMAC) syndrome is caused by heterozygous mutations in *GATA2*, resulting in the loss of function of a gene that regulates many aspects of development from hematopoiesis to lymphatic formation. It is also known as combined dendritic cell (DC), monocyte, B and natural killer (NK) lymphoid cell deficiency; familial myelodysplasia/leukemia with lymphedema (Emberger syndrome); and familial leukemia/myelodysplasia. All of these names recognize the same recently described immunodeficiency disorder characterized by profoundly decreased or absent circulating monocytes, DCs, NK cells, and B cells, associated with an increased risk of opportunistic infections and hematological malignancies [1, 2]. Patients typically present during early adulthood with severe or recurrent nontuberculous mycobacterial (NTM) infections, although opportunistic fungal infections and disseminated human papillomavirus (HPV) infections also occur [1, 2]. Both autosomal dominant inheritance and sporadic cases have been identified [1, 2]. Bone marrow transplant has been curative in some cases [2, 3]. Here we describe a 23-year-

old Asian man who presented with fever of unknown origin and was ultimately diagnosed with recurrent NTM infection due to MonoMAC syndrome. Infectious disease physicians are among the clinical specialists who are likely to encounter patients with this serious but potentially curable condition, and should become familiar with its presentation, diagnosis, and treatment.

CASE REPORT

A 23-year-old Filipino man presented to the Westchester Medical Center in June 2012 with nodular skin lesions on the anterior aspect of his distal lower extremities of approximately 4 weeks duration. He also complained of intermittent fevers (38.3°C–38.9°C), fatigue, poor appetite, and a 12-pound weight loss over the same period of time. These symptoms were preceded by several months of intermittently productive cough.

The patient had been diagnosed with disseminated *Mycobacterium szulgai* lung infection involving cervical and mediastinal lymph nodes in August of 2007, the same year he immigrated to the United States. Blood cell count at that time revealed lymphocytopenia (lymphocyte count: 270 cells/mm³) and monocytopenia (monocyte count: 27 cells/mm³). Two months later he developed neutropenia (nadir absolute neutrophil count: 64 cells/mm³) that responded well to treatment with granulocyte colony-stimulating factor. Bone marrow biopsy showed hypocellularity with granulocytic hypoplasia. He was successfully treated with right upper lobectomy and resection of necrotic thoracic lymph nodes in addition to 18 months of antimycobacterial therapy. Past medical history was also significant for recurrent ear infections during childhood, 4 episodes of community-acquired pneumonia since age 12, and recurrent warts on his feet and hands. His brother had had recurrent warts but was otherwise healthy. His sister and mother were healthy, but his father had died of acute bowel infarction.

On physical examination, there were bilateral knee effusions and scattered tender, erythematous, subcutaneous nodules on the pretibial areas. White blood cell count was 3000 cells/mm³ (42% neutrophils, 10% lymphocytes, 1% monocytes, 44% eosinophils, 2% bands); hemoglobin level was 12.7 g/dL; platelet count was 117 × 10⁹/L. The CD4⁺ T-cell count was 141 cells/mm³ and the CD4/CD8 ratio was 0.99. Ninety-eight percent of the patient's total lymphocyte count corresponded to T cells (normal percentages: T cells 60%–80%, B cells 10%–20%, and NK cells 5%–10%), indicating B and NK lymphopenia. Electrolytes, creatinine, and liver function tests were within normal limits.

Received 19 February 2013; accepted 17 May 2013; electronically published 31 May 2013.

Correspondence: Jose F. Camargo, MD, Division of Infectious Diseases, New York Medical College, Munger Pavilion, Rm 245, Valhalla, NY 10595 (josefcamargo@gmail.com).

Clinical Infectious Diseases 2013;57(5):697–9

© The Author 2013. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cit368

Table 1. Main Characteristics of MonoMAC Syndrome

<p>Infections</p> <ul style="list-style-type: none"> • Nontuberculous mycobacterial infections Typically <i>Mycobacterium avium</i> complex Other slow-growing species: <i>M. kansasii</i>, <i>M. scrofulaceum</i>, <i>M. bovis</i>, <i>M. szulgai</i> Rapid-growing species: <i>M. fortuitum</i>, <i>M. abscessus</i>, <i>M. massiliense</i> • Viral infections: typically severe or persistent human papilloma virus infection (>50% of patients); herpesvirus infections (Epstein-Barr virus; disseminated varicella zoster virus) are less common. Fatal influenza H1N1 has been reported • Fungal infections: disseminated histoplasmosis (most common), cryptococcal meningitis and invasive aspergillosis
<p>Cytopenias</p> <ul style="list-style-type: none"> • Myeloid cells: monocytes^a and dendritic cells^b • Lymphoid cells: typically natural killer and B cells^a. CD4⁺ lymphopenia^c (including CD4⁺ T-regulatory cells) has been described • Other: anemia, neutropenia, and thrombocytopenia associated with myelodysplastic syndrome or acute myeloid leukemia
<p>Noninfectious complications</p> <ul style="list-style-type: none"> • Pulmonary alveolar proteinosis, pulmonary hypertension • Malignancy: myelodysplastic syndrome, leukemia, Epstein-Barr virus-associated smooth muscle tumors • Autoimmune phenomena: erythema nodosum, arthritis, lupus-like syndrome • Primary lymphedema

^a In the largest case series of MonoMAC syndrome (n = 18), reduced numbers of circulating monocytes (mean, 13 cells/mm³; normal, 210–660 cells/mm³), B cells (mean, 9 cells/mm³; normal, 49–424 cells/mm³) and natural killer cells (mean, 16 cells/mm³; normal, 87–505 cells/mm³) were reported [1].

^b Both tissue and circulating dendritic cells, with the exception of epidermal Langerhans cells [2].

^c A positive family history for *Mycobacterium avium* complex or myelodysplastic syndrome/acute myeloid leukemia, the presence of profound monocytopenia, cytogenetic abnormalities in a hypoplastic bone marrow, and *GATA2* mutations favor the diagnosis of MonoMAC over idiopathic CD4⁺ lymphocytopenia [7].

HIV, hepatitis B, and hepatitis C antibody testing was negative. Serum cryptococcal antigen, serum galactomannan, urine *Histoplasma* antigen, and *Coccidioides immitis* and *Histoplasma capsulatum* serologies were all negative. The patient had a positive tuberculin skin test (20 mm) but the QuantiFERON-TB Gold In-Tube test was negative. Stool ova and parasite examination and *Strongyloides* antibody test were negative. Serum immunoglobulin M and immunoglobulin G antibodies against *Coxiella burnetii* and *Brucella* species were negative. Serum immunoglobulin levels were within the normal range. Bacterial blood cultures were negative. Synovial fluid obtained from the right knee showed 1600 white cells/mm³ with a neutrophil predominance. Bacterial, fungal, and acid-fast bacilli (AFB) cultures of the synovial fluid were negative. Antineutrophil cytoplasmic antibodies, antinuclear antibodies, complement levels and the angiotensin-converting enzyme level were within normal limits. Computed tomography of the chest showed patchy and nodular pulmonary infiltrates within the right middle, left upper, and left lower lobes with associated mediastinal lymphadenopathy measuring up to 1.2 cm in diameter. Computed tomography of the abdomen showed multiple enhancing hypervascular lesions throughout the liver measuring up to 1.2 cm and a 2.3-cm heterogeneous mass with nodular enhancement in the right lobe of the liver.

A biopsy of the skin lesions showed panniculitis consistent with erythema nodosum; bacterial, fungal, and AFB cultures were negative. A percutaneous fine-needle aspiration biopsy of the lesions in the right hepatic lobe showed an Epstein-Barr virus (EBV)-associated smooth muscle tumor; bacterial, fungal,

and AFB cultures were negative. A transbronchial biopsy of the lung showed nonnecrotizing granulomas, but fungal and AFB stains were negative. Culture from 2 of 3 separate expectorated sputum samples and from bronchoalveolar lavage (BAL) fluid yielded *M. avium* complex (MAC). The patient's fever, skin lesions, and respiratory and constitutional symptoms resolved within 2 weeks of anti-MAC therapy consisting of ethambutol, rifabutin, and clarithromycin. The constellation of peripheral cytopenias, recurrent NTM, HPV infections, EBV-associated smooth muscle tumors, and autoimmune phenomena led to the suspicion of MonoMAC syndrome. Genetic testing found a heterozygous mutation in *GATA2* (c.1186C > T; p.R396W) confirming the diagnosis of *GATA2* deficiency. This mutation has been reported previously in patients with MonoMAC syndrome [4]. His brother and sister tested negative for *GATA2* mutations. The patient has now been referred for bone marrow transplant.

DISCUSSION

In addition to MonoMAC, other adult-onset primary immunodeficiency disorders can be associated with NTM infections. These include the warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, which results from dominant gain of function mutations in chemokine receptor CXCR4 leading to retention of mature neutrophils in the bone marrow [5]; and a more recently described immunodeficiency syndrome characterized by the presence of anti-interferon- γ autoantibodies in Asian adults with disseminated NTM [6].

WHIM is unlikely to explain this patient's presentation, as he had normal serum immunoglobulin levels and a hypocellular bone marrow. Although we did not measure serum anti-interferon- γ antibodies in our patient, the presence of peripheral cytopenias, hypocellular bone marrow, and a *GATA2* mutation support the diagnosis of MonoMAC.

At least 25 cases of MonoMAC have been reported [1, 2, 7, 8]. The main characteristics of MonoMAC syndrome are listed in Table 1. At present, there does not appear to be any racial/ethnic predilection with reported cases in Whites, Asians, and Hispanics. The syndrome was first described by Vinh et al after identifying a group of 18 patients (mean age: 31 years) with disseminated NTM and other opportunistic infections [1]. Seventy-eight percent of the patients in this cohort developed NTM disease, with slow-growing mycobacteria accounting for most of these infections. MAC was identified in blood and/or other sterile sites in more than one-half of these cases [1]. Other infections seen in MonoMAC syndrome are presented in Table 1.

Noninfectious conditions have also been described in MonoMAC [1, 2, 8, 9] (Table 1). Erythema nodosum and pulmonary alveolar proteinosis have each been seen in up to one-third of patients [1] and can be the presenting feature [2]. Patients with pulmonary alveolar proteinosis, including those without documented *GATA2* mutations, have an increased risk of opportunistic fungal and mycobacterial infections [10].

Profound peripheral blood monocytopenia and B and NK cell lymphopenia are characteristic of patients with MonoMAC [1, 2, 7, 8]. Notably, monocytopenia in these patients can exist for more than a decade before a diagnosis is made [2]. Other cytopenias seen in MonoMAC are listed in Table 1. Despite the near absence of circulating monocytes and DCs, tissue macrophages and epidermal Langerhans cells are preserved in MonoMAC [1, 2, 11]. Similarly, despite marked B-cell lymphopenia, serum immunoglobulin levels remain within normal limits and tissue plasma cells remain detectable in skin and bone marrow biopsies of patients with MonoMAC [1, 11]. Although it is unknown whether tissue NK cells are also spared in MonoMAC, our patient had detectable NK cells in synovial fluid.

The bone marrow of patients with MonoMAC is characterized by hypocellularity, fibrosis, and multilineage dysplasia [1, 2, 11]. Cytogenetic abnormalities are common [1, 11]. Progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) is one of the most serious complications of this syndrome. One-half of the 18 patients reported by Vinh et al were diagnosed with MDS/AML by age 32, and complications associated with hematological malignancy accounted for 4 of the 5 deaths in this cohort [1]. Conceivably, some of the previous reports of NTM infections in patients with MDS/AML [12] might represent unrecognized cases of *GATA2* mutation.

Mortality of MonoMAC syndrome can be as high as 28% [1]. Allogeneic hematopoietic stem cell transplantation has been

shown to be an effective strategy to reconstitute the depleted hematopoietic compartments and reverse the clinical phenotype seen in affected patients [2, 3]. It is unknown whether there is any role for the use of growth factors such as granulocyte macrophage colony-stimulating factor to correct the peripheral monocytopenia, whether antimicrobial prophylaxis against MAC and specific immunization protocols (eg, HPV vaccination) are indicated, or whether prevention of infections can prevent neoplastic complications later in life.

Notes

Acknowledgments. Because of space constraints, we regret our inability to cite other excellent papers that have also examined the clinical significance of *GATA2* mutations.

Financial support. This work was supported in part by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Vinh DC, Patel SY, Uzel G, et al. Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. *Blood* **2010**; 115:1519–29.
2. Bigley V, Haniffa M, Doulatov S, et al. The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency. *J Exp Med* **2011**; 208:227–34.
3. Cuellar-Rodriguez J, Gea-Banacloche J, Freeman AF, et al. Successful allogeneic hematopoietic stem cell transplantation for *GATA2* deficiency. *Blood* **2011**; 118:3715–20.
4. Hsu AP, Sampaio EP, Khan J, et al. Mutations in *GATA2* are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood* **2011**; 118:2653–5.
5. Hernandez PA, Gorlin RJ, Lukens JN, et al. Mutations in the chemokine receptor gene *CXCR4* are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet* **2003**; 34:70–4.
6. Browne SK, Burbelo PD, Chetchotisakd P, et al. Adult-onset immunodeficiency in Thailand and Taiwan. *N Engl J Med* **2012**; 367:725–34.
7. Chu VH, Curry JL, Elghetany MT, Curry CV. MonoMAC versus idiopathic CD4+ lymphocytopenia. *Haematologica* **2012**; 97:e9–11.
8. Ishida H, Imai K, Honma K, et al. *GATA-2* anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia. *Eur J Pediatr* **2012**; 171:1273–6.
9. Kazenwadel J, Secker GA, Liu YJ, et al. Loss-of-function germline *GATA2* mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for *GATA2* in the lymphatic vasculature. *Blood* **2012**; 119:1283–91.
10. Punatar AD, Kusne S, Blair JE, Seville MT, Vikram HR. Opportunistic infections in patients with pulmonary alveolar proteinosis. *J Infect* **2012**; 65:173–9.
11. Calvo KR, Vinh DC, Maric I, et al. Myelodysplasia in autosomal dominant and sporadic monocytopenia immunodeficiency syndrome: diagnostic features and clinical implications. *Haematologica* **2011**; 96:1221–5.
12. Kobashi Y, Yoshida K, Niki Y, Oka M. Sibling cases of *Mycobacterium avium* complex disease associated with hematological disease. *J Infect Chemother* **2006**; 12:331–4.